NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Somapacitan for treating growth hormone deficiency in people 3 to 17 years [ID6178]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

COST COMPARISON APPRAISAL

Somapacitan for treating growth hormone deficiency in people 3 to 17 years [ID6178]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Novo Nordisk:
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **External Assessment Report** prepared by Newcastle NIHR TAR Team, Newcastle University

4. **External Assessment Group response to factual accuracy check of EAR**

5. **Clinical expert response to questions**
   a. Joanne Blair, nominated by Novo Nordisk
   b. Ross Burrows, nominated by Neonatal and Paediatric Pharmacy Group

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA): cost-comparison

Somapacitan for treating growth hormone deficiency in children [ID6178]

Document B

Company evidence submission

23 June 2023

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Abbreviations

AE	Adverse event
AHV	Annualised height velocity
AGHD	Adult growth hormone deficiency
BMAD	Bone mineral apparent density
BMD	Bone mineral density
BSPED	British Society for Paediatric Endocrinology and Diabetes
CE	Conformité Européenne
CI	Confidence interval
CVD	Cardiovascular disease
DIC	Deviance information criteria
DNA	Deoxyribose nucleic acid
eCRF	electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
ERT	eReasearch technology
ETD	Estimated treatment difference
FAS	Full analysis set
FDA	Food and Drug Administration
FE	Fixed effect
GH	Growth hormone
GHD	Growth hormone deficiency
GHRHR	Growth hormone receptor releasing hormone
GHRS	Growth Hormone Research Society
GP	General practitioner
hGH	Human growth hormone
HRQoL	Health-related quality of life
HV	Height velocity
IGF-I	Insulin-like growth factor-I
IGFBP-3	Insulin-like growth factor binding protein 3
ITC	Indirect treatment comparison
IWRS	Interactive web response system
KOL	Key opinion leader
LAGH	Long-acting growth hormone

LAR	Legally authorised representative
MHRA	Medicines and Healthcare products Regulatory Agency
MMRM	Mixed model for repeated measurements
MPHD	Multiple pituitary hormone deficiency
MTA	multiple technology appraisal
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
PK	Pharmacokinetic
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Per protocol
PRO	Patient reported outcome
PSSRU	Personal social services research unit
QoL	Quality of life
RCT	Randomised controlled trial
RE	Random effect
SAGH	Short-acting growth hormone
SAS	Safety analysis set
SD	Standard deviations
SDS	Standard deviation score
SGA	Short for gestational age
SLR	Systematic literature review
SmPC	Summary of product characteristics
STA	Single technology assessment
UK	United Kingdom
US	United States

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

B.1.1 *Decision problem*

B.1.1.1 *Population*

Somapacitan will be indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD) and in adults with growth hormone deficiency (adult GHD). The submission focuses on children aged 3 years and above, and adolescents with GHD and is in line with the scope issued by the National Institute for Health and Care Excellence (NICE) (Table 1).

The evidence is based on the pivotal REAL 4 Phase III study, which assessed the efficacy and safety of weekly somapacitan compared with daily Norditropin® (somatropin) in paediatric patients with GHD. The REAL 3 Phase II study assessed the efficacy and safety of multiple dose regimens of weekly somapacitan compared with daily Norditropin® in children with GHD and is presented (main and extension trial phases) as supporting evidence.

B.1.1.2 *Comparators*

The main comparator in this submission is the once-weekly rhGH therapy somatrogon (Ngenla®, Pfizer) as it was recommended by NICE in February 2023 for use in children and young people aged 3 years and over with GHD (TA863) (1).

Within the scope, NICE included daily recombinant human growth hormone (rhGH; somatropin) and weekly rhGH (somatrogon) as relevant comparators. In the UK, seven preparations of daily rhGH treatment (somatropin) are available: Genotropin® (Pfizer); Humatrope® (Lilly); Norditropin® (Novo Nordisk); NutropinAq® (Ipsen); Omnitrope® (Sandoz); Saizen® (Merck Serono); and Zomacton® (Ferring) (2). These comparators have several licenced indications (TA188); however, all are indicated for use in the target population of this submission.

The evidence base for weekly somapacitan vs daily somatropin is direct head-to-head evidence from clinical trials. In the absence of head-to-head trials, somapacitan has also been compared with weekly somatrogon using a pairwise indirect treatment analysis (ITC). Both the clinical trial data and the ITC demonstrate the similar treatment effects of somapacitan vs comparators. Therefore, a simple cost comparison analysis is presented in the submission.

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 young people from 3 years of age diagnosed with growth hormone deficiency.	As per scope	N/A
Intervention	Somapacitan	As per scope	N/A
Comparator(s)	• Somatropin • Somatrogon	As per scope	N/A
Outcomes	• 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	Additional outcomes (for qualitative inclusion in the submission dossier): • Injection pain • Treatment adherence	• In the ITC (see Section B.3.9), somapacitan demonstrated reduced injection site pain compared with somatrogon • Poor adherence is associated with reductions in treatment efficacy, and worsened clinical outcomes compared with compliant patients (28, 29)
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. As 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. 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 NHS and Personal Social Services perspective.	A cost-comparison analysis that assumes similar efficacy and safety to both somatropin (based on head-to-head trials) and somatrogon (based on indirect comparison) and results in annual treatment cost parity with somatrogon (Ngenla®) and similar annual treatment cost with the somatropin preparations. Only acquisition costs are considered, as other NHS and Personal Social Services perspective costs are considered	A cost-comparison approach is the most appropriate and efficient way to evaluate somapacitan vs the relevant comparators. Once-weekly somapacitan provides equivalent health benefits to once-daily rhGH (somatropin) as demonstrated by head-to-head trials, with the additional benefit of reduced (once-weekly) injection frequency. An ITC shows that somapacitan also provides similar health benefits

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	The availability and cost of biosimilar and generic products should be taken into account.	equal across available treatment options.	to once-weekly somatrogon across key clinical endpoints. Somapacitan treatment is expected to result in similar costs to technologies recommended in published NICE technology appraisal guidance (TA188 and TA863).
Special considerations including issues related to equity or equality	Not included in scope	1) Potential for gender bias 2) Socioeconomic factors	An awareness of potential gender biases is important for the adequate care of girls with short stature. Socioeconomic status should also be considered, as disadvantaged children are at risk of poorer health outcomes than those living in more favourable socioeconomic circumstances. Please see Section B.1.4 for a discussion of equality considerations.

Abbreviations: ITC, indirect treatment comparison; N/A, not applicable; NHS, national health service; NICE, National Institute for Health and Care Excellence; rhGH, recombinant human growth hormone.

B.1.2 *Description of the technology being evaluated*

A summary of the technology being evaluated is provided in Table 2. Further details are provided in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Non-proprietary name: Somapacitan Brand name: Sogroya®
Mechanism of action	Somapacitan is a long-acting, recombinant hGH derivative with a linker and albumin binder covalently attached. Somapacitan binds to GH receptors, initiating downstream signalling cascades and increasing serum IGF-I levels to promote cellular growth and proliferation. Somapacitan has an albumin-binding moiety attached to the peptide backbone; this allows for non-covalent, reversible binding of the GH molecule to endogenous albumin, which delays the absorption and elimination of somapacitan, reducing renal clearance of the drug and prolonging the in vivo half-life. The receptor potency, PK and PD properties of somapacitan make it suitable for once-weekly subcutaneous administration in patients with GHD.
Marketing authorisation/ CE mark status	Somapacitan does not currently have UK marketing authorisation for the population in this submission (paediatric GHD). A marketing authorisation application for somapacitan was submitted to the MHRA in May 2023. In May 2023, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending somapacitan for paediatric GHD. UK licence is expected in August 2023 via the European Commission Decision Reliance Procedure. Somapacitan is currently approved for adults with GHD in the UK, US, Japan, Europe and other selected markets. The PDS290 injection device was awarded a CE certification mark on the 24th April 2019. The certification indicates that the device is made under ISO standards, in line with annex 1.
Indications and any restriction(s) as described in the SmPC	It is anticipated that somapacitan will be indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).
Method of administration and dosage	Somapacitan is administered as a once-weekly subcutaneous injection. The recommended starting dosage of somapacitan is 0.16 mg/kg body weight/week. A 5 mg/1.5 mL, 10 mg/1.5 mL and 15mg/1.5mL device in the PDS290 pen-injector will be available when the paediatric indication is commercially launched with NICE guidance. The somapacitan dose is anticipated to be individualised and adjusted, based on growth velocity, adverse reactions, body weight and serum IGF-I concentrations.
Additional tests or investigations	N/A
List price and average cost	[redacted]

of a course of treatment	[redacted]
Patient access scheme (if applicable)	Not applicable

Abbreviations: CE, Conformité Européenne; EMA, European Medicines Agency; GH, growth hormone; GHD, growth hormone deficiency; hGH, human growth hormone; IGF-I, insulin-like growth factor-1; ISO, international organisation for standardisation; MHRA, Medicines and Healthcare products Regulatory Agency; NHS, National Health Service; PD, pharmacodynamic; PK, pharmacokinetic; SmPC, Summary of Product Characteristics; UK, United Kingdom; US, United States.

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

B.1.3.1 *Disease overview*

GHD is a rare disease characterised by insufficient secretion of GH by the pituitary gland (3), and is one of the most common endocrine-related causes of short stature (4). In children and adolescents, GH is responsible for increasing bone length and density (3, 5, 6), regulating body composition (3), and acts as a counter-regulatory hormone that antagonises the effects of insulin on glucose metabolism (7-9). GH affects whole-body lipid metabolism and exerts its biological effect through changes in transcription regulation and acute changes in the catalytic activity of several enzymes (8). These regulatory processes contribute to the overall growth and maturation of children and adolescents into adults.

GH acts both directly on tissue targets, and indirectly by induction of transcription factors (3, 10, 11). The binding of GH to its receptors on cell membranes induces the transcription of genes encoding insulin-like growth factor-1 (IGF-I), IGF-2, IGF-binding protein-3 (IGFBP-3) and acid-labile subunit (ALS). The main GH effector is IGF-I with the interplay between the two molecules known as the GH–IGF-I axis, a complex system involving negative feedback mechanisms. The GH–IGF-I axis has a leading role in growth and development (12, 13), and is involved in regulating cellular division and growth across all cell types (14). As well as controlling growth, GH and IGF-I have clinically significant effects on carbohydrate, lipid and protein metabolism (7, 12, 14-18).

Children with GHD most commonly present with growth failure and maturation delays (3, 17). Clinical features also include delayed dentition, an immature face, a prominent forehead and depressed midfacial development, a high-pitched voice, increased fat mass that is predominantly centrally distributed, male hypogenitalism, decreased muscle mass, and delayed puberty (3, 19, 20). GHD also adversely affects patients' body composition, metabolic profile, bone mineral density (BMD) and quality of life (QoL). The clinical presentation of GHD varies depending on the age of onset; for example, neonates and infants may initially have non-specific signs and symptoms such as lethargy and poor weight gain (3). GHD in childhood is associated with persistent growth failure and short stature, while in adolescents the most common presentation is growth retardation and delayed puberty (3, 21).

GHD can be congenital or acquired (3, 17) and may occur in isolation (isolated GHD; IGHD) (22) or in conjunction with other pituitary hormone deficits (multiple pituitary hormone deficiency; MPHD) (3). The majority (up to 70%) of patients with GHD have isolated GHD with no known cause (idiopathic) (4). Congenital causes of IGHD include mutations in the growth hormone 1 (*GH1*) and growth hormone receptor releasing hormone (*GHRHR*) genes; MPHD can be caused by mutations in several pituitary-specific transcription factors (3). Acquired causes of IGHD and MPHD include external damage or trauma to the pituitary gland caused by CNS tumours, physical trauma, inflammation, infections or radiotherapy (3).

B.1.3.2 *Epidemiology*

The estimated prevalence of GHD in the UK is 1 in 4,000 to 1 in 3,500 (2, 23). International prevalence estimates range from 1 in 10,000 to 1 in 4,000 (24). It is therefore estimated that, of all children born in the UK each year, approximately 175–200 are born with GHD or develop it later in life (23, 25). Boys are more frequently diagnosed with GHD than girls (ratio of 1.58:1) (26).

According to a survey of endocrine clinics published in 2006 by the British Society for Paediatric Endocrinology and Diabetes (BSPED), 4,758 patients have been receiving rhGH in the UK, of which 4,168 were in England and Wales (27).

B.1.3.3 *Clinical pathway of care*

The current standard of care in the management of GHD is rhGH, also known as somatropin (a synthetic form of hGH produced by recombinant DNA technology) (2). Treatment is administered as once-daily subcutaneous injections. In addition, the once-weekly rhGH somatrogon (Ngenla®, Pfizer) has recently been recommended by NICE (TA863). The primary goal of treatment in children with GHD is to normalise height during childhood and adolescence (19, 28), with patients ultimately reaching adult height in the normal range (15). In a physician survey of paediatric endocrinologists based in England,[a] all clinical experts identified once-daily GH therapy as the standard of care for children with GHD, and agreed that available products are considered to have comparable efficacy (29).

The place of rhGH treatment in the treatment pathway depends on the child's particular condition and their age at diagnosis. GHD is typically identified and diagnosed at one of two age ranges: at 5–6 years when children begin school, or a few years later when associated with delayed pubertal growth spurt (10–13 years in girls and 12–16 years in boys) (30). Guidelines recommend that once rhGH is initiated, patients should be examined every 4–6 months (2–3 assessments per year) (28), since GH dosage is based on patient weight and clinical response, and will need to be revised as patients grow. In the survey referenced above, expert consensus was that endocrinologists meet with patients every 4 months in the first year, then every 6 months afterwards (29).

[a] Interviews were conducted between December 2022 and January 2023 with four paediatric endocrinologists based in England.

The choice of rhGH treatment should be made on an individual basis after informed discussion between the responsible clinician and the patient and/or their carer (2). The advantages and disadvantages of available products should be discussed, taking into consideration therapeutic need and the likelihood of adherence to treatment. In the clinician interviews, the consensus was that patients and their families are given the choice of GH therapy after discussions with a specialist nurse (29).

Children treated with GH should be regularly assessed by a specialist in child growth. GH treatment should always be instigated by a physician with special knowledge of GH insufficiency and its treatment (31). GH treatment should be initiated as early as possible to achieve optimum efficacy; studies show that children who start GH treatment earlier for GHD have a better chance of reaching their genetic potential height compared with those who delay their treatment (32-35).

Treatment should be discontinued after the first year if there is a poor response despite optimal GH dose (i.e., if 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 (2). 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*

B.1.3.4.1 Clinical, humanistic and economic burden of GHD

Children with GHD have a lower height velocity (HV) compared with healthy children, causing them to not achieve their maximum height potential (also known as growth failure) (36). Children with GHD typically have normal body proportions, but are often shorter, chubbier, and may be perceived to be younger compared with gender-matched peers of a similar age (36). Notably, very few (4%) children with GHD cite short stature as the only disease-related symptom (36), suggesting that most individuals experience multiple clinical manifestations of the disease (3, 5). In an international study to examine the burden of GHD on children and adolescents (interviews and focus groups conducted in the UK, Germany and the US), the most commonly reported symptoms in addition to short stature were poor appetite (47% of respondents), reduced strength or poor muscle development (47%), poor energy levels (34%), reduced endurance (30%) and poor sleep (30%) (36).

Children with GHD also have a greater incidence of comorbidities compared with demographically matched controls (37), including cardiovascular disease (CVD), metabolic conditions (37, 38), and abnormal lipid and glucose metabolism (8, 38-40), which can also increase the risk of CVD later in life (37). Children with GHD have also been shown to have significantly lower bone mineral density (BMD) and bone mineral apparent density (BMAD) compared with age- and sex-matched reference values (6). Reduced BMD increases the risk of reduced peak bone mass and subsequent bone loss, which are linked to osteopathic diseases later in life (41).

Several studies have reported the negative impact of GHD on health-related quality of life (HRQoL) (42-44). In the international study discussed above, authors identified three key aspects of daily life that are affected by symptoms of GHD: physical aspects, social wellbeing, and emotional wellbeing (36). Of physical aspects affected, the overarching theme was the impact on activity levels, with GHD patients and parents reporting reduced performance in physical activities/sports (59% of respondents), difficulty reaching things (44%), and limits of what children could do because of their size (19%).

The reported social impacts were often related to the child's visibly smaller size, and the most common emotional impact identified was disliking or feeling bothered by their height/size. A UK study also found that children with short stature are significantly more likely to be bullied than their taller peers (p=0.003 for pupil-reported bullying in secondary school, and p=0.018 for pupil-reported bullying in both junior and secondary schools), and that short pupils report a greater degree of isolation (p=0.032 vs controls) (44).

Globally, there is a paucity of studies describing the economic impact of untreated GHD compared with patients without GHD. However, in a recent (2021) US study to analyse healthcare costs, somatropin use and adherence among children with GHD, all-cause costs[b] (excluding somatropin costs) were 5–6 times higher for GHD patients compared with those without GHD. Treated GHD patients incurred lower costs than untreated patients with GHD, suggesting that improved adherence may lower healthcare costs; the adjusted cost ratio between treated and untreated GHD was 0.69 and 0.59 for commercially insured and Medicaid patients, respectively (37).

B.1.3.4.2 Unmet needs

Despite the recognised benefits of GH therapy in children with GHD, poor adherence to once-daily GH therapy is common (17, 45). Poor adherence is associated with reductions in treatment efficacy, and worsened clinical outcomes compared with compliant patients (17, 45-47). In a UK study, patients who missed more than two injections of daily GH per week had a significantly lower HV compared with those who missed none (−41%, p<0.05) (48). In another study, children with GHD who completed GH treatment had a change in height standard deviation score (SDS) of 1.8 compared with 0.9 for children who ceased GH treatment early (46).[c] Non-compliance has been shown to increase over time and is a significant issue for long-term treatment (49, 50). In the clinician survey described earlier, three out of four experts stated that patients report missing doses of daily GH (29).

Poor adherence to GH therapy also contributes to the economic burden of GHD as a result of increased healthcare costs due to additional diagnostic tests or hospitalisation, and unnecessary changes to the drug dose (47). Poor adherence to medication also contributes to the global economic burden of unused and wasted prescription medications, which has an estimated gross annual cost of £300 million to NHS England

[b] Costs in this study were adjusted for differences in patient baseline characteristics. While data from different countries will differ, affecting generalisability of findings, this US study is included to highlight the trend that children with GHD have higher healthcare costs compared with children without GHD.

[c] In children who ceased treatment early, the median treatment duration was 3.4 years compared with 5.5 for children who completed treatment (i.e. 2.1 fewer years).

alone (51). Across different diseases, poor adherence is associated with worsening clinical outcomes and additional comorbidities (52), which may result in additional costs later in life (53).

The most commonly reported reasons for not adhering to once-daily GH schedules include the burden of treatment administration – such as the frequency of daily injections, injection anxiety and injection-associated pain – and a lack of patient/parent confidence in administering treatment (42, 47). Caregivers may feel uneasy during administration and worry about causing their child pain (42). In the interviews with clinicians in England, all experts reported that difficulty sticking to a daily injection schedule is among the most common reasons for patients missing GH doses (29).

A recent (2022) time trade off (TTO) study, conducted in the UK and Canada (54), highlighted the burden of injection pain in terms of its impact on HRQoL. Two surveys were conducted, using eight defined health states (defined in collaboration with two clinical experts and one health economics expert). Of all the health states, the injection pain health state was associated with the highest disutility in both the UK and Canada from the perspective of a person with GHD (0.030 and 0.030, respectively [survey 1]) and as a parent of a child with GHD (0.039 and 0.050, respectively [survey 2]). Other factors reported to adversely affect adherence to current once-daily GH therapies are lack of storage flexibility, lack of choice of device, and low device ease of use (54).

There is, therefore, a clear unmet need in children with GHD for GH products that reduce the burden of treatment administration. A recent discrete choice experiment demonstrated that patient preference is for a less frequent injection regimen for treating GHD (55). In the interviews with clinicians in England, all experts agreed that once-weekly GH therapy would improve patient adherence to treatment, compared with daily therapies (29). Thus, a GH therapy that provides less frequent dosing and is delivered in a storage-flexible, easy-to-use device with minimal injection pain, would benefit patients and has the potential to improve treatment adherence and outcomes.

B.1.4 *Equality considerations*

In the UK, a higher frequency of boys than girls has been noted among children with GHD treated with rhGH (56), an observation that is consistent globally (57, 58). Boys are also over-represented among hospital referrals for short stature (59, 60). Thus, an awareness of potential gender biases is important for the adequate care of girls with short stature.

Several studies have evaluated the effects of socioeconomic status on adherence to GH therapy in children (61-63). In a literature review, key factors identified in relation to poor adherence to GH therapy were psychological/emotional problems, socioeconomic/ everyday problems, and issues with technical handling of the drug delivery device. The authors emphasised the need for healthcare professionals to be sensitive to socioeconomic factors that can affect adherence, including poverty, low levels of education, unemployment, unstable living conditions, transport costs, and poor social support networks (63).

As poor adherence to GH treatment is associated with poorer clinical outcomes compared with compliant patients (45-47), disadvantaged children are at risk of poorer health outcomes than those living in more favourable socioeconomic circumstances.

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

B.2.1 *Clinical outcomes and measures*

The single technology appraisal (STA) of once-weekly somatrogon (Ngenla®) (TA863) did not require a cost-effectiveness analysis, and therefore outcomes from TA188 only are included in Table 3.

The key clinical outcomes used in the cost-effectiveness analysis in the previous NICE multiple technology appraisal (MTA) (TA188) are summarised in Table 3; this appraisal assessed the clinical and cost-effectiveness of seven preparations of once-daily rhGH (somatropin) for the treatment of growth failure in children (May 2010, last reviewed June 2022). TA188 recommends somatropin (available as Genotropin®, Humatrope®, Norditropin®, NutropinAq®, Omnitrope®, Saizen® and Zomacton®) for the treatment of children with growth failure in the NHS in England.

Similar to the somatrogon appraisal (TA863), the current submission proposes no considerable shift in the measurement of clinical outcomes; therefore, no shift is expected from the previous conclusions drawn by the committee as part of TA188 or TA863, in terms of either benefit or uncertainties.

Table 3: Clinical outcomes and measures appraised in published NICE guidance for the comparator(s)

NICE guidance	Outcome	Measurement scale	Used in cost-effectiveness model?	Impact on ICER†	Committee's preferred assumptions	Uncertainties
NICE TA188	Final height gained	cm	Yes	NR	The Assessment Group assumed an adherence rate of 85%	Near final height is sometimes reported where it is assumed that final height has been reached using the above criteria, but it is acknowledged that growth may not yet be quite complete
	HSDS	SDS	Yes	Yes. A higher utility per HSDS (0.061 increasing to 0.073) gave a lower ICER (£23,196 decreasing to £21,725)	The manufacturers assumed that a gain in height was associated with improvement in quality of life, which was assessed using the EQ-5D utility scale	Different estimates of cost-effectiveness were largely because of differences in the choice of utility estimates (the utility increment associated with GH treatment ranged from 0.040 to 0.189) and difference in assumptions on effectiveness
	Growth velocity	cm/year	NR	NR	NR	NR
	Growth velocity SDS	cm/year	NR	NR	NR	NR
	Body composition	BMI, lean mass, percent body fat	NR	NR	Changes in body composition associated with somatropin treatment would result in a reduction in the risk of developing diabetes and death related to diabetes	The Assessment Group assumed that children in the treated and untreated groups would have no difference in terms of age, sex, social class, weight and long-standing illness, and would differ only in height

	Cognitive function	NR	NR	NR	NR	NR
	HRQoL	EQ-5D	Yes	NR	The Assessment Group derived the utility estimates for HRQoL for the treated and untreated groups from the differences in height alone	Because of the high uncertainty around the estimates of HRQoL, the Assessment Group assumed no benefit associated with a change in body composition in the base case
	AEs related to treatment	Rate of AEs	NR	NR	The Assessment Group assumed that there would be no reduction in mortality as a result of rhGH treatment. There is a lack of data to assume otherwise.	NR

† The ICERs were most sensitive to the choice of utility values, time horizon, discount rates, treatment duration, doses during the transition phase for those with growth hormone deficiency, the proportion of people achieving final height, and drug price.
Abbreviations: AE, adverse event; BMI, body mass index; EQ-5D, EuroQol-5D; HRQoL, health-related quality of life; HSDS, height standard deviation score; ICER, incremental cost-effectiveness ratio; NICE, National Institute of Health and Care Excellence; NR, not reported; SDS, standard deviation score; TA, technology appraisal; UK, United Kingdom.
Sources: NICE TA188 Section 4 (2); NICE assessment group report (64).

B.2.2 *Resource use assumptions*

The costs and resource use assumptions used in the cost-effectiveness model described in TA188 were based on those used in the HTA report published by Takeda et al (65). Resource use described in TA863 was considered; however, somatrogon was expected to incur similar costs to that of daily GHs and thus only treatment costs were presented. The resources and associated costs included were divided into treatment costs, monitoring costs and adverse event (AE) costs. Resource use was the same across all technologies and the only differentiating factor was the cost of each technology.

In TA188, the annual cost of monitoring was assumed to be two outpatient visits per year, based on clinical opinion; these costs were taken from NHS Reference Costs (66). Treatment costs were calculated using drug unit costs taken from the British National Formulary (67). Unit costs and resource use are shown in Table 4 and Table 5, respectively.

Somapacitan has a comparable efficacy and safety profile to once-daily GH (somatropin) treatment. This submission proposes no changes to the treatment pathway for patients treated with somapacitan over the existing comparators, and thus the only costs considered relevant for the cost-comparison analysis are medicine acquisition costs. In the survey of clinicians in England, all experts agreed that resource use would be similar for somapacitan and once-daily GH therapies (29).

Table 4: Unit costs used in the TA188 cost-effectiveness model

Costs component	Cost	Source
Cost per outpatient attendance first contact face to face paediatric endocrinology (HRG code 302F)	£206.28	NHS ref costs 2007/8 (67)
Cost per outpatient attendance subsequent contact face to face paediatric endocrinology (HRG code 302F)	£127.97	NHS ref costs 2007/8 (67)
Specialist community nurse per patient contact (1 hour)	£73	PSSRU 2008 (66)
Community nurse per patient visit (1 hour)	£64	PSSRU 2008 (66)
Blood tests (for full blood count, chemical profile, thyroid and IGF)	£51	PSSRU 2008 (66)
X-Ray-hand (bone age test)	£28.64	NHS ref costs 2006/7 (67)
Pituitary function test (glucagon, insulin stress test) includes 2 hours nurse time	£207.50	SUHT 2008 (68)

Abbreviations: HRG, healthcare resource group; IGF, insulin-like growth factor; NHS, National Health Service; PSSRU, personal social services research unit; SUHT, Southampton university hospital trust; TA, technology appraisal.

Table 5: Administration and monitoring resource use

	GHD
No treatment monitoring	
Outpatient visit	2 per year
Blood test	1 per year
1st year of treatment	
Specialist nursing home visit	1 hour
Community nurse home visits	4 hours
Outpatient visit	2 per year
Blood test	1 per year
Pituitary function test	0.2 per year
GH treatment in subsequent year	
Outpatient visit	2 per year
Blood test	1 per year
Hand x-ray	1 per year
Pituitary function test	0.2 per year
End of treatment	
Outpatient visit	1 per year

Abbreviations: GH, growth hormone; GHD, growth hormone deficiency.
Source: NICE TA188 (2).

B.3. Clinical effectiveness

Across all somapacitan trials, the clinical evidence demonstrates that somapacitan provides comparable efficacy and safety to once-daily GH (somatropin), with the additional benefit of a once-weekly dosing schedule

- The efficacy and safety of somapacitan have been evaluated for the treatment of children with GHD in a pivotal Phase III randomised controlled trial (REAL 4) and a Phase II dose-finding study (REAL 3)
- In REAL 4, somapacitan was statistically non-inferior for all height- and biomarker-related outcomes, compared with somatropin, after 52 weeks of treatment. Height-related outcomes are clinically meaningful disease markers; improvements in these outcomes reduce the clinical burden of GHD and improve HRQoL (19, 69)

Efficacy outcomes: REAL 4 (Phase III)

Main trial phase (up to Week 52)

- For the primary outcome, treatment with somapacitan was statistically non-inferior at increasing HV compared with once-daily somatropin at Week 52 (ETD −0.5 cm/year [95% CI; −1.1, 0.2]). Comparable HV gains were confirmed in sensitivity analyses
- From baseline to Week 52 there were no statistically significant differences between somapacitan and somatropin in height SDS (ETD −0.05 [95% CI; −0.18, 0.08]), HVSDS (ETD −0.78 [95% CI; −1.63, 0.08]), change in bone age (ETD −0.02 [95% CI; −0.06, 0.01]), change in IGF-I SDS (ETD 0.03 [95% CI; −0.30, 0.36]), or change in IGFBP-3 (ETD 0.01 [95% CI; −0.22, 0.23])
- Treatment burden scores, as measured by the GHD-PTB (burden on the parent/ legally authorised representative [LAR]), were significantly improved (lowered) with somapacitan vs somatropin after 52 weeks; ETDs were −5.3 (95% CI; −10.0, −0.7) for the emotional domain, −6.7 (95% CI; −11.6, −1.9) for the interference domain, and −6.0 (95% CI; −10.0, −2.1) for total score. GHD-CTB scores at Week 52, and change from baseline to Week 52 in GHD-CIM scores, were similar between somapacitan and somatropin
- Mean adherence according to diary[d] was higher with somapacitan (95.8%) vs somatropin (88.3%) to Week 52
- Somapacitan and somatropin devices were both evaluated as easy or very easy to use by 96% of patients (using the G-DAT questionnaire)

Extension phase (Weeks 52–104)

- The continued efficacy of somapacitan was demonstrated in the REAL 4 extension, with increases in HV sustained to Week 104 in both the somatropin/ somapacitan and somapacitan/somapacitan groups

[d] Number of reported dosings divided by number of planned dosings, multiplied by 100.

Efficacy outcomes: REAL 3 (Phase II)

Main trial and safety extension phases (up to Week 52 and Week 156)

- For the primary outcome, a dose-response relationship with somapacitan was observed after 26 weeks. There was no statistically significant difference in HV between somapacitan 0.16 or 0.08 mg/kg/week compared with somatropin at Week 26
- A dose response relationship was observed in the somapacitan treatment arms after 52 weeks. Somapacitan 0.16 mg/kg/week significantly increased HV after 52 weeks of treatment vs somatropin (ETD 1.8 [95% CI; 0.5, 3.1])
- The continued efficacy of somapacitan was demonstrated in the REAL 3 safety extension (to Week 156) (see Appendix J)

Long-term safety extension (up to Week 208) (see Appendix J)

- The continued efficacy of somapacitan was confirmed**.** Treatment-naïve patients that switched from once-daily to once-weekly therapy experienced improvements in height related endpoints and treatment burden measures

Safety outcomes

- Somapacitan was well-tolerated in the REAL 4 and REAL 3 trials. Rates of injection site reaction AEs were low in the somapacitan and somatropin treatment groups. No neutralising antibodies were detected, no treatment discontinuations were recorded, and no deaths occurred
- In the REAL 3 long-term safety extension (results up to Week 208, see Appendix J), no new safety issues were identified. No issues were identified in patients switching from once-daily somatropin to once-weekly somapacitan

Indirect analyses indicate that somapacitan provides equivalent efficacy to the only other once-weekly GH currently recommended by NICE (somatrogon)

- A pairwise ITC was conducted to evaluate somapacitan vs other long-acting GH therapies in children, in the absence of head-to-head studies. Four trials were included in the base case network (REAL 4, REAL 3, Opko II and Opko III)
- Across efficacy outcomes (up to 52 weeks), the analyses show no statistically significant differences between somapacitan and somatrogon for annualised HV, HVSDS and height SDS
- Across safety outcomes, analyses showed that somapacitan and somatrogon were well-tolerated, with comparable safety to somatropin. Lower rates of injection site reactions were observed with somapacitan compared with somatrogon

B.3.1 *Identification and selection of relevant studies*

A systematic literature review (SLR) was conducted to identify clinical evidence regarding the efficacy and safety of long-acting GH (LAGH) for the treatment of paediatric GHD (70). The search strategies used in the SLR were designed to identify studies of all LAGHs for the treatment of GHD, to inform a number of workstreams relating to somapacitan. However, only studies of somapacitan (the technology being appraised) and somatrogon (the only LAGH currently approved by NICE [TA863]) are of relevance to the current submission.

The SLR study question was specified using the PICOS framework (Population, Intervention, Comparator, Outcome, and Study type) to ensure that potentially relevant studies were selected in a systematic manner with a minimal risk of introducing bias, in accordance with guidance published by the Centre for Reviews and Dissemination and the Cochrane review. Trials using LAGH that only included children with GHD (i.e., no other growth disorders), were included in the SLR. Please see Appendix D for full details of the process and methods used to identify and select relevant clinical evidence.

The SLR identified one Phase III trial (REAL 4), and one Phase II dose-finding trial (REAL 3) of somapacitan in the population of interest to this submission. Both trials compared somapacitan with somatropin (Norditropin®).

B.3.2 *List of relevant clinical effectiveness evidence*

The relevant studies identified in the SLR are listed in Table 6, with more detailed trial information provided in Table 7.

The main trial phase of REAL 4 has been completed and is presented in the submission. Available results from an ongoing safety extension to REAL 4 are also presented (up to Week 104).

Efficacy data for the main phase and first extension phase of REAL 3 are presented (up to Week 52). REAL 3 safety results are presented up to Week 156 (safety extension). Available results from the ongoing long-term safety extension to REAL 3 (up to Week 208), which includes patients who switched from once-daily somatropin to once-weekly somapacitan, are presented in Appendix J.

See Section B.3.3.1 for information on the design of REAL 4 and REAL 3.

Table 6: List of relevant clinical evidence

Trial no.	Population	Intervention	Comparator	Primary study ref(s)	Refs identified but not used further	Is study excluded from further discussion? If yes state rationale
REAL 4	Paediatric patients with GHD • Boys: ≥2.5–<11.0 years at screening • Girls: ≥2.5–<10.0 years at screening	• Somapacitan 0.16 mg/kg/week, (n=132)	• Somatropin (Norditropin®) 0.034 mg/kg/day, (n=68)	• CSR (up to Week 52) (71) • CSR (up to Week 104) (72) • Miller et al, 2022 (73)	N/A	No (pivotal Phase III study)
REAL 3	Paediatric patients with GHD • Boys: ≥2.5–≤10.0 years at screening • Girls: ≥2.5–≤9.0 years at screening)	• Somapacitan 0.16 mg/kg/week (n=14) • Somapacitan 0.08 mg/kg/week (n=15) • Somapacitan 0.04 mg/kg/week (n=16)	• Somatropin (Norditropin®) 0.034 mg/kg/day (n=14)	• CSR (74) • Sävendahl et al, 2020 (75) • Sävendahl et al, 2022 (76) • Sävendahl et al, 2023 (77)	N/A	No

Abbreviations: CSR, clinical study report; GHD, growth hormone deficiency; N/A, not applicable.

Table 7: Clinical effectiveness evidence

Study	REAL 4	REAL 3
Study design	Phase III, multicentre, multinational, randomised, open-label, active-controlled trial (52-week main trial period)	Phase II, multicentre, multinational, randomised, double-blinded with regard to the different dose levels of somapacitan, dose-finding trial (26-week main trial period)
Population	Children with GHD • Boys: ≥2.5–<11.0 years at screening • Girls: ≥2.5–<10.0 years at screening	Children with GHD • Boys: ≥2.5–≤10.0 years at screening • Girls: ≥2.5–≤9.0 years at screening
Intervention(s)	Somapacitan (Sogroya®)	Somapacitan (Sogroya®)
Comparator(s)	Somatropin (Norditropin®)	Somatropin (Norditropin®)
Indicate if study supports application for marketing authorisation	Yes	Yes

Reported outcomes specified in the decision problem	• Annual HV
	• Height SDS (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
		• Changes from baseline to Week 26 in:
		  ○ HV
		  ○ Height SDS
		  ○ HVSDS
		  ○ IGF-I SDS
		  ○ IGFBP-3 SDS
		• Bone age progression vs chronological age
		• Serum somapacitan concentrations and changes throughout the trial
		• Adverse events
		• Health-related quality of life

All other reported outcomes	• Change from baseline to Week 52 and Week 104 in HVSDS
	• IGF-I SDS
	• IGFBP-3 SDS
	• Injection pain and device complications
	• Treatment adherence
		• Changes from baseline and Week 26 to Week 52, Week 156, and week 208 in:
		  ○ HV
		  ○ Height SDS
		  ○ HVSDS
		  ○ IGF-I SDS
		  ○ IGFBP-3 SDS
		  ○ Bone age progression vs chronological age serum
		• Scores of the following child reported outcome (PRO) questionnaires were used to investigate the impact of somapacitan relative to somatropin

Study	REAL 4	REAL 3
		on well-being, psychosocial functioning and treatment satisfaction in GH treatment naïve pre-pubertal children with GHD: ○ Changes in emotional well-being score, physical health score, social well-being score and total score from baseline to Week 26, Week 52, Week 156, and Week 208 in GHD-CIM ○ Total score of GHD-CTB at Week 26, Week 52, Week 156, and Week 208 ○ Total score of GHD-PTB at Week 26, Week 52, Week 156, and Week 208 • Evaluation of safety for up to 364 weeks of treatment including incidence of adverse events, incidence of injection site reactions, and occurrence of anti-somapacitan and anti-hGH antibodies

Abbreviations: GHD, growth hormone deficiency; GHD-CIM, growth hormone deficiency–child impact measure; GHD-CTB, growth hormone deficiency child treatment burden; GHD-PTB, growth hormone deficiency parent treatment burden; HV, height velocity; HVSDS, height velocity standard deviation score; IGF-I, insulin-like growth factor-1; IGF-I SDS, insulin-like growth factor standard deviation score; IGFBP-3, insulin-like growth factor binding protein–3; PRO, patient reported outcomes; SDS, standard deviation score.

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

B.3.3.1 *Comparative summary of RCT methodology*

The methodology of the pivotal Phase III REAL 4 and Phase II REAL 3 trials is summarised below.

Table 8: Comparative summary of trial methodology

Trial number	REAL 4 (NCT03811535)	REAL 3 (NCT02616562)
Trial design	REAL 4 is a Phase III, multicentre, multinational, randomised, open-labelled trial. • Patients were randomized 2:1 to receive once-weekly somapacitan or once-daily somatropin for 52 weeks during the main trial period • This was followed by an ongoing 3-year safety extension (Weeks 52–208) in which all subjects are receiving once-weekly somapacitan (results for Weeks 52–104 are currently available) The total trial duration to the end of the safety extension is 4 years.	REAL 3 is a Phase II, randomised, multinational, multiple dose, dose-finding, double-blinded,† parallel group trial, consisting of: • 26-week main trial period and 26-week extension period (to Week 52), in which patients were randomised 1:1:1:1 to receive once-weekly somapacitan (0.16, 0.08 or 0.04 mg/kg/week) or once-daily somatropin • 2-year safety extension (Weeks 52–156) in which: ○ all subjects initially randomised to double-blinded somapacitan were allocated to open-label somapacitan (0.16 mg/kg/week) ○ subjects randomised to somatropin continued with their somatropin treatment • 4-year long-term safety extension (Weeks 156–364), which included three patient cohorts (results for Weeks 156–208 are currently available): ○ Cohort I: All subjects from the preceding trial were treated with once-weekly somapacitan 0.16 mg/kg/week (subjects previously randomised to somatropin were switched to somapacitan) ○ Cohort II and Cohort III: Two additional age groups were enrolled and assigned to once-weekly somapacitan 0.16 mg/kg/week (see eligibility criteria below for details) • 30-day follow-up period The total trial duration to the end of the long-term safety extension is 7 years.

Eligibility criteria	**Key eligibility criteria** Prepubertal patients (boys: ≥2.5–<11.0 years at screening, Testis volume <4 mL; girls: ≥2.5–<10.0 years at screening, Tanner stage 1 for breast development [no palpable glandular breast tissue]) with a confirmed diagnosis of GHD determined by two different GH stimulation tests, impaired height, impaired height velocity, and IGF-I < –1.0 below SDS compared with age and gender normalised range, and no prior exposure to GH therapy. **Exclusion criteria** • Known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth • Inflammatory disease requiring corticosteroid treatment • Children requiring inhaled glucocorticoid therapy • Diagnosis of attention deficit hyperactivity disorder • Concomitant administration of other treatments that may affect growth (e.g. methylphenidate) • History or presence of malignancy or intercranial tumour	***Main and safety extension phase (up to Week 156)*** **Key eligibility criteria** All prepubertal patients (boys: Tanner stage 1 for pubic hair and testis volume less than 4 mL, age ≥2.5–≤10.0 years at screening; girls: Tanner stage 1 for breast development (no palpable glandular breast tissue) and pubic hair, age ≥2.5–≤9.0 years at screening) with a confirmed diagnosis of GHD, have impaired height of >2.0 SD below mean height for age, annualised height velocity below the 25th percentile for chronological age, and no prior exposure to GH therapy. **Exclusion criteria** • Any clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing/length measurements (e.g. chromosomal aneuploidy, congenital abnormalities, and spinal abnormalities) • Children born SGA • Concomitant administration of treatments that have an effect on growth (e.g. methylphenidate) • History or presence of malignancy or intercranial tumour ***Long-term safety extension phase (up to Week 208)*** **Key eligibility criteria** • Cohort I inclusion criteria were as for the main trial phase • Cohort II inclusion criteria: Patients aged (<2.5 years) and a minimum weight of 5 kg at screening with a confirmed diagnosis of GHD. For GH treatment-naïve children: No prior exposure to GH therapy and/or IGF-I treatment and IGF-I SDS <–1.0 at screening, compared with age and sex normalised range • Cohort III inclusion criteria: Pubertal patients (boys: >10 years and ≤17 years at screening; girls: >9 years and ≤17 years at screening) with a confirmed diagnosis of GHD. For GH-treatment-naïve patients, diagnosis confirmed 12 months prior to screening by two stimulation tests. For non-treatment-naïve patients diagnosis confirmed according to local practice. For GH treatment

		naïve patients, no prior exposure to GH therapy or IGF-I treatment. Open epiphyses, defined as bone age <14 years for females and bone age <16 years for males **Exclusion criteria** Exclusion criteria in the long-term safety extension for cohorts I, II and III were the same as for the main trial period.
Settings and locations where the data were collected	86 sites in 20 countries (Austria, Canada, France, Germany, India, Israel, Italy, Japan, Korea, Latvia, Poland, Russia, Serbia, Slovenia, Spain, Switzerland, Thailand, Ukraine, UK and US)	29 sites in 11 countries (Austria, Brazil, Germany, India, Israel, Japan, Slovenia, Sweden, Turkey, Ukraine and US)
Trial drugs	**Intervention: Somapacitan** • 0.16 mg/kg/week, (n=132) **Comparator: Somatropin** • 0.034 mg/kg/day, (n=68)	**Intervention: Somapacitan** • 0.16 mg/kg/week, (n=14) • 0.08 mg/kg/week, (n=15) • 0.04 mg/kg/week, (n=16) **Comparator: Somatropin** • 0.034 mg/kg/day, (n=14)
Permitted and disallowed concomitant medication	Concomitant medications used at baseline included: • Thyroid hormones • Vitamin D and analogues • Piperazine derivatives • Calcium, combinations with vitamin D, and other drugs • Leukotriene receptor antagonists • Other antihistamines for systemic use • Selective beta-2-adrenoreceptor agonists • Melatonin receptor agonists • Multivitamins with minerals • Anilides • Calcium	Concomitant medications used at baseline included: • Thyroid hormones • Vitamin D and analogues • Leukotriene receptor antagonists • Bacterial and viral vaccines • Corticosteroids, plain • H2-receptor antagonists • Other antihistamines for systemic use • Second-generation cephalosporins • Multiple combinations of the above Excluded medications included any that may affect growth rate.

	• Iron preparations • Multivitamins, other combinations • Osmotically acting laxatives • Other lipid modifying agents • alimentary tract and metabolism products • Corticosteroids, including potent variations • Enzyme preparations • Epinephrine • Heparin group • Heparins or heparinoids for topical use • Iron trivalent, oral preparations • Multivitamins, plain • Other antiepileptics • Other emollients and protectives • Propionic acid derivatives • Tonics • Vitamins, other combinations • Multiple combinations of the above Excluded medications included any that may affect growth rate	
Primary outcomes (including scoring methods and timings of assessments)	HV at Week 52, measured in cm/year	Change in HV during the first 26 weeks of treatment, measured in cm/year

Other outcomes used in the economic model/specified in the scope	• Change from screening to Week 52 in bone age (years)
	• Change from baseline to Week 52 in:
	  ○ Height SDS (−10 to +10)
	  ○ HVSDS (−10 to +10)
	• Pharmacodynamic changes from baseline to Weeks 52, 104, 156, and 208 in:
	  ○ IGF-I SDS (−10 to +10)
	  ○ IGFBP-3 SDS (−10 to +10)
	• Adverse effects of treatment
	• HRQoL
		• Changes from baseline to Week 26 in the following variables:
		  ○ Height SDS
		  ○ HVSDS
		  ○ IGF-I SDS
		  ○ IGFBP-3 SDS
		• Changes from baseline and Week 26 to Week 52 in:
		  ○ Height SDS
		  ○ HVSDS
		  ○ IGF-I SDS
		  ○ IGFBP-3 SDS
		• HV (cm/year) change from Week 0 to Week 52
		• Bone age progression vs chronological age
		• Serum somapacitan concentrations and changes throughout the trial
		• HRQoL
		• Adverse events

Pre-planned subgroups	N/A	N/A

† The somapacitan dose was double-blinded.
Abbreviations: GH, growth hormone; GHD, growth hormone deficiency; GHD-CIM, growth hormone deficiency–child impact measure; GHD-CTB, growth hormone deficiency child treatment burden; GHD-PTB, growth hormone deficiency parent treatment burden; HSDS, height standard deviation score; HV, height velocity; HVSDS, height velocity standard deviation score; IGF-I, insulin-like growth factor-1; IGF-I SDS, insulin-like growth factor standard deviation score; IGFBP-3, insulin-like growth factor binding protein–3; N/A, not applicable; PRO, patient reported outcomes; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age; UK, United Kingdom; US, United States.

B.3.3.2 *Patient disposition*

B.3.3.2.1 REAL 4

In total, 348 children were screened and 200 children with GHD were randomised and exposed to treatment in the main trial period (up to Week 52). Of these, 132 children received somapacitan and 68 received somatropin. All 200 children completed the 52-week main trial period, and 199 (99.5%) children completed the treatment period. One child discontinued somapacitan treatment prematurely due to a violation of eligibility criteria.

A total of 199 subjects were exposed to treatment in the safety extension (following Week 52). Four children in the somapacitan/somapacitan group and 1 subject in the somatropin/somapacitan group discontinued trial product in the safety extension period (from Week 52 to Week 104). None of the discontinuations were due to AEs. All discontinued subjects in the extension period were withdrawn from the trial.

B.3.3.2.2 REAL 3

Main trial and safety extension period (up to Week 52 and Week 156)

In total, 59 children with GHD were randomised and exposed to treatment. Of these, 56 (94.9%) children completed the 26-week main trial period and the 26-week extension trial period. Subsequently, 52 (88.1%) children completed three years of the trial (up to 156 weeks), of which 50 (84.7%) children completed the long-term safety extension without premature discontinuation of randomised treatment.

Eight children discontinued trial product before the end of the 2-year safety extension (156-week total trial period): six subjects in the somapacitan treatment arms (four in the 0.04/0.16 mg/kg/week group, one in the 0.08/0.16 mg/kg/week group, and one in the 0.16/0.16mg/kg/week group) and two in the somatropin treatment arm. The two children who discontinued in the somatropin arm did so due to AEs (nephrotic syndrome and drug hypersensitivity). In the somapacitan arms, two were withdrawn from treatment by a parent/LAR, and four discontinued treatment due to protocol violations.

For patient disposition in the long-term safety extension, see Appendix J.

B.3.3.3 *Patient demographics and baseline characteristics*

B.3.3.3.1 REAL 4

Overall, baseline demographics were similar between the somapacitan and somatropin groups, except for baseline height, body weight, GH peak, HV, height velocity standard deviation score (HVSDS), height SDS and IGF-I SDS, which were slightly lower in the somatropin group compared with the somapacitan group. Patient demographics at baseline and baseline disease-specific characteristics are summarised in Table 9 and Table 10, respectively.

Table 9: Baseline demographics of patients in REAL 4 – categorical variables

Trial number (acronym) Baseline characteristic	Somapacitan	Somatropin
REAL 4 (NCT03811535) (n=200)	n=132	n=68
Age group, n (%)		
<6 years	64 (48.5)	33 (48.5)
≥6 years	68 (51.5)	35 (51.5)
Sex, n (%)		
Male	99 (75.0)	50 (73.5)
Female	33 (25.0)	18 (26.5)
Race		
White	78 (59.1)	36 (52.9)
Asian	46 (34.8)	28 (41.2)
Black or African American	0 (0)	1 (1.5)
Other	1 (0.8)	0 (0)
Not reported	7 (5.3)	3 (4.4)
Ethnicity, n (%)		
Hispanic or Latino	4 (3.0)	1 (1.5)
Not Hispanic or Latino	119 (90.2)	63 (92.6)
Not reported	9 (6.8)	4 (5.9)
GHD cause, n (%)		
Idiopathic	115 (87.1)	61 (89.7)
Organic	17 (12.9)	7 (10.3)

Abbreviations: GHD, growth hormone deficiency.

Table 10: Baseline disease-specific characteristics of participants in REAL 4 – continuous variables

Trial number (acronym) Baseline characteristic	Somapacitan	Somatropin
REAL 4 (NCT03811535) (n=200)	n=132	n=68
Age, years, mean (SD)	6.4 (2.2)	6.4 (2.4)
Body weight, kg, mean (SD)	16.7 (4.60)	16.0 (4.95)
BMI, kg/m^2, mean (SD)	15.7 (1.59)	15.6 (1.38)
GH peak, ug/L, mean (SD)	4.93 (2.50)	4.10 (2.77)
Mean HV (cm/year)	4.3 (1.4)	4.1 (1.4)
Mean HVSDS	−2.35 (1.51)	−2.52 (1.55)
Mean height (cm)	102.3 (12.5)	100.2 (15.0)
Mean height SDS	−2.99 (1.02)	−3.47 (1.52)
Mean IGF-I SDS	−2.03 (0.97)	−2.33 (1.03)

Abbreviations: BMI, body mass index; GHD, growth hormone deficiency; HV, height velocity; IGF-I, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score.

B.3.3.3.2 REAL 3

In the main trial period up to Week 26 (and up to Week 156 in the extension phase), the four treatment arms were generally well matched and there were no clinically relevant differences between treatment groups. Baseline characteristics including HV, HVSDS and IGF-I SDS were similar across treatment arms. Patient demographics at baseline and baseline disease-specific characteristics are summarised in Table 11 and Table 12, respectively.

For patient demographics and baseline characteristics in the long-term safety extension, see Appendix J.

Table 11: Baseline demographics of patients in REAL 3 – categorical variables

Trial number (acronym) Baseline characteristic	Somapacitan (0.04 mg/kg/week)	Somapacitan (0.08 mg/kg/week)	Somapacitan (0.16 mg/kg/week)	Somapacitan pooled	Somatropin (0.034 mg/kg/day)
REAL 3 (NCT02616562) (N=57)	n=14	n=15	n=14	n=43	n=14
Age group, n (%)					
<6 years	7 (50.0)	9 (60.0)	8 (57.1)	24 (55.8)	7 (50.0)
≥6 years	7 (50.0)	6 (40.0)	6 (42.9)	19 (44.2)	7 (50.0)
Sex, n (%)					
Male	7 (50.0)	10 (66.7)	8 (57.1)	25 (58.1)	9 (64.3)
Female	7 (50.0)	5 (33.3)	6 (42.9)	18 (41.9)	5 (35.7)
Ethnicity, n (%)					
Hispanic or Latino	1 (7.1)	0 (0)	0 (0)	1 (2.3)	0 (0)
Not Hispanic or Latino	13 (92.9)	15 (100.0)	14 (100.0)	42 (97.7)	14 (100.0)
Race					
White	6 (42.9)	9 (60.0)	6 (43.9)	21 (48.8)	7 (50.0)
Asian	8 (57.1)	6 (40.0)	8 (57.1)	22 (51.2)	6 (42.9)
Black or African American	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)
GHD cause, n (%)					
Idiopathic	14 (100.0)	14 (93.3)	13 (92.9)	41 (95.3)	12 (85.7)
Organic	0 (0)	1 (6.7)	1 (7.1)	2 (4.7)	2 (14.3)

Abbreviations: GHD, growth hormone deficiency.

Table 12: Baseline disease-specific characteristics of participants in REAL 3 – continuous variables

Trial number (acronym) Baseline characteristic	Somapacitan (0.04 mg/kg/week)	Somapacitan (0.08 mg/kg/week)	Somapacitan (0.16 mg/kg/week)	Somapacitan pooled	Somatropin (0.034 mg/kg/day)
REAL 3 (NCT02616562) (N=57)	n=14	n=15	n=14	n=43	n=14
Age, years, mean (SD)	5.8 (1.8)	5.8 (1.8)	6.1 (2.3)	5.9 (2.0)	5.9 (2.0)
Height, cm, mean (SD)	95.4 (14.0)	97.2 (11.3)	97.7 (16.4)	96.8 (13.7)	98.3 (13.8)
Body weight, kg, mean (SD)	14.2 (4.22)	14.0 (3.54)	14.9 (5.23)	14.4 (4.3)	15.5 (5.03)
BMI, kg/m^2, mean (SD)	15.3 (1.1)	14.6 (1.1)	15.1 (1.2)	15.0 (1.1)	15.6 (1.4)
GH peak, ug/L, mean (SD)	2.9 (2.2)	3.6 (2.1)	4.1 (2.4)	3.5 (2.2)	4.0 (2.0)
Mean (SD) HV (cm/year)†	4.0 (1.8)	4.8 (1.4)	3.8 (1.5)	4.2 (1.6)	3.5 (1.6)
Mean (SD) HVSDS	−2.9 (1.9)	−1.8 (1.7)	−2.9 (1.8)	−2.5 (1.8)	−3.1 (2.1)
Mean (SD) height SDS	−4.1 (1.9)	−3.5 (1.5)	−3.8 (2.0)	−3.8 (1.8)	−3.4 (1.1)
Mean (SD) IGF-I SDS	−2.5 (1.0)	−2.5 (0.8)	−2.0 (1.0)	−2.4 (0.9)	−2.1 (0.7)

Abbreviations: BMI, body mass index; GH, growth hormone; GHD, growth hormone deficiency; HV, height velocity; IGF-I, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score.

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

B.3.4.1 *Populations analysed*

B.3.4.1.1 REAL 4

- The full analysis set (FAS) included all randomised children, analysed as randomised. The FAS was used for the evaluation of efficacy endpoints
- The per protocol (PP) analysis set included children from the FAS who did not violate any inclusion/exclusion criteria and had used the randomised treatment for at least 47 weeks (for children receiving somapacitan) or 329 days (for children receiving somatropin) corresponding to 90% of the planned exposure, during the main trial period, analysed as treated. The PP set was used to confirm the robustness of the primary statistical analysis
- The safety analysis set (SAS) included all randomised children that received at least one dose of treatment, analysed as treated. The SAS was used for the evaluation of safety endpoints

B.3.4.1.2 REAL 3

- The FAS included all randomised children, analysed as randomised; the FAS was used for the evaluation of efficacy endpoints. Only in exceptional cases may children be excluded from the FAS. Children were analysed “as treated”
- The PP analysis set included children from the FAS who did not violate any inclusion/exclusion criteria and had used the randomised treatment for at least 22 weeks (for children receiving somapacitan) or 154 days (for children receiving somatropin) during the main trial period. Children were analysed “as treated”; The PP analysis set is only relevant for the analysis of the primary endpoint in the main trial period
- The SAS included all randomised children that received at least one dose of treatment, children were analysed “as treated”. The SAS was used for the evaluation of safety endpoints

B.3.4.2 *Estimands*

B.3.4.2.1 REAL 4

Distinct estimand strategies were used based on recommendations by the Food and Drug Administration (FDA), Pharmaceuticals and Medical Devices Agency (PMDA) and European Medicines Agency (EMA):

- The treatment policy strategy (per FDA/PMDA recommendations) used the calculated between-treatment difference in mean annualised HV at Week 52 for all randomised children, regardless of treatment adherence or initiation of ancillary therapy. The estimand assessed the expected benefit a future paediatric population with GHD can achieve when prescribed somapacitan compared with somatropin. By not placing restrictions on treatment adherence, this estimand aimed to achieve a difference closest to that expected in clinical practice

- The hypothetical strategy (per EMA recommendations) (ancillary therapy not available) used the between-treatment difference in mean annualised HV at Week 52 when ancillary therapy had not been available prior to Week 52 (i.e. assuming no initiation of ancillary therapy). This estimand is expected to minimise potential confounding from ancillary therapy use (e.g. other GH products) when assessing the treatment effect on longitudinal growth. The use of ancillary therapy may lead to attenuation or exaggeration of the treatment effect of interest. As a result, the hypothetical strategy aims to reflect the treatment difference attributable to the initially randomised treatments

Results for the primary endpoint, HV, were analysed for both estimands. The treatment policy strategy estimand was calculated using the in-trial observation period; the hypothetical strategy estimand was calculated using the on-treatment observation period. IGF-I SDS and IGFBP-3 were analysed using both treatment periods. All remaining endpoints were analysed using the in-trial observation period only.

B.3.4.3 *Statistical information*

Table 13: Summary of statistical analyses in the RCTs

Trial name	REAL 4	REAL 3
Hypothesis objective	To compare the effect of somapacitan vs somatropin on longitudinal growth in children with GHD.	To evaluate the efficacy of multiple dose regimens of once-weekly somapacitan after 26 weeks, in GH-treatment-naïve pre-pubertal children with GHD compared with once-daily somatropin.
Statistical analysis	**Primary endpoint efficacy analysis:** Non-inferiority of somapacitan was confirmed when the lower boundary of the two-sided 95% CI was above −1.8 cm/year or equivalent when the p-value for the one-sided test of H_0: D ≤−1.8 cm/year vs H_A: D >−1.8 cm/year was < 2.5%, where D was the mean treatment difference (somapacitan − somatropin). If non-inferiority was confirmed, superiority was confirmed if the lower boundary of the two-sided 95% CI was above 0 cm/year. **Sensitivity analysis:** A tipping point analysis was conducted for the primary outcome (and estimands) based on a penalty for imputed values in the somapacitan arm of 1.8 cm/year, giving a power of 87% (adjusted treatment effect: 0.9*0 − 0.05*1.8= −0.09), under the assumption that 5% of children do not have landmark visit data.	**Primary endpoint efficacy analysis:** Annualised HV was analysed used a MMRM, with treatment, age group, sex, region, and sex by age group interaction term as factors and height at baseline as a covariate, all nested within week as a factor. An unstructured covariance matrix was used to describe variability for the repeated measurements for a child. From the MMRM, treatment differences at Week 26 for somapacitan vs somatropin were estimated.
Sample size, power calculation	The sample size calculation was based on the primary estimand. It was expected that children discontinuing randomised treatment would start on	Sample size calculations (cohort I) were based on an SD of 3.1 cm/year for HV at Week 26 and a delta value of −3.8 cm/year (where delta corresponds to the non-inferiority margin in a non-

Trial name	REAL 4	REAL 3
	ancillary treatment when no medical reasons prohibited this. **Treatment policy estimand:** Sample size was determined using a non-inferiority margin of −1.8 cm/year and a one-sided two-group t-test with a significance level of 2.5% for a 2:1 randomisation ratio between somapacitan and somatropin. A conservative SD of 3.5 cm/year for HV at Week 52 was chosen. With a SD of 3.5 cm/year and 90% power for the primary analysis, a sample size of 192 children was calculated. **Hypothetical strategy estimand:** Sample size was determined using the same assumptions as for the treatment policy estimand. For a total of 192 children, the power was 88%.	inferiority trial) and a one-sided significance level of 2.5%. This resulted in 15 children per treatment arm. There was a maximum expected dropout of 7%, resulting in randomisation of 15 children per treatment arm (for 87% power and a 95% CI for the ETD). The addition of cohort II and III was based on a regulatory request from FDA. No formal sample size calculation was performed for these cohorts.
Data management, patient withdrawals	According to the protocol, missing Week 52 values were imputed using a Markov Chain Monte Carlo method. This imputation was carried out for each treatment group separately and 100 copies of the data set were generated (seed=5297). The number of copies was increased if the estimation process did not result in robust estimates. For each complete data set, HV at Week 52 was analysed using an ANCOVA model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height as covariate.	Data were collected via the EDC system. eDiary data were used for capture of subject trial product administration. These data were considered source data and were not transferred to the eCRF but to the vendor ERT and thereafter to Novo Nordisk as data files. Data quality checks were performed using electronic and manual verification methods. Appropriate measures were used to ensure confidentiality of subject data, and database locks were planned during the trial. When a visit was missed, attempts were made to collected information by telephone and children were invited for the next scheduled visit. To ensure children had sufficient trial product until the next scheduled dispensing, the child was required to collect additional dispensing as soon as possible.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; EDC, electronic data capture; eCRF, electronic case report form; EMA, European Medicines Agency; ERT, eReasearch technology; ETD, estimated treatment difference; FDA, Food and Drug Administration; GH, growth hormone; GHD, growth hormone deficiency; HV, height velocity; MMRM, mixed model for repeated measurements; PMDA, Pharmaceuticals and Medical Devices Agency; RCT, randomised controlled trial; SD, standard deviation.

B.3.5 *Critical appraisal of the relevant clinical effectiveness evidence*

Table 14: Quality assessment results for the RCTs

	REAL 4	How the point was addressed in REAL 4	REAL 3	How the point was addressed in REAL 3
Was randomisation carried out appropriately?	Yes	All screened patients received a unique patient number and were centrally randomised using an IWRS and assigned to the next available treatment according to randomisation schedule.	Yes	A trial-specific, web-based randomisation system IWRS was used for screening, screening failure randomisation, stratification, medication arrival, dispensing, treatment discontinuation, completion, code break, drug accountability, documentation of destruction and data change. Each child was assigned a unique 6-digit subject number which remained the same throughout the trial.
Was the concealment of treatment allocation adequate?	N/A	Open-label study. Sponsor staff involved in medical monitoring and interpretation of data were blinded during trial conduct up to unblinding of the randomisation codes.	Yes	The main trial period was double-blinded with regard to different dose levels of once-weekly somapacitan, but open-labelled with regard to daily somatropin as an active control arm.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Demographics were similar in both arms of the trial.	Yes	Demographics were similar in all four arms of the trial.
Were the care providers, participants and outcome assessors blind to treatment allocation?	N/A	Open-label study. The trial was observer blinded with regard to primary endpoint. Investigators did not have access to results for biomarkers, anti-drug antibodies or PK throughout the trial.	Yes	The clinical study group and the investigator remained blinded throughout the trial. The somapacitan safety committee could recommend unblinding of any data for further analysis, and in this case, an independent ad hoc group would be established in order to maintain the blinding of the trial personnel.

	REAL 4	How the point was addressed in REAL 4	REAL 3	How the point was addressed in REAL 3
Were there any unexpected imbalances in drop-outs between groups?	No	One child in the somapacitan group discontinued treatment prematurely due to being included in the trial in violation of inclusion and/or exclusion criteria.	No	A total of 8 children discontinued trial product before the end of the 104-week safety extension trial period (156 weeks): 6 in the somapacitan treatment arms (0.04/0.16 mg/kg/week: 4 children; 0.08/0.16mg/kg/week: 1 child; 0.16/0.16mg/kg/week: 1 child) and 2 in the somatropin treatment arm. Of the 8 children discontinuing trial product, 2 discontinued treatment due to AEs (nephrotic syndrome and drug hypersensitivity), 2 were withdrawn from treatment by parent/LAR and 4 discontinued treatment due to protocol violations. Six of the 8 children discontinuing trial product also withdrew from trial. The remaining 2 children attended all trial visits and thus completed the trial period
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were related to the clinical goals of GH therapy.	No	All outcomes were related to the clinical goals of GH therapy.
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	A FAS included all randomised children that received at least one dose of randomised treatment. Only in exceptional cases may children be excluded from the FAS. Children were analysed “as treated”. According to the protocol, missing Week 52 values were planned to be imputed. Missing Week 52 values were imputed using a Markov Chain Monte Carlo method.	Yes	A FAS included all randomised children that received at least one dose of randomised treatment. Only in exceptional cases may children be excluded from the FAS. Children were analysed “as treated”. When an entire visit was missed and it was not possible to re-schedule the visit in the allowed time window, attempts were made to ensure information was collected by telephone contact. Children were invited for the next scheduled visit according to scheduling

Abbreviations: AE, adverse event; FAS, full analysis set; GH, growth hormone; IWRS, interactive web response system; N/A, not applicable; PK, pharmacokinetics; RCT, randomised controlled trial.

B.3.6 *Clinical effectiveness results of the relevant studies*

B.3.6.1 *REAL 4*

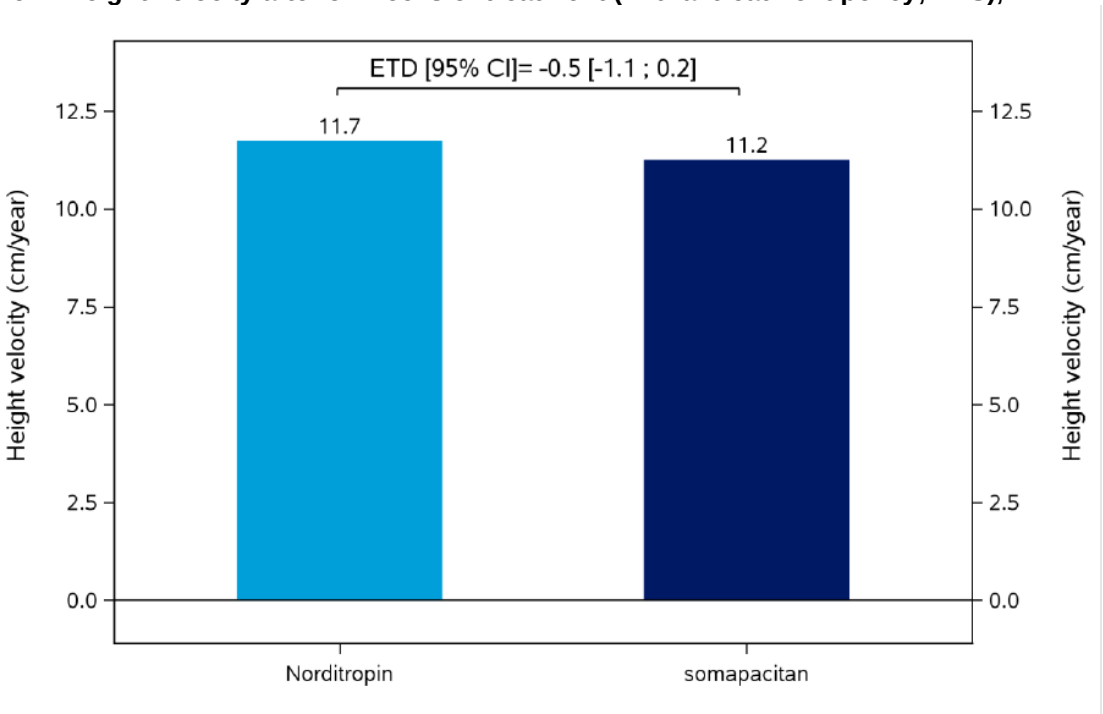
B.3.6.1.1 Primary efficacy outcome

Height velocity at 52 weeks using in-trial treatment policy estimand

The primary endpoint was HV at Week 52, measured in cm/year. There was no statistically significant difference in HV between somapacitan and somatropin after 52 weeks of treatment (ETD −0.5 cm/year [95% CI; −1.1, 0.2]) (Figure 1), demonstrating non-inferiority. Both treatments were equally effective in stimulating HV in treatment-naïve GH-deficient children.

For both treatment groups, the estimated means from in-trial data (11.2 and 11.7 cm/year for somapacitan and somatropin, respectively) were similar to the observed means (SD) (11.2 [2.5] and 11.8 [2.9] cm/year for somapacitan and somatropin, respectively) at 52 weeks.

Figure 1: Height velocity after 52 weeks of treatment (in-trial treatment policy; FAS), REAL 4

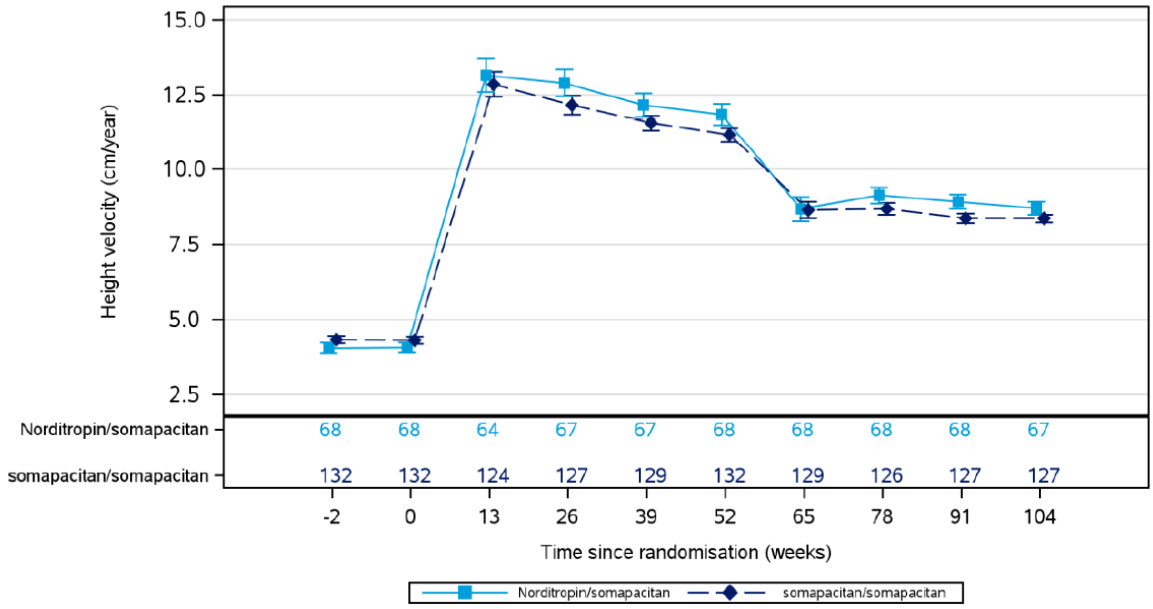


Abbreviations: CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set.
Figure was based on estimated mean.
Height velocity at Week 52 was analysed using an analysis of co-variance model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height as co-variate. There were no missing values at Week 52, so no multiple imputation was done.

Secondary analysis of primary outcome

The observed HV showed an approximate 3-fold increase from Week 0 to Week 13 with mean (SD) values at Week 0 of 4.3 (1.4) and 4.1 (1.4) cm/year and at Week 13 of 12.9 (4.7) and 13.2 (4.4) cm/year for somapacitan and somatropin, respectively. After 52 weeks, these increases were sustained and the observed 52-week primary endpoint values were 11.2 (2.5) cm/year for the somapacitan group and 11.8 (2.9) cm/year for the somatropin group (Figure 2).

Figure 2: Mean HV by visit (on-treatment hypothetical strategy; FAS), REAL 4



Abbreviations: FAS, full analysis set; HV, height velocity.
Error bars: ± standard error (mean)
Observed data.
Height velocity at baseline was based on the pre-screening height measurement used for inclusion criteria 5.
*Estimated mean from statistical analysis.

A sensitivity analysis was performed to account for the interpolation of one child for whom the Week 52 HV measure was delayed by 3 months. The analysis did not change the results or conclusions from the main statistical analysis using on-treatment data and non-inferiority was confirmed (Table 15). The tipping point sensitivity analysis demonstrated that missing the Week 52 value for the one discontinued child did not have any significant effect on the overall results or conclusions.

Table 15: Sensitivity analysis (interpolation of late visit 7) of height velocity after 52 weeks of treatment (on-treatment hypothetical strategy; FAS), REAL 4

	FAS	N	Estimate	95% CI	Non-inferiority confirmed	Superiority	
						Confirmed	p-value
Height velocity (cm/year)							
At Week 52							
Somapacitan	132	132	11.2	-	-	-	-
Somatropin	68	68	11.7	-	-	-	-
Treatment difference at Week 52							
Somapacitan − Somatropin	-	-	−0.5	−1.1, 0.2	Yes	No	NA

Abbreviations: CI, confidence interval; FAS, full analysis set; NA, not applicable.
Height velocity at 13, 26, 39 and 52 weeks was analysed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction terms as factors and baseline height as a covariate, all nested within week as a factor.
The non-inferiority margin was −1.8 cm/year.
For child 302002 the height velocity at Week 52 is based on an interpolation between the observed height at Visit 5 and at Visit 7, the 52 weeks and the age at Week 52.

Height velocity at 52-weeks using the per protocol analysis set

In total, 14 children (10 and 4 from the somapacitan and somatropin groups, respectively) were included in the trial, although they violated an inclusion or exclusion criteria.[e] A PP analysis data set was defined as children not violating any inclusion or exclusion criteria and having used the randomised treatment for at least 47 weeks. No other protocol deviations led to exclusion from the PP analysis set. Supplementary data analysis was performed on the PP data set and the resulting estimates (ETD −0.5 [95% CI; −1.2, 0.2]) were almost identical to the results from the full on-treatment observation period data set and with the same conclusion (non-inferiority of somapacitan relative to somatropin was confirmed; Table 16).

[e] The 14 children who violated an inclusion or exclusion criteria remained on treatment as the protocol deviations were assessed to not incur any safety issues. One child discontinued. For the 13 children remaining on treatment, the violations primarily comprised minor deviations in criteria related to height or BMI or deviations related to children having one or two GH stimulation tests performed more than the maximum of 12 months prior to randomisation.

Table 16: Supplementary analysis of height velocity after 52 weeks of treatment (on-treatment hypothetical strategy; PP analysis set), REAL 4

	FAS	N	Estimate	95% CI	Non-inferiority confirmed	Superiority	
						Confirmed	p-value
Height velocity (cm/year)							
At Week 52							
Somapacitan	122	122	11.2	-	-	-	-
Somatropin	64	64	11.7	-	-	-	-
Treatment difference at Week 52							
Somapacitan − Somatropin	-	-	−0.5	(−1.2, 0.2)	Yes	No	NA

Abbreviations: CI, confidence interval; FAS, full analysis set; NA, not applicable; PP, per protocol.
Height velocity at 13, 26, 39 and 52 weeks was analysed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction terms as factors and baseline height as a covariate, all nested within week as a factor.
The non-inferiority margin was −1.8 cm/year.

Height velocity after 104 weeks of treatment

Increases in HV were sustained up to Week 104 for both treatment groups compared with baseline values (Week 0). The observed mean (SD) 104-week HV was 8.4 (1.5) cm/year for somapacitan/somapacitan and 8.7 (1.8) cm/year for somatropin/somapacitan (Figure **2**). A decrease in HV was observed from Week 52 to Week 65 due to a change in the HV calculation (up to Week 52, the height at Week 0 was used as baseline, while after Week 52, the height at Week 52 was used as baseline).

B.3.6.1.2 Secondary efficacy outcomes

Height velocity standard deviation score (HVSDS)

HVSDS after 52 weeks using the treatment policy estimand

There was no statistically significant difference in change in mean HVSDS between somapacitan and somatropin after 52 weeks (change of 8.05 and 8.82 in the somapacitan and somatropin groups, respectively; ETD −0.78 [95% CI; −1.63, 0.08]).

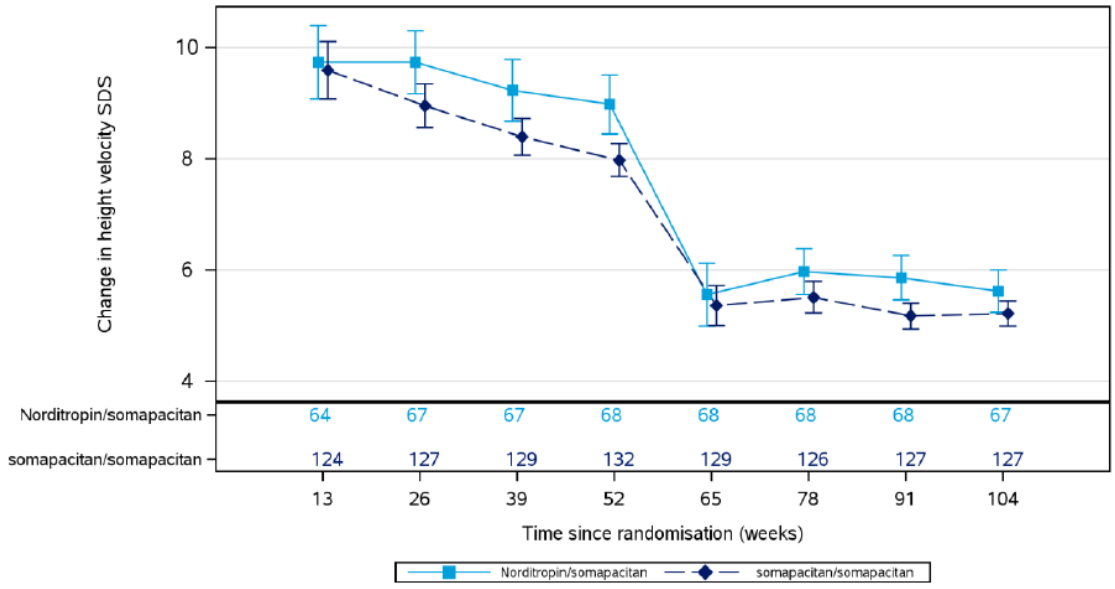
The observed mean (SD) HVSDS values for the two treatment groups using in-trial data increased from Week 0 to Week 13, changing from −2.35 (1.51) to 7.23 (5.40) and from −2.52 (1.55) to 7.31 (4.54) in the somapacitan and somatropin groups, respectively. Overall, these increases were maintained to 52 weeks with values of 5.61 (2.85) for somapacitan and 6.45 (3.51) for somatropin (Figure 3).

HVSDS after 104 weeks of treatment

After 104 weeks of treatment, the increase in HVSDS compared with baseline values was similar in both children treated with somapacitan for the full trial period and in children who switched from somatropin to somapacitan after Week 52 (Figure 3). The observed changes from baseline in 104-week HVSDS for the two treatment groups were 5.21 (2.58) and

5.62 (3.15) for somapacitan/somapacitan and somatropin/somapacitan, respectively. Similar to the change in HV, a minor drop was observed between Week 52 and Week 65 for the HVSDS results due to the change in the selected baseline for the calculations.

Figure 3: Mean change from baseline in HVSDS by visit (on-treatment hypothetical strategy; FAS), REAL 4



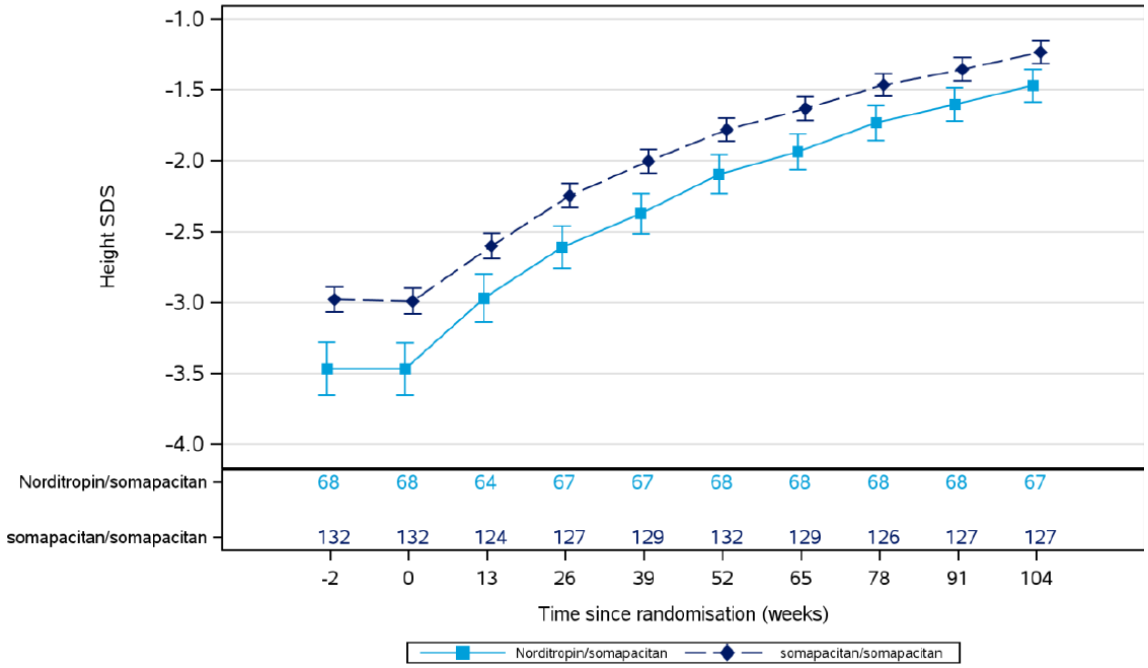
Abbreviations: FAS, full analysis set; HVSDS, height velocity standard deviation score.
Error bars: ± standard error (mean).
Observed data.
Height velocity at baseline was based on the pre-screening height measurement used for inclusion criteria 5.
*Estimated mean from statistical analysis.

Height SDS

There was no statistically significant difference in change in height SDS from baseline to Week 52 between somapacitan and somatropin (ETD −0.05 [95% CI; −0.18, 0.08]) (Figure 4). The observed mean (SD) height SDS values in both treatment groups increased consistently from Week 0 to Week 52, changing from −2.99 (1.02) to −1.78 (0.95) and from −3.47 (1.52) to −2.09 (1.12) for somapacitan and somatropin, respectively (Figure 5). The estimated mean changes from baseline in height SDS of 1.25 and 1.30 were similar to observed mean (SD) changes of 1.21 (0.54) and 1.37 (0.69) for somapacitan and somatropin, respectively, after 52 weeks.

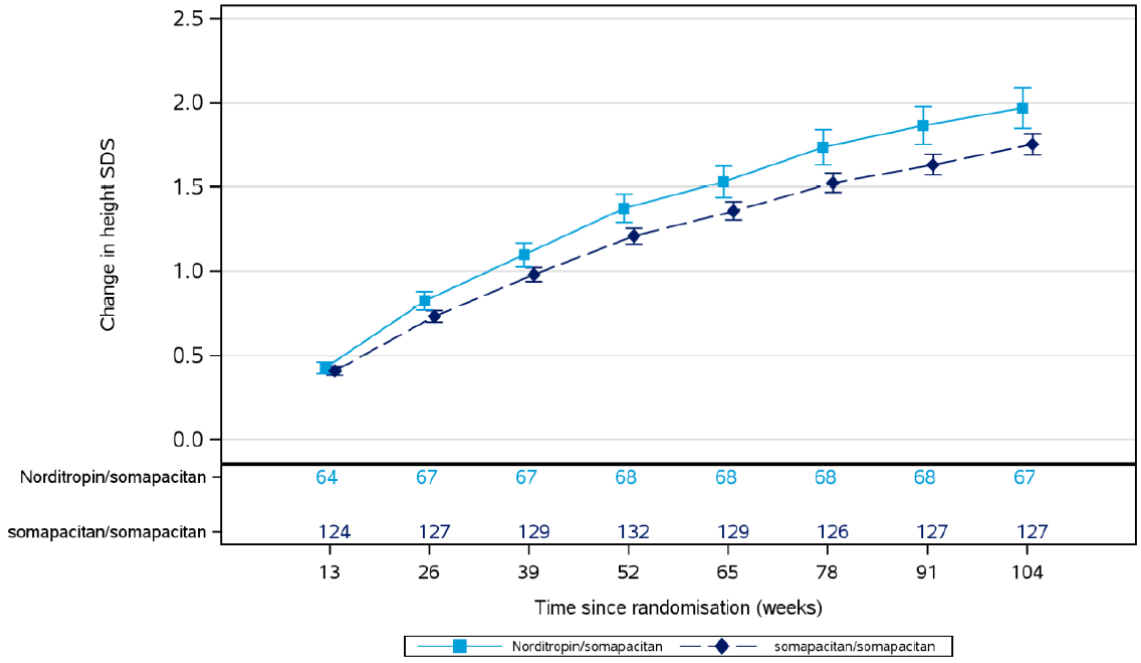
Mean (SD) height SDS increased from Week 52 to Week 104 for both the somapacitan/somapacitan group (−1.78 [0.95] to −1.23 [0.91]) and the somatropin/somapacitan group (−2.09 [1.12] to −1.47 [0.94]) (Figure 4). After 104 weeks of treatment, a similar increase in change from baseline in height SDS was observed in children treated with somapacitan for the full period, as observed in the subjects switching from somatropin to somapacitan at Week 52 (Figure 5). Changes from baseline after 104 weeks were 1.75 (0.72) and 1.97 (0.98) for the somapacitan/somapacitan and somatropin/somapacitan groups, respectively.

Figure 4: Height SDS by visit (in-trial; FAS), REAL 4



Abbreviations: FAS, full analysis set; SDS, standard deviation score.
Error bars: ± standard error (mean), SDS.
Observed data.

Figure 5: Mean change from baseline in height SDS by visit (in-trial; FAS), REAL 4



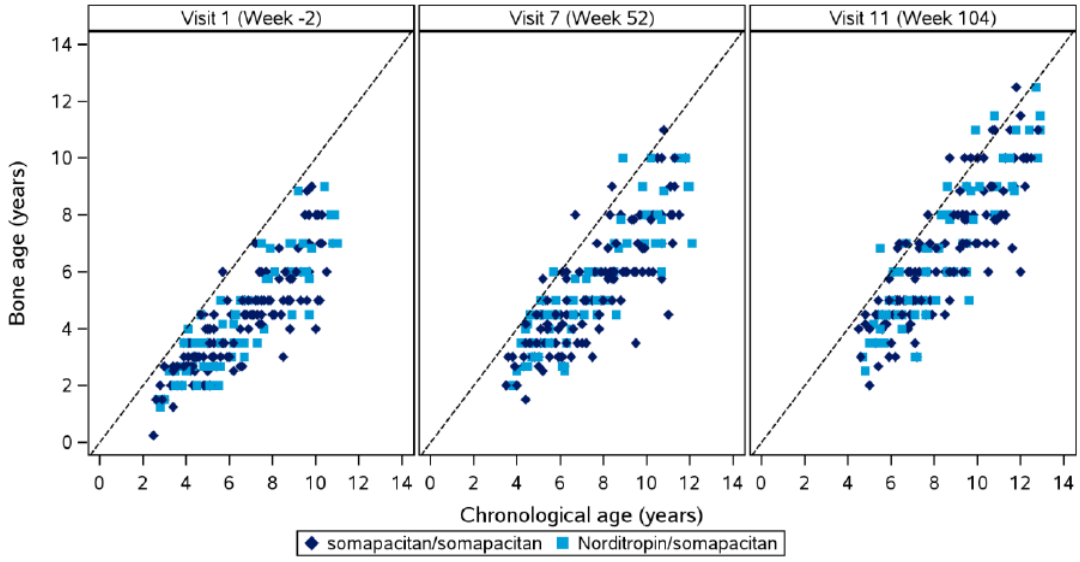
Abbreviations: FAS, full analysis set; SDS, standard deviation score.
Error bars: ± standard error (mean), SDS.
Observed data.

Bone age (years)

The bone age vs chronological age ratio was below one[f] for most children after 52 weeks of treatment (Figure 6). Analysis showed that the difference in change from baseline to 52 weeks in this ratio between somapacitan and somatropin was not statistically significant (change of 0.06 and 0.08, respectively; ETD −0.02 [95% CI; −0.06, 0.01]).

The ratio was below 1 for the majority of the subjects after 104 weeks of treatment. Change from baseline in bone age by visit showed consistent increases in both treatment groups up to Week 104 (Figure 6).

Figure 6: Scatter plot of bone age progression to chronological age by visit (in trial; FAS), REAL 4



Abbreviations: FAS, full analysis set.

IGF-I SDS results using in-trial data

There was no statistically significant difference in change in mean IGF-I SDS levels from baseline to Week 52 between the somapacitan and somatropin groups (change of 2.36 and 2.33, respectively; ETD 0.03 [95% CI; −0.30, 0.36]).

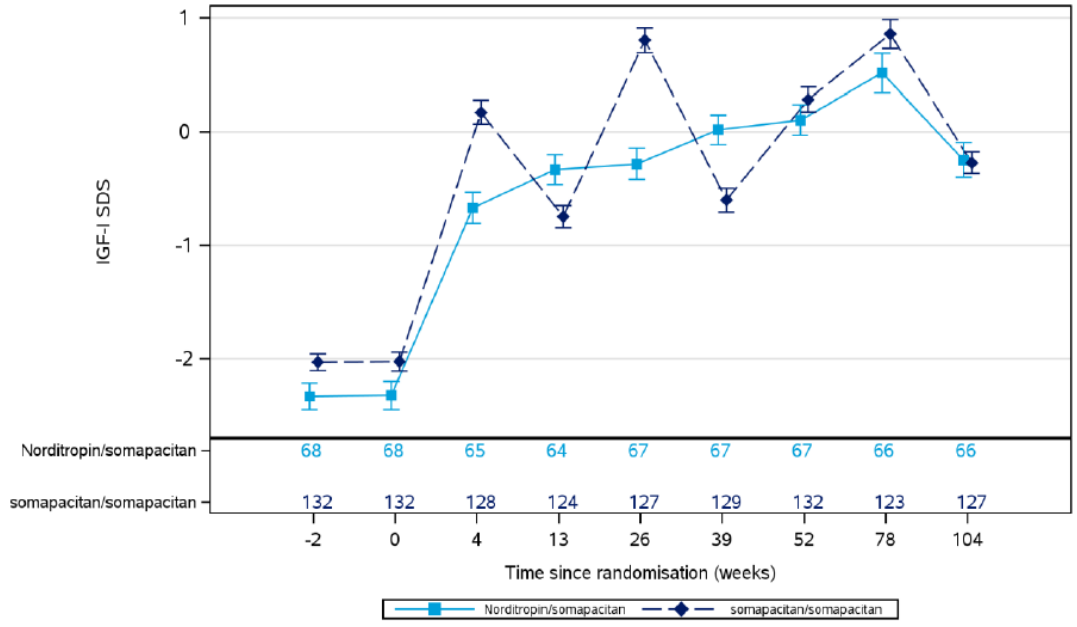
Mean IGF-I SDS levels increased from baseline levels and were within normal range (−2 to +2) in both treatment groups after 52 weeks (Figure 7). The mean observed IGF-I SDS (SD) change from baseline after 52 weeks was similar in the two groups with values of 2.32 (1.27) and 2.41 (1.09) for somapacitan and somatropin, respectively. The estimated mean IGF-I SDS values for somapacitan and somatropin after 52 weeks of 2.36 and 2.33, respectively, were similar to the observed values (Figure 8).

Mean IGF-I SDS levels increased from baseline levels and were within normal range (−2 to +2) up to Week 104 for both treatment groups (Figure 7). The mean (SD) IGF-I SDS levels at Week 104 were −0.27 (1.06) and −0.25 (1.25) for somapacitan/somapacitan and somatropin/somapacitan, respectively. The switch from daily somatropin to weekly somapacitan treatment is reflected by the similar IGF-I SDS values observed for the

[f] A bone age vs chronological age of less than one indicates immature bone development for age.

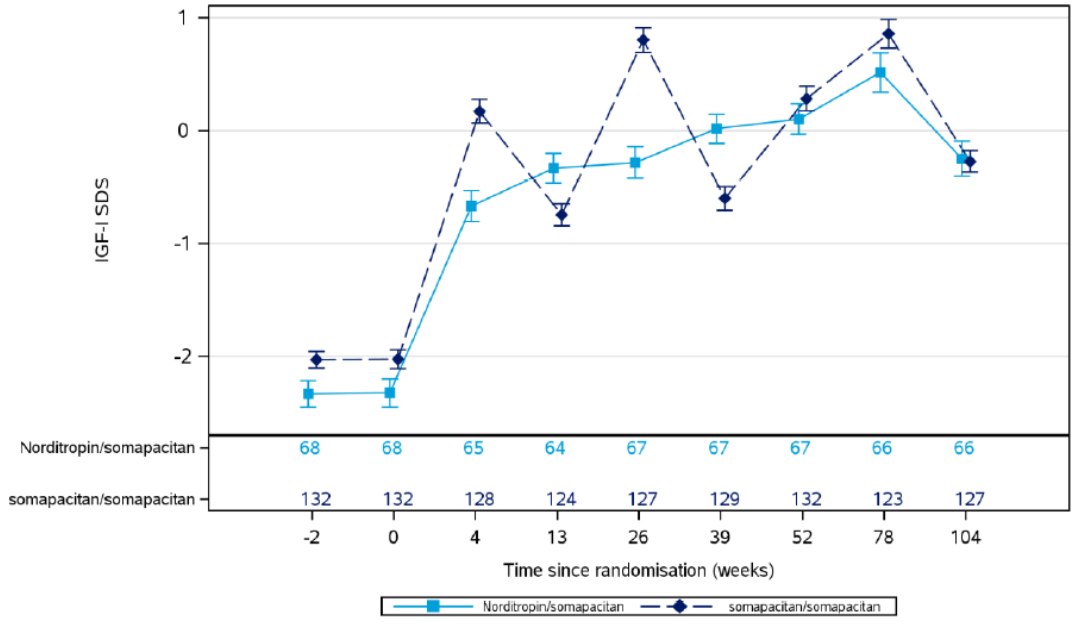
treatment groups at the Week 78 and Week 104 visits. The mean (SD) observed IGF-I SDS change from baseline after 104 weeks was similar in the two treatment groups with values of 1.78 (0.98) for somapacitan/somapacitan and 2.05 (1.33) for somatropin/somapacitan (Figure 8).

Figure 7: Mean IGF-I SDS by visit (in-trial; FAS), REAL 4



Abbreviations: FAS, full analysis set; IGF-I SDS, Insulin-like growth factor-1 standard deviation score.
Error bars: ± standard error (mean)
Observed data

Figure 8: Mean IGF-I SDS change from baseline (in-trial; FAS), REAL 4



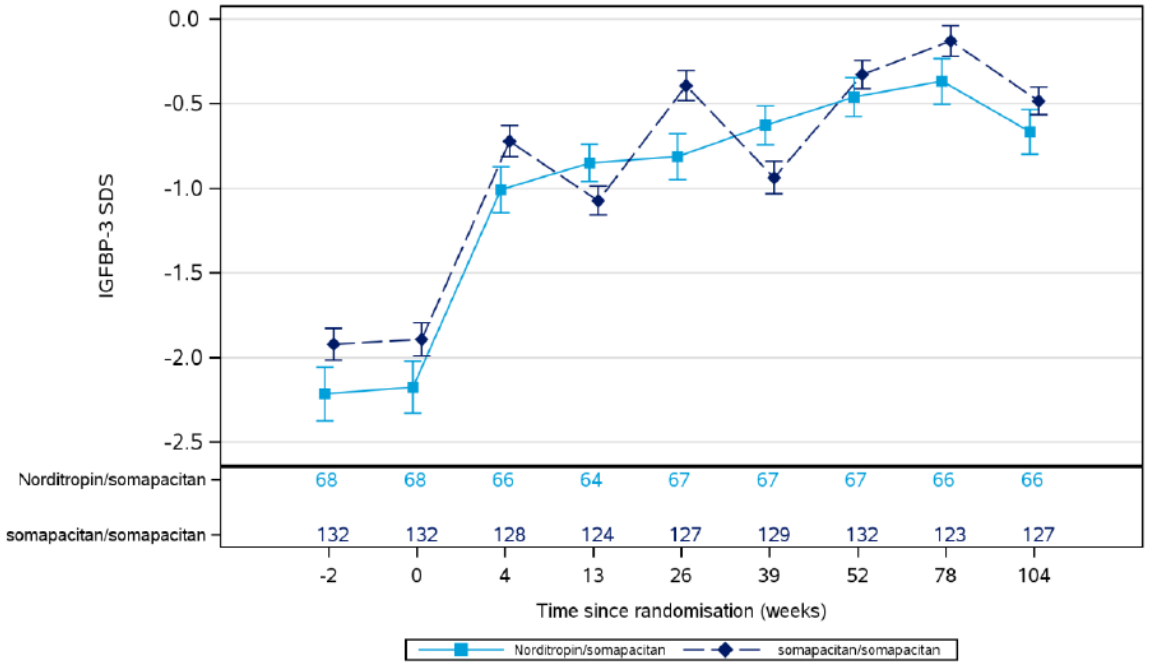
Abbreviations: FAS, full analysis set; IGF-I SDS, Insulin-like growth factor-1 standard deviation score.
Error bars: ± standard error (mean)
Observed data

IGFBP-3 SDS results using in-trial data

There was no statistically significant difference in change in IGFBP-3 SDS levels from baseline to Week 52 between somapacitan and somatropin (ETD 0.01 [95% CI; −0.22, 0.23]). Overall, IGFBP-3 levels increased from baseline to Week 52 (Figure 9), for both the somapacitan and somatropin treatment groups, consistent with IGF-I levels. The estimated values for both treatment groups after 52 weeks were 1.6, similar to observed values of 1.58 (0.92) and 1.68 (1.02) for somapacitan and somatropin, respectively.

Mean IGFBP-3 SDS levels increased from baseline and were consistently within the normal range (−2 to +2) throughout all 104 weeks for both treatment groups. Mean (SD) IGFBP-3 SDS levels were similar in the somapacitan/somapacitan (−0.48 [0.92]) and somatropin/somapacitan (−0.67 [1.07]) treatment groups after 104 weeks (Figure 9).

Figure 9: Change in IGFBP-3 SDS by visit (in-trial; FAS), REAL 4



Abbreviations: FAS, full analysis set; IGFBP-3 SDS, insulin-like factor binding protein 3 standard deviation score.
Error bars: ±standard error (mean).
Observed data.

B.3.6.1.3 Exploratory endpoints

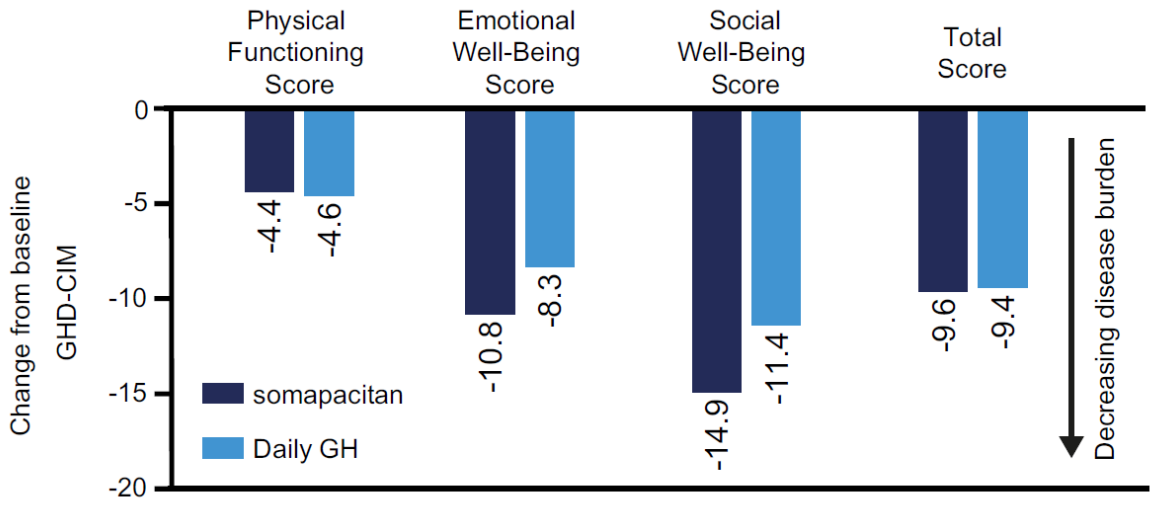
PROs were assessed using disease specific questionnaires:

- Growth hormone deficiency–child impact measure (**GHD-CIM**)
- Treatment burden measure – child growth hormone deficiency – observer (TB-CGHD-O). Also called the growth hormone deficiency – child treatment burden (**GHD-CTB**)
- Treatment burden measure – child growth hormone deficiency – parent (TB-CGHD-P). Also called the growth hormone deficiency – parent treatment burden (**GHD-PTB**)
- Growth hormone device assessment tool (**G-DAT**)
- Growth Hormone Patient Questionnaire-Parent/Guardian (**GH-PPQ**)

GHD-CIM

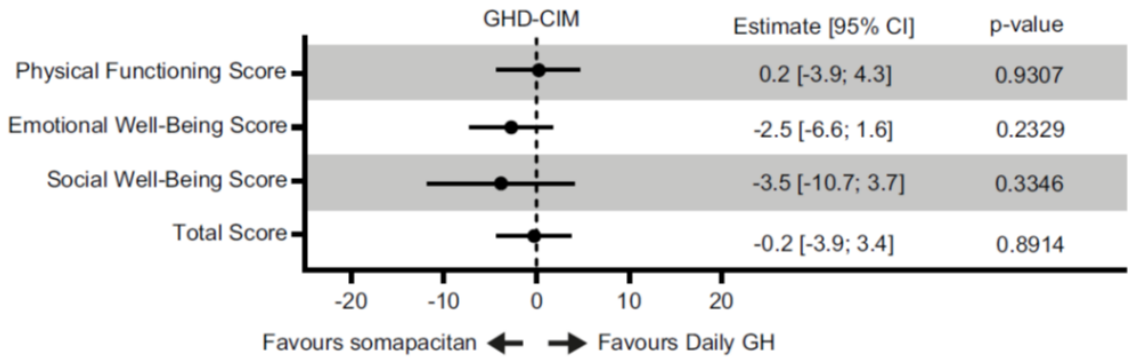
Improvements, assessed as decreased scores relative to baseline, were observed for all domains of the GHD-CIM questionnaire (physical functioning, emotional well-being, social well-being and total score) for both treatment groups at 52 weeks. At the end of the 52-week main trial period, all GHD-CIM scores were similar between somapacitan and somatropin (including physical functioning, emotional well-being, social well-being, and total score) (Figure 10 and Figure 11).

Figure 10: Change from baseline to Week 52 in GHD-CIM scores (FAS), REAL 4



Abbreviations: FAS, full analysis set; GH, growth hormone; GHD-CIM, growth hormone deficiency – child impact measure.
Figure is based on estimated mean. A lower number indicates a greater burden reduction.
Change from baseline to Week 52 in GHD-CIM scores was analysed using a mixed model for repeated measurements, with treatment, gender, age group, region, GH peak group and gender by age group by region interaction and baseline value as a covariate, all nested within week as a factor.

Figure 11: ETDs for change from baseline to 52 weeks in GHD-CIM scores (FAS), REAL 4



Abbreviations: CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set; GH, growth hormone; GHD-CIM, growth hormone deficiency–child impact measure.

GHD-CTB (observer) and GHD-PTB (parent)

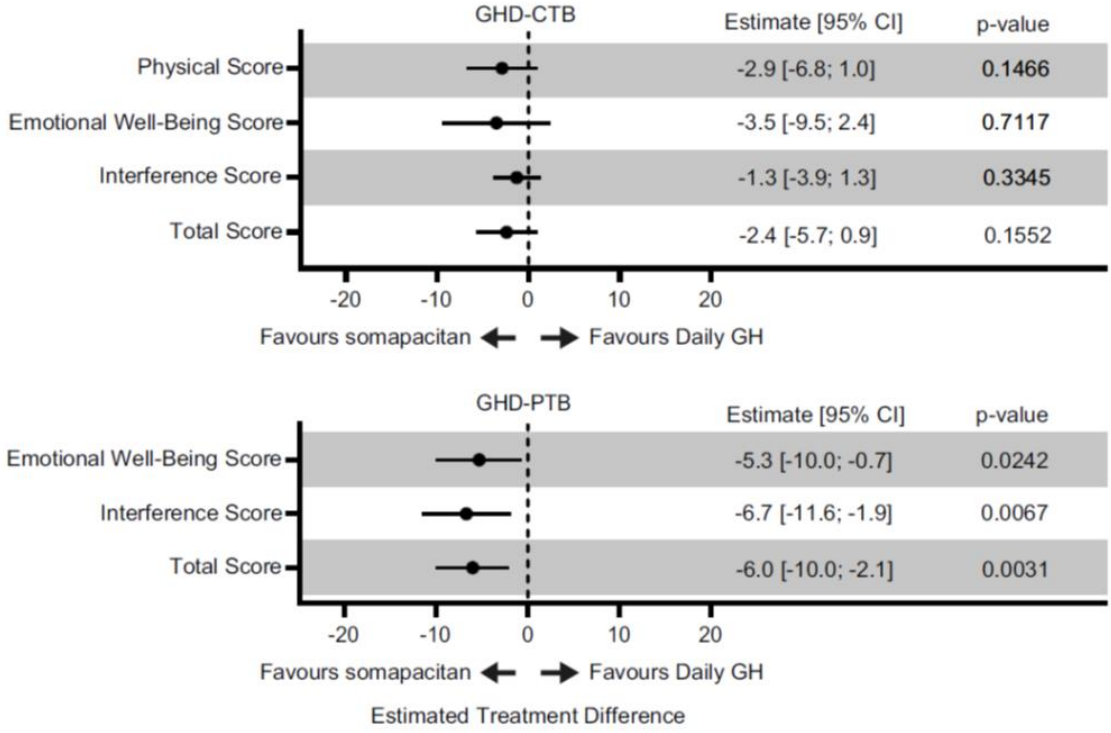
Non-biased clinicians or healthcare professionals (observers) and parents completed the GHD-CTB and GHD-PTB questionnaires, respectively.

GHD-CTB scores for all three domains (physical, emotional, interference) and total score did not show statistically significant differences between somapacitan and somatropin after 52 weeks (Figure 12).

GHD-PTB scores for emotional (ETD −5.3 [95% CI; −10.0, −0.7]) and interference (ETD −6.7 [95% CI; −11.6, −1.9]) domains and total score (ETD −6.0 [95% CI; −10.0, −2.1) were significantly improved (lowered) with somapacitan compared with somatropin after 52 weeks (p=0.0242, p=0.0067 and p=0.0031, respectively; Figure 12).

Thus, responses to the questionnaires indicate a reduced treatment burden on parents/LARs when their children are treated with once-weekly somapacitan vs once-daily GH.

Figure 12: ETDs for change in GHD-CTB and GHD-PTB scores after 52 weeks of treatment (FAS), REAL 4



Abbreviations: CI, confidence interval; ETD, estimated treatment difference; FAS, full analysis set; GHD-CTB, growth hormone deficiency–child treatment burden; GHD-PTB, growth hormone deficiency–parent treatment burden.

G-DAT

The G-DAT questionnaire was used to evaluate and compare ease of use for the somapacitan and somatropin devices in the trial. Somapacitan and somatropin devices were evaluated as easy or very easy to use (96% and 96% of patients, respectively) and store (95% and 94%, respectively) (Table 17).

Table 17: Summary of G-DAT questionnaire responses to the questions "How difficult or easy is it to:", REAL 4

	Somapacitan n=109, n (%)	Somatropin n=54, n (%)
Learn how to use your device		
Very difficult	1 (0.9)	0 (0)
Difficult	1 (0.9)	0 (0)
Neither difficult or easy	8 (7.3)	1 (1.9)
Easy	46 (42.2)	24 (44.4)
Very easy	53 (48.6)	29 (53.7)

	Somapacitan n=109, n (%)	Somatropin n=54, n (%)
Keep your device functioning properly		
Very difficult	0 (0)	0 (0)
Difficult	3 (2.8)	0 (0)
Neither difficult or easy	8 (7.3)	2 (3.7)
Easy	52 (47.7)	32 (59.3)
Very easy	46 (42.2)	20 (37.0)
Choose the correct dose		
Very difficult	0 (0)	0 (0)
Difficult	0 (0)	0 (0)
Neither difficult or easy	9 (8.3)	2 (3.7)
Easy	33 (30.2)	26 (48.1)
Very easy	67 (61.5)	26 (48.1)
Inject the dose		
Very difficult	1 (0.9)	0 (0)
Difficult	0 (0)	0 (0)
Neither difficult or easy	9 (8.3)	1 (1.9)
Easy	58 (53.2)	30 (55.6)
Very easy	41 (37.6)	23 (42.6)
Store your device		
Very difficult	0 (0)	0 (0)
Difficult	0 (0)	0 (0)
Neither difficult or easy	5 (4.6)	3 (5.6)
Easy	48 (44.0)	29 (53.7)
Very easy	56 (51.4)	22 (40.7)
Overall, how difficult or easy is it to use the device		
Very difficult	0 (0)	0 (0)
Difficult	1 (0.9)	0 (0)
Neither difficult or easy	3 (2.8)	2 (3.7)
Easy	60 (55.0)	24 (44.4)
Very easy	45 (41.3)	28 (51.9)

Abbreviations: FAS, full analysis set; G-DAT, growth hormone device assessment tool.

GH-PPQ at Week 56

The GH-PPQ is a disease-specific questionnaire to assess GH treatment preference, and was used to evaluate the switch from somatropin to somapacitan after the final visit in the main phase of the trial (at Week 52). The questionnaire was completed by the parent/legally authorised representative (LAR) for subjects, 4 weeks after they had switched from somatropin to somapacitan (Week 56).

Parents/LARs for 50 out of the total of 68 subjects switching from somatropin to somapacitan at Week 52 responded to the questionnaire. Of these 50 respondents, 45 (90%) preferred somapacitan to somatropin, while five respondents answered that they had no preference. None of the respondents preferred somatropin.

The majority (38 of 45) of the respondents preferring somapacitan had a strong or very strong preference for once-weekly somapacitan compared with a once-daily somatropin treatment regimen. The main reasons selected in the GH-PPQ for the preference included: “number of times needing to do injections”, “less worried about remembering to give the injections” and “child less worried or annoyed by getting injections”. Of these 45 parents/LARs, 35 stated they expected higher adherence to the current once-weekly regimen than to somatropin; one parent/LAR expected to be more adherent to somatropin, while the remaining nine parents/LARs had no preference with regards to expected adherence to either drug.

B.3.6.1.4 Efficacy conclusions for REAL 4

The results of REAL 4 demonstrate the comparable efficacy of once-weekly somapacitan vs daily somatropin for treating children with GHD, with benefits maintained for up to 104 weeks of treatment.

Primary endpoint

- For the primary endpoint, somapacitan demonstrated similar HV at Week 52 compared with somatropin (11.2 and 11.7, respectively). Non-inferiority for somapacitan vs somatropin at Week 52 was confirmed for both the treatment policy and hypothetical estimands, indicating comparable efficacy. These results were supported by sensitivity and per protocol analyses
- In the extension phase, increases in HV were sustained up to Week 104 in both treatment groups (somatropin/somapacitan and somapacitan/somapacitan)

Secondary endpoints

- For the supporting secondary endpoints, increases in mean HVSDS, height SDS, and bone age with somapacitan compared with baseline values were sustained over the 52-week trial period, and the 52-week extension. There were no statistically significant differences between the treatment groups, indicating similar efficacy for these endpoints
- Mean IGF-I SDS levels improved to normal range (−2 to +2) following treatment with somapacitan and somatropin and were sustained during the 52-week trial period and the 52-week extension period. There were no statistically significant differences between somapacitan and somatropin

Exploratory endpoints

- The treatment burden on the parent/LAR, as measured by the GHD-PTB, was statistically significantly in favour of somapacitan relative to somatropin after 52 weeks of treatment for both domain scores (emotional well-being and interference) and for overall score
- Patient- and parent-reported improvements in disease burden, as measured across all domain scores (physical functioning, emotional well-being, social well-being) of GHD-CIM, were comparable between somapacitan and somatropin after 52 weeks of treatment
- The majority of patients (>95%) treated with somapacitan found the device to be 'easy' or 'very easy' to use and to store, as assessed by the G-DAT questionnaire
- In the GH-PPQ (questionnaire to assess GH treatment preference), 90% (45 of 50) respondents preferred somapacitan to somatropin; the other five respondents answered that they had no preference

Overall, somapacitan demonstrated non-inferiority to somatropin for all clinically relevant height and biomarker related endpoints, with 313 fewer injections over one year of treatment. Somapacitan was also associated with a reduced treatment burden for caregivers compared with somatropin, and patients found the device easy to use and store. These results suggest that somapacitan delivers similar clinical outcomes to once-daily GH, with the additional benefit of a more favourable treatment schedule.

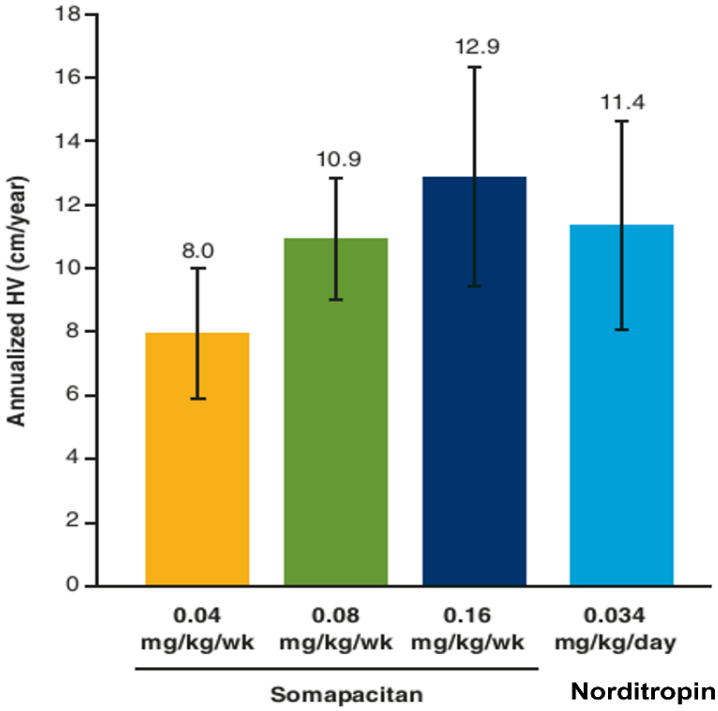
B.3.6.2 *REAL 3*

B.3.6.2.1 Primary efficacy outcome

Mean observed change in height velocity from baseline to Week 26

A dose-response relationship with somapacitan was observed after 26 weeks (Figure 13). The estimated annualised HV at Week 26 was 7.8, 10.9, and 13.1 cm/year for somapacitan for dose regimens 0.04, 0.08, and 0.16 mg/kg/week, respectively, and 11.4 cm/year for somatropin.[g] There was no statistically significant difference between somapacitan 0.16 or 0.08 mg/kg/week vs somatropin at Week 26.

Figure 13: Mean height velocity at Week 26, REAL 3



Abbreviations: HV, height velocity; SD, standard deviation; wk, week.
Data are mean (SD), observed values, full analysis set.
Values are observed means and differ slightly from the estimated means reported in the text.
Source: Savendahl et al, 2020 (75).

B.3.6.2.2 Secondary efficacy outcomes

Results for Weeks 0–52 (26-week main trial and 26-week extension period) are presented here. Results for the safety extension (Weeks 52–156) and the long-term safety extension (Weeks 156–208) are presented in Appendix J.

Height velocity (up to Week 52)

A dose response relationship in the point estimates was observed with the somapacitan treatment arms (estimated mean HV of 7.5, 9.7, and 11.7 cm/year for somapacitan dosing of 0.04, 0.08, and 0.16 mg/kg/week, respectively). HV after 52 weeks of treatment was

[g] HV values are estimated means that have been adjusted for baseline characteristics.

evaluated by the ETDs between each somapacitan and somatropin treatment arms (Table 18). Somapacitan 0.16 mg/kg/week statistically significantly increased HV after 52 weeks of treatment compared with somatropin (ETD 1.8 [95% CI; 0.5, 3.1]). There was no statistically significant difference between somapacitan 0.08 mg/kg/week and somatropin (ETD −0.2 [95% CI; −1.5, 1.1]). Somatropin significantly increased HV compared with somapacitan 0.04 mg/kg/week (ETD −2.4 [95% CI; −3.7, −1.1]).

Table 18: Statistical analysis of HV after 52 weeks of treatment; FAS, REAL 3

Height velocity	FAS	N	Estimate	95% CI
At Week 52				
Somatropin (0.034 mg/kg/day)	14	14	9.9	
Somapacitan (0.04 mg/kg/day)	14	14	7.5	
Somapacitan (0.08 mg/kg/day)	15	15	9.7	
Somapacitan (0.16 mg/kg/day)	14	14	11.7	
Treatment difference at Week 52				
Somapacitan (0.04 mg/kg/day)			−2.4	[−3.7, −1.1]
Somapacitan (0.08 mg/kg/day)			−0.2	[−1.5, 1.1]
Somapacitan (0.16 mg/kg/day)			1.8	[0.5, 3.1]

Abbreviations: CI, confidence interval; FAS, full analysis set.
Height velocity at 39 and 52 weeks will be analysed using a mixed model for repeated measurements, with treatment, age group, sex, region and sex by age group interaction as factors and height at baseline as a covariate, all nested within week as a factor.

Height SDS (up to Week 52)

A positive change from baseline to Week 52 in mean height SDS was observed for all three somapacitan dose groups and the somatropin group. Point estimates in the somapacitan dose groups resulted in a dose-response relationship (Table 19). Somapacitan 0.16 mg/kg/week significantly increased height SDS from baseline compared with somatropin (ETD 0.35 [95% CI; 0.05, 0.65]) after 52 weeks of treatment. There was no statistically significant difference between somapacitan 0.08 mg/kg/week and somatropin (ETD −0.10 [95% CI; −0.39, 0.20]) measured.

Table 19: Statistical analysis of change in height SDS after 52 weeks of treatment; FAS, REAL 3

Height SDS	**FAS**	**N**	**Estimate**	**95% CI**	**p-value**
At Week 52					
Somatropin (0.034 mg/kg/day)	14	14	1.07		
Somapacitan (0.04 mg/kg/day)	14	14	0.49		
Somapacitan (0.08 mg/kg/day)	15	15	0.98		
Somapacitan (0.16 mg/kg/day)	14	14	1.42		

Height SDS	FAS	N	Estimate	95% CI	p-value
Treatment difference at Week 52					
Somapacitan (0.04 mg/kg/day) – Somatropin (0.034 mg/kg/day)			−0.58	[−0.88, −0.28]	p=0.0003
Somapacitan (0.08 mg/kg/day) – Somatropin (0.034 mg/kg/day)			−0.10	[−0.39, 0.2]	p=0.5128
Somapacitan (0.16 mg/kg/day) – Somatropin (0.034 mg/kg/day)			0.35	[0.05, 0.65]	p=0.0216

Abbreviations: CI, confidence interval; FAS, full analysis set; SDS, standard deviation score.
Change from baseline in height SDS will be analysed using a mixed model for repeated measurements, with treatment, age group, sex, region and sex by age group interaction as factors and height SDS at baseline as a covariate, all nested within week as a factor.

Change in HVSDS (up to Week 52)

Treatment with somapacitan dose groups resulted in a dose-related response in HVSDS up until Week 52, after which all somapacitan treated children were allocated to the same dose level of 0.16 mg/kg/week up to Week 364. There was no statistically significant difference between somapacitan 0.08 mg/kg/week and somatropin (ETD −0.55 [95% CI; −1.18, 2.29]) or between somapacitan 0.16 mg/kg/week and somatropin (ETD 1.64 [95% CI; −0.02, 3.31]) after 52 weeks of treatment. The baseline HVSDS value for somapacitan 0.08 mg/kg/week was numerically higher than the HVSDS values for the other three treatment arms.

Change in IGF-I SDS (up to Week 52)

Treatment with somapacitan resulted in a dose-response trend for IGF-I SDS, with an estimated mean increase at Week 52 of 0.96, 1.87 and 3.37 for somapacitan 0.04, 0.08 and 0.16 mg/kg/week, respectively. Somapacitan 0.16 mg/kg/week significantly increased IGF-I SDS compared with somatropin (ETD 1.56 [95% CI; 0.66, 2.46]) after 52 weeks of treatment. No statistically significant differences were observed between somapacitan 0.04 mg/kg/week (ETD −0.85 [95% CI; −1.78, 0.08]) or somapacitan 0.08 mg/kg/week and somatropin (ETD −0.05 [95% CI; −0.86, 0.97]). Mean baseline IGF-I SDS values were similar for all treatment arms.

Change in IGFBP-3 SDS (up to Week 52)

A dose-response relationship in the point estimates was observed in the somapacitan dosed groups. At Week 52, the change in IGFBP-3 SDS was statistically significantly higher for somapacitan 0.16 mg/kg/week compared with somatropin (ETD 0.93 [95% CI; 0.13, 1.73], p=0.0234). No statistically significant difference was observed between somapacitan 0.04 mg/kg/week and somatropin or between somapacitan 0.08 mg/kg/week and somatropin.

Bone age progression vs chronological age (up to Week 52)

No marked difference in bone age progression vs chronological age between the treatment groups was noted (see Figure 12 in Appendix J). Bone age increased slightly in all groups, with a change from baseline in bone age vs chronological age ratio of 0.09, 0.03, 0.09, and 0.02 for somapacitan 0.04, 0.08, 0.16 mg/kg/week, and daily GH, respectively. No changes in skeletal proportions were reported.

B.3.6.2.3 Exploratory endpoints

Results for exploratory endpoints in REAL 3 are presented in Appendix J.

B.3.6.2.4 Efficacy conclusions for REAL 3

The results of REAL 3 demonstrate the comparable efficacy of once-weekly somapacitan vs daily somatropin for treating children with GHD, over 52 weeks of treatment. The benefits of somapacitan treatment were further maintained for up to 4 years. Please see Appendix J for results from the safety extension (to Week 156) and the long-term safety extension (results are currently available to Week 208).

Primary endpoint

- Treatment with somapacitan resulted in a dose-response relationship for the mean observed change in HV after 26 weeks. Somapacitan 0.16 and 0.08 mg/kg/week showed no statistically significant difference in HV compared with somatropin at Week 26, suggesting comparable efficacy

Secondary endpoints

- For the supporting secondary endpoints, the HV dose-response relationship was still observed after 52 weeks of treatment and was significantly greater for somapacitan 0.16 mg/kg/week compared with somatropin (ETD 1.8 [95% CI; 0.5, 3.1])
- Change from baseline to Week 52 in height SDS was statistically significantly greater for somapacitan 0.16 mg/kg/week vs somatropin (ETD 0.35 [95% CI; 0.05, 0.65])
- There was no statistically significant difference in HVSDS change from baseline to Week 52 between somapacitan 0.16 mg/kg/week and somatropin (ETD 1.64 [95% CI; −0.02, 3.31])
- A dose-response trend for IGF-I SDS and IGFBP-3 SDS after 52 weeks was observed for the somapacitan treatment arms. Change in IGF-I SDS from baseline to Week 52 was statistically significantly greater for somapacitan 0.16 mg/kg/week vs somatropin (ETD 1.56 [95% CI; 0.66, 2.46])
- Somapacitan 0.16 mg/kg/week was favoured over somatropin across all domains for the GHD-CIM, TB-CGHD-O (GHD-CTB), and TB-CGHD-P (GHD-PTB)

Overall, these results suggest that somapacitan improves clinically relevant height outcomes in a dose response relationship. Somapacitan also demonstrates maintained improvements in children previously treated with GH (Appendix J). Results show that somapacitan has a lower treatment burden vs somatropin, suggesting that patients may favour once-weekly dosing over a once-daily schedule (Appendix J).

B.3.7 *Subgroup analysis*

No subgroup analysis was performed in REAL 4 or REAL 3.

B.3.8 *Meta-analysis*

Per the decision problem (Section B.1.1), the key comparators for somapacitan are somatropin and somatrogon. In the absence of direct, head-to-head trial data comparing somapacitan with somatrogon, an indirect treatment comparison was conducted (Section B.3.9).

B.3.9 *Indirect and mixed treatment comparisons*

A pairwise ITC was conducted to evaluate the efficacy and safety of somapacitan compared with other available long-acting growth hormone (LAGH) therapies in children with GHD, in the absence of head-to-head trials.

B.3.9.1 *Trials used to inform the analysis*

An SLR conducted in October 2021 and updated in March 2023 (see Section B.3.1) identified studies in which LAGHs were assessed for the treatment of paediatric GHD. In the absence of trials involving a direct comparison of LAGHs, a feasibility assessment of indirect analyses of studies was conducted.

The SLR identified five unique studies that met the PICOS criteria. Opko Japan was not considered relevant (Section B.3.9.2), and therefore four clinical trials (73, 75, 78, 79) were used for the analysis reported in this submission. Two studies assessed somapacitan, and two evaluated somatrogon. Based on the available evidence, the analyses were divided into two parts, Part 1 (≤52 weeks) and Part 2 (>52 weeks). With single-arm evidence beyond 52 weeks, it was not considered feasible to conduct an indirect analysis for Part 2 (>52 weeks); therefore for the purpose of this submission only treatment effects ≤52 weeks were evaluated. For further details see the pairwise ITC report (80).

All four included studies provided evidence for treatment effects at ≤52 weeks in randomised controlled phases. A summary of the trials used to carry out the ITC, grouped by treatment, is presented in Table 20.

Table 20: Summary of trials used to carry out the ITC

Trials (and references)	Comparator arm in the clinical trial			Publication included in Previous NICE TA
	Somapacitan	Somatrogon	Somatropin	
REAL 3 (75) NCT02616562	✓		✓	No
REAL 4 (73) NCT03811535	✓		✓	No
Opko II (79, 81) NCT01592500		✓	✓	Yes
Opko III (78) NCT02968004		✓	✓	Yes

Abbreviations: ITC, indirect treatment comparison; TA, technology appraisal.

B.3.9.2 *Studies excluded from the analysis*

Studies were excluded from the ITC analysis if the comparators were not currently reimbursed in England. Of the three comparator LAGHs evaluated in trials identified in the SLR, lonapegsomatropin and eftansomatropin did not fulfil this criterion. Five studies describing the efficacy of lonapegsomatropin and eftansomatropin were excluded from the analysis.

The Phase III trial Opko Japan was excluded from the analysis reported in this submission (base case) as it evaluated somatropin at a different dose to that used in the Novo Nordisk-sponsored studies (0.025 mg/kg/day in Opko Japan and 0.034 mg/kg/day in Novo Nordisk-sponsored studies). Moreover, the pairwise ITC report presents an alternative evidence network which includes all four trials from the base case and the Phase III trial Opko Japan (82). The results from that analysis are in line with the analysis presented in this submission.

B.3.9.3 *Methods and outcomes of included studies*

B.3.9.3.1 Rationale for choice of outcome measure and scale

Efficacy

The efficacy outcomes considered of clinical relevance were the following comparisons of height outcomes:

- annualised height velocity (AHV)
- AHV SDS
- height SDS

AHV is calculated as the difference in height between two timepoints (in centimetres) divided by the difference between the two timepoints (in years). HVSDS is a standardised measure of HV based on a child's age and sex. Likewise, height SDS is a standardised measure of height based on a child's age and sex. The rationale for efficacy outcomes considered was that AHV, SDS, and height SDS were of most clinical relevance given the goals of the treatment, which is to increase growth and reflect the benefits of height outcomes. These outcomes are recommended measurements by the Growth Hormone Research Society (GHRS) when establishing the effectiveness of GH therapy (19).

Safety

The safety outcomes considered of relevance in the analysis were injection site reactions and antibodies (neutralising and non-neutralising). In the analysis, the feasibility of assessing efficacy outcomes at Week 26 and Week 52 was assessed. For safety outcomes, the feasibility of constructing networks was not assessed, as only qualitative summaries of results were planned.

B.3.9.3.2 Participants included

The population of interest was defined as treatment-naïve pre-pubescent boys or girls (≥2 and ≤12 years) with GHD and impaired HV. Patients diagnosed with one of the other indications of GHs (e.g., small for gestational age) were excluded. There were no other differences between patient populations.

The patient characteristics across the four trials used to inform Part 1 were assessed. The assessment of patient characteristics focused on the following characteristics identified as potential prognostic factors:

- Age
- Gender
- Race
- Height, height SDS or AHV SDS at baseline
- Peak GH

Where data were reported, the above characteristics were generally balanced across treatment arms in the trials (Table 21 and Table 22). The main prognostic factors were part of the statistical analysis for most trials and were therefore controlled for imbalance.

Some dissimilarities across trials were recorded. Regarding gender, there was a spread in the proportions of male patients across trials, from approximately 61% male in REAL 3 to approximately 75% in REAL 4. The mean age in Opko III was higher than in other trials, including REAL 4 (7.7 and 6.4 years, respectively). Height SDS and AHV SDS were slightly lower in Opko II compared with other trials.

Table 21: Patient baseline characteristics by trial and treatment arm

Trial	Arm	Age, years Mean (SD)	N (%) of males	Race, N (%)	Weight, kg Mean (SD)	BMI, kg/m^2 Mean (SD)	BMI SDS Mean (SD)	HV SDS Mean (SD)	Height SDS Mean (SD)	IGF-1 Mean (SD)	IGF-1 SDS Mean (SD)
Somapacitan											
REAL 3	Somapacitan 0.16 mg/kg/wk N=14	6.1 (2.3)	8 (57.1)	White: 6 (42.9) Asian: 8 (57.1) Black or African American: 0 (0)	14.9 (5.23)	15.1 (1.2)	−0.48 (0.85)	−2.9 (1.8)	−3.8 (2.0)	NR	−2.0 (1.0)
	Somatropin 0.034 mg/kg/d N=14	6.0 (2.0)	9 (64.3)	White: 7 (50) Asian: 6 (42.9) Black or African American: 1 (7.1)	15.5 (5.03)	15.6 (1.4)	−0.13 (0.87)	−3.1 (2.1)	−3.4 (1.1)	NR	−2.1 (0.7)
REAL 4	Somapacitan 0.16 mg/kg/wk N=132	6.4 (2.2)	99 (75.0)	White: 78 (59.1) Asian: 46 (34.8) Black or African American: 0 (0) Not reported: 7 (5.3) Other: 1 (0.8)	16.7 (4.60)	15.7 (1.59)	− 0.17 (0.97)	−2.35 (1.51)	−2.99 (1.02)	47.5 ng/ml	−2.03 (0.97)
	Somatropin 0.034 mg/kg/d N=68	6.4 (2.4)	50 (73.5)	White: 36 (52.9) Asian: 28 (41.2) Black or African American: 1 (1.5) Not reported: 3 (4.4) Other: 0 (0)	16.0 (4.95)	15.6 (1.38)	− 0.25 (1.05)	−2.52 (1.55)	−3.47 (1.52)	37.31 ng/ml	−2.33 (1.03)
Somatrogon											
Opko II	Somatrogon 0.66 mg/kg/wk N=14	6.1 (2.2)	9 (64.3)	White: 14 (100.0%) Non-white: 0 (0)	NR	NR	NR	−3.01 (1.42)	−4.21 (1.45)	−1.97 (0.83) ng/mL	NR
	Somatropin 0.034 mg/kg/d N=11	5.7 (1.9)	8 (72.7)	White: 10 (90.9%) Non-white: 1 (9.1%)	NR	NR	NR	−3.29 (1.91)	−4.22 (1.58)	−2.15 (0.94) ng/mL	NR

Opko III	Somatrogon 0.66 mg/kg/wk N=109	7.83 (range: 3.01–11.96)	82 (75.2)	White: 81 (74.3) Black or African American: 0 Asian: 24 (22.0) American Indian or Alaska Native: 1 (0.9) Native Hawaiian or Other Pacific Islander: 0 Other: 3 (2.8)	NR	NR	−0.28 (1.04)	NR	−2.94 (1.29)	NR	−1.95
	Somatropin 0.034 mg/kg/d N=115	7.61 (range: 3.05–11.85)	79 (68.7)	White: 86 (74.8) Black or African American: 2 (1.7) Asian: 21 (18.3) American Indian or Alaska Native: 0 Native Hawaiian or Other Pacific Islander: 1 (0.9) Other: 5 (4.3)	NR	NR	−0.20 (1.01)	NR	−2.78 (1.27)	NR	−1.72

Abbreviations: BMI, body mass index; d, day; IGF-1, insulin-like growth factor; NR, not reported; SD, standard deviation; wk, week.

Table 22: Pooled patient baseline characteristics by trial

Trial	N	Age, years Mean (SD)	N (%) of males	Race, N (%)	Weight, kg Mean (SD)	BMI, kg/m^2 Mean (SD)	BMI SDS Mean (SD)	HV SDS Mean (SD)	Height SDS Mean (SD)	IGF-1 Mean (SD)	IGF-1 SDS Mean (SD)
Somapacitan											
REAL 3†	28	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
REAL 4	200	6.4 (2.3)	149 (74.5)	White: 114 (57.0) Asian: 74 (37.0) Black or African American: 1 (0.5) Not reported: 10 (5.0) Other: 1 (0.5	16.5 (4.72)	15.7 (1.52)	NR	−2.41 (1.52)	−3.15 (1.23)	NR	−2.13 (1.00)
Somatrogon											
Opko II‡	24	NR	NR	NR	NR	NR	NR	NR	−3.98 (1.22)	NR	NR
Opko III	124	7.72 (range: 3.01-11.96)	161 (71.9)	White: 167 (74.6) Black or African American: 2 (0.9) Asian: 45 (20.1) American Indian or Alaska Native: 1 (0.4) Native Hawaiian or Other Pacific Islander: 1 (0.4) Other: 8 (3.6)	NR	NR	−0.24 (1.02)	NR	−2.86 (1.28)	NR	NR

Abbreviations: BMI, body mass index; d, day; IGF-1, insulin-like growth factor; N, number of patients; NR, not reported; SD, standard deviation; wk, week.
†Baseline characteristics were reported individually according to the type of treatment received.
‡ Baseline characteristics were reported individually according to the type of treatment received, except for height SDS.

B.3.9.4 *Risk of bias*

No risks of bias were identified with respect to the trials and methodology.

B.3.9.5 *Methodology*

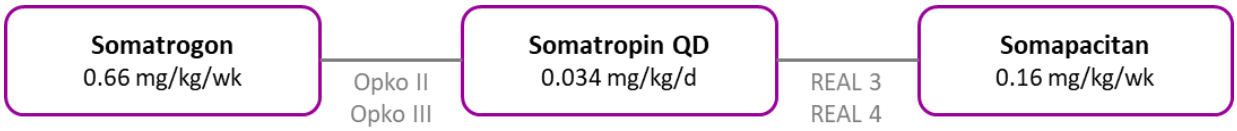
Indirect analyses assessing efficacy outcomes in Part 1 were determined to be feasible. With only single arm evidence available beyond Week 52, indirect analyses assessing efficacy outcomes in Part 2 were not feasible; these outcomes, as well as safety outcomes, were assessed through qualitative summaries only. For indirect analyses, all outcomes were analysed using a normal likelihood, identity link model.

B.3.9.5.1 Evidence networks

Base case evidence network

The base case network (Figure 14) includes the four trials considered in the feasibility assessment.

Figure 14: Base case scenario evidence network



Abbreviations: d, day; QD, once-daily; wk, week.

Outcome specific evidence networks

Four trials were considered for inclusion in the outcome-specific evidence networks. An overview of data availability across included trials is presented in Table 23.

Table 23: Overview of data availability across included trials to inform Part 1

Outcome	REAL 3	REAL 4	Opko II	Opko III	Number of studies in network
Study intervention	**Somapacitan 0.16 mg/kg/wk**	**Somapacitan 0.16 mg/kg/wk**	**Somatrogon 0.66 mg/kg/wk**	**Somatrogon 0.66 mg/kg/wk**	
Study control	**Somatropin 0.034 mg/kg/d**	**Somatropin 0.034 mg/kg/d**	**Somatropin 0.034 mg/kg/d**	**Somatropin 0.034 mg/kg/d**	
AHV at 52 weeks†	✓	✓	✓	✓	4
AHV at 26 weeks†	✓	✓	✓	✓	4
HVSDS at 52 weeks	✓	✓	✓‡	-	3
HVSDS at 26 weeks	✓	✓	-	-	N/A
Height SDS at 52 weeks	✓	✓	✓	✓	4
Height SDS at 26 weeks	✓	✓	✓	✓	4

Note: Tick indicates estimate and assessment of uncertainty, unless otherwise stated. Trials not included in the base case evidence network are in light grey.
† Primary measure of interest. ‡Results presented only in plots.
Abbreviations: AHV, annualised height velocity; BC, base case; BMI, body mass index; GH, growth hormone; HV, height velocity; N/A, not applicable; SDS, standard deviation score.

B.3.9.5.2 Statistical methods

Where feasible, the comparative efficacy of LAGHs was assessed via indirect analysis. Based on the prior feasibility assessment, indirect analyses were determined to be feasible for efficacy outcomes observed from baseline to Week 52, specifically AHV, height SDS, and HVSDS. Indirect analyses for efficacy outcomes observed after week 52 were determined to be unfeasible. Thus, the statistical methods described refer only to the indirect analyses of efficacy outcomes from Part 1 of the analysis (≤52 weeks).

Pooling of multiple arms of the same treatment into a single node

In trials with multiple doses of the same LAGH treatment, only the recommended dose (or intended dose if market authorisation pending) was used for analysis.

In this network, there were multiple arms of somatropin; these were combined and considered as a single somatropin node, which was a common comparator for other treatments. A key assumption of this network was that the somatropin treatment arms were considered similar enough to be combined into a single treatment node, which was seen as feasible because Genotropin® and Norditropin® are both somatropin products. In the base case network, somatropins of the same dose were pooled (0.034 mg/kg/day).

Consistency of evidence

As the network contains no loops, formal assessment of consistency was not performed.

Software and implementation details

The programming language R (version 4.1.3) was used for implementation. Analysis was conducted utilising function nma in version 0.5.0 of the publicly available package multinma (83). Four chains of 10,000 iterations were run; 5,000 for burn-in and 5,000 for sampling.

Prior distributions

The prior represents the prior probability distribution; a vague prior contains no information about the parameters of interest. Vague priors are used for the study specific treatment effect μ_i and treatment effect sizes relative to reference treatment 1 (d_{1k}) in the form of a normal distribution with a mean of 0 and variance of 10,000, as recommended by NICE technical support document (84).

Due to the size of the network and limited trial replication, vague priors were not used for between-trial heterogeneity in the random effect (RE) model. Instead, information that all the SAGHs are bioequivalent and the LAGHs share a mode of action was taken into account, and a prior was calculated through a class-level meta-analysis with fixed effects (FE), for each endpoint. The estimated standard deviation for the treatment difference between LAGHs and SAGHs was then used as a prior for between-trial SD (σ) in the treatment-level RE models for the endpoint.

Measures of model complexity and fit

Model comparisons (FE vs RE) were based on comparing the average residual deviance (i.e. residual deviance divided by number of data points), in addition to the deviance information criterion (DIC) (84). In general, a model is favoured if it has a lower DIC (a difference of 3–5 points or more between the DIC from the FE and RE models indicates a strong preference for the model with the lower DIC) and a posterior residual deviance closer to the number of data points. See Appendix K for details.

B.3.9.6 *Results*

B.3.9.6.1 Part 1 (≤52 weeks)

Trial and base case network results (FE and RE models) are presented below. For all efficacy endpoints, the difference in both DIC and residual deviation between the FE and RE models did not indicate strong model preference; however, there was a slight decrease with the RE model in both metrics, suggesting a better model fit. Furthermore, the difference in trial results when there was trial replication indicated that the assumptions underlying the FE model might not be appropriate. Therefore, the RE model was selected for all endpoints.

Annualised HV

Trial results

AHV data were available from all four trials at Week 26 and Week 52 (Table 24). AHV was the primary endpoint in all trials; the primary endpoint was evaluated at Week 52 in three trials and at Week 26 in one trial (REAL 3). Increases in AHV reflect improved longitudinal growth. Overall, somapacitan and somatrogon generally showed similar or greater improvements in AHV compared with somatropin.

Two trials compared somapacitan 0.16 mg/kg/week with somatropin (REAL 3 and REAL 4). In REAL 3, improvements in AHV did not differ between somapacitan 0.16 mg/kg/week and somatropin at Week 26. However, somapacitan 0.16 mg/kg/week was shown to have statistically significantly greater improvements compared with somatropin at Week 52. In REAL 4, improvements in AHV did not differ between somapacitan 0.16 mg/kg/week and somatropin at Week 26 or Week 52.

Two trials compared somatrogon 0.66 mg/kg/week and somatropin (Opko II, Opko III). Somatrogon 0.66 mg/kg/week was shown to be non-inferior to somatropin in one trial (Opko III) based on a predefined non-inferiority margin of −1.8 cm/year. In the second trial (Opko II), mean AHV was numerically similar between somatrogon 0.66 mg/kg/week and somatropin; the difference between the two arms was not reported.

Table 24: AHV trial results; ITC Part 1

Trial	Arm	AHV			
		Mean	Difference	Mean	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3	Somapacitan 0.16 mg/kg/wk	12.9† (SE: 0.67)	1.7 (−0.2, 3.6)	11.7† (SE: 0.46)	1.8 (0.5, 3.1)
	Somatropin 0.034 mg/kg/d	11.4† (SE: 0.66)		9.9† (SE: 0.46)	
REAL 4	Somapacitan 0.16 mg/kg/wk	12.25† (SE: 0.27)	−0.51 (−1.41, 0.39)	11.2† (SE: 0.19)	−0.5 (−1.1, 0.2)
	Somatropin 0.034 mg/kg/d	12.75† (SE: 0.37)		11.7† (SE: 0.27)	
Somatrogon					
Opko II	Somatrogon 0.66 mg/kg/wk	13.5 (SD: 5)	NR	11.93 (SD: 3.5)	NR
	Somatropin 0.034 mg/kg/d	15 (SD: 2.9)		12.5 (SD: 2.1)	
Opko III	Somatrogon 0.66 mg/kg/wk	10.59† (9.96, 11.22)	0.55 (-0.13, 1.23)	10.1† (9.58, 10.63)	0.33 (−0.24, 0.89)
	Somatropin 0.034 mg/kg/d	10.04† (9.47, 10.62)		9.78† (9.29, 10.26)	

Data are mean (95% CI) unless otherwise indicated.
Abbreviations: AHV, annualised height velocity; d, day; ITC, indirect treatment comparison; NR, not reported; SD, standard deviation; SE, standard error.
† Least square mean.

Base case network results

Results from the base case are presented in Table 25 (and Appendix K) for the FE and RE analysis. Results from the RE model showed no significant differences between somapacitan and somatrogon or somatropin at Week 26 or Week 52. Results were generally similar with the FE model.

Table 25: Base case results for AHV at Week 26 and Week 52; ITC Part 1

Treatment	Difference (95% CrI) (vs somapacitan)	
	FE model	RE model
Week 26		
Somatrogon	0.54 (−0.63, 1.70)	0.40 (−1.09, 1.77)
Somatropin	0.12 (−0.69, 0.93)	0.04 (−0.97, 0.99)
DIC	17.15	16.55
Residual deviance	11.13	10.29
Week 52		
Somatrogon	0.26 (−0.63, 1.15)	0.09 (−1.23, 1.18)
Somatropin	0.03 (−0.55, 0.61)	−0.11 (−1.00, 0.62)
DIC	22.50	19.74
Residual deviance	16.50	13.04

Abbreviations: AHV, annualised height velocity, CrI, credible interval; DIC, deviance information criteria; FE, fixed effect, ITC, indirect treatment comparison; RE, random effects
Results are presented as median treatment differences and an associated 95% CrI for comparators versus somapacitan. Positive differences favour comparator treatments.
Bolded cells indicate the 95% CrI does not contain 0.

Height velocity SDS

Trial results

HVSDS data were available from three trials at Week 52 and two trials at Week 26 (Table 26). HVSDS is a standardised measure of HV based on a child's age and sex. Thus, results for HVSDS are expected to be similar compared with results for AHV. Increases in HVSDS indicate a reduction in HV deficit compared with age- and sex-matched children. Overall, somapacitan and somatrogon generally showed similar or greater improvements in HVSDS compared with somatropin.

Two trials compared somapacitan 0.16 mg/kg/week and somatropin (REAL 3 and REAL 4). In REAL 3, mean HVSDS did not differ between somapacitan 0.16 mg/kg/week and somatropin at Week 26 and Week 52. In REAL 4, mean HVSDS also did not differ between somapacitan 0.16 mg/kg/week and somatropin at Week 52.

One trial compared somatrogon 0.66 mg/kg/week and somatropin (Opko II). The mean difference in HVSDS were numerically similar between somatrogon 0.66 mg/kg/week and somatropin; however, the significance of the difference was not reported.

Overall, results were generally similar in terms of direction of effect for the HVSDS outcome compared with the AHV outcome as previously reported. Somapacitan and somatrogon generally showed similar or numerically greater improvements compared with somatropin. However, the somatrogon trials had fewer available data for the HVSDS outcome compared with AHV.

Table 26: HVSDS trial results; ITC Part 1

Trial	Arm	HVSDS			
		Mean	Difference	Mean	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3	Somapacitan 0.16 mg/kg/wk	7.19† (SE: 0.9)	1.61 (−0.97, 4.19)	5.72† (SE: 0.58)	1.64 (−0.02, 3.31)
	Somatropin 0.034 mg/kg/d	5.58† (SE: 0.92)		4.07† (SE: 0.59)	
REAL 4	Somapacitan 0.16 mg/kg/wk	6.62† (SE: 0.33)	−0.62 (-1.74, 0.49)	5.62† (SE: 0.25)	−0.82 (-1.68, 0.04)
	Somatropin 0.034 mg/kg/d	7.24† (SE: 0.46)		6.44† (SE: 0.35)	
Somatrogon					
Opko II	Somatrogon 0.66 mg/kg/wk	NR		6.57 (SE: 0.6)	NR
	Somatropin 0.034 mg/kg/d			7.38 (SE: 0.44)	

Data are mean (95% CI) unless otherwise indicated.
Abbreviations: CI, confidence interval; d, day; HVSDS, height velocity standard deviation score; ITC, indirect treatment comparison; NR, not reported; SD, standard deviation; SE, standard error.
† Least square mean.

Base case network results

Results from the base case are presented in Table 27 (and Appendix K). Overall, no differences between somatrogon and somapacitan were observed in the RE analysis. Results were generally similar in the FE analysis. Results for the somapacitan vs somatrogon comparison differ in that the results numerically favoured somatrogon in the AHV analysis but favoured somapacitan in the HVSDS analysis. In either case, results did not indicate that somapacitan and somatrogon differed.

Table 27: Base case results for HVSDS at Week 52; ITC Part 1

	Difference (95% CrI) (vs somapacitan)	
	FE model	RE model
Week 52		
Somatrogon	−0.52 (-2.12, 1.11)	−0.66 (−2.78, 1.24)
Somatropin	0.30 (−0.45, 1.05)	0.14 (−1.02, 1.07)
DIC	16.83	14.80
Residual deviance	11.92	9.34

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed effect, HVSDS, height velocity standard deviation score; ITC, indirect treatment comparison; RE, random effects.
Results are presented as median treatment differences and an associated 95% CrI for comparators versus somapacitan. Positive differences favour comparator treatments.
Bolded cells indicate the 95% CrI does not contain 0.

Height SDS

Trial results

Height SDS data were available from four trials at Week 26 and Week 52 (Table 28). Increases in height SDS indicate a reduction in growth deficit compared with age- and sex-matched children. Overall, somapacitan and somatrogon generally showed similar or greater improvements in height SDS compared with somatropin.

Two trials compared somapacitan 0.16 mg/kg/week and somatropin (REAL 3 and REAL 4). In REAL 3, change from baseline in height SDS did not differ between somapacitan 0.16 mg/kg/week and somatropin at Week 26, but somapacitan 0.16 mg/kg/week had a statistically significantly greater change compared with somatropin at Week 52. In REAL 4, there was no difference between somapacitan 0.16 mg/kg/week and somatropin at Week 26 or Week 52.

Two trials compared somatrogon 0.66 mg/kg/week and somatropin (Opko II, Opko III). In Opko II, somatrogon 0.66 mg/kg/week and somatropin had numerically similar changes at Week 26 and Week 52, but the difference was not reported. In Opko III, the changes did not differ between somatrogon 0.66 mg/kg/week and somatropin at Week 26 and Week 52. Similar trends were observed with height SDS results compared with AHV at both Week 26 and Week 52.

Table 28: Height SDS trial results at Week 26 and Week 52; ITC Part 1

Trial	Arm	Height SDS			
		Change	Difference	Change	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3	Somapacitan 0.16 mg/kg/wk	0.87† (SE: 0.08)	0.16 (-0.06, 0.38)	1.42† (SE: 0.1)	0.35 (0.05 to 0.65)
	Somatropin 0.034 mg/kg/d	0.71† (SE: 0.08)		1.07† (SE: 0.1)	
REAL 4	Somapacitan 0.16 mg/kg/wk	0.73† (SE: 0.03)	-0.09 (-0.20, 0.02)	1.25† (SE: 0.04)	-0.05 (-0.18, 0.08)
	Somatropin 0.034 mg/kg/d	0.82† (SE: 0.04)		1.30† (SE: 0.05)	
Somatrogon					
Opko II	Somatrogon 0.66 mg/kg/wk	0.90 (SD: 0.39)	NR	1.45 (SD: 0.61)	NR
	Somatropin 0.034 mg/kg/d	1.00 (SD: 0.35)		1.51 (SD: 0.47)	
Opko III	Somatrogon 0.66 mg/kg/wk	0.54 (0.48, 0.61)	0.06 (-0.01, 0.13)	0.92 (0.82 to 1.02)	0.05 (-0.06, 0.16)
	Somatropin 0.034 mg/kg/d	0.48 (0.42, 0.54)		0.87 (0.78 to 0.96)	

Abbreviations: d, day; ITC, indirect treatment comparison; SD, standard deviation; SDS, standard deviation score; SE, standard error; wk, week. Data are mean (95% CI) unless otherwise indicated.
† Least square mean.

Base case network results

Results from the base case are presented in Table 29 (and Appendix K) for the FE and RE analysis. Results from the RE model showed no significant differences between somapacitan and somatrogon. Results from the FE model were similar. Similar trends were observed with height SDS results compared with AHV results at Week 26 and Week 52.

Table 29: Base case results for height SDS at Week 26 and Week 52; ITC Part 1

	Difference (95% CrI) (vs somapacitan)	
	FE model	**RE model**
Week 26		
Somatrogon	0.10 (−0.02, 0.21)	0.08 (−0.08, 0.23)
Somatropin	0.05 (−0.04, 0.14)	0.04 (−0.07, 0.14)
DIC	17.10	16.65
Residual deviance	11.11	10.38
Week 52		
Somatrogon	0.02 (−0.14, 0.19)	0.00 (−0.23, 0.20)
Somatropin	−0.02 (−0.13, 0.10)	−0.03 (−0.20, 0.10)
DIC	18.88	17.74
Residual deviance	12.87	11.35

Abbreviations: CrI, credible interval; DIC, deviance information criteria; FE, fixed effect, ITC, indirect treatment comparison; RE, random effects; SDS: standardised deviation score.
Results are presented as median treatment differences and an associated 95% CrI for comparators versus somapacitan. Positive differences favour comparator treatments.
Bolded cells indicate the 95% CrI does not contain 0.

Safety

Overall AEs

Across the trials, somapacitan and somatrogon were generally well-tolerated and demonstrated comparable safety to somatropin. Most of the AEs reported were mild to moderate in severity. The proportion of patients experiencing at least one AE across trials varied from approximately 60% to 100% through 52 weeks of treatment (Table 30).

Table 30: AEs through 52 weeks of treatment; ITC Part 1

Trial	Arm	N	Any AE, n (%)	Serious AE, n (%)	Severe AE, n (%)
REAL 3	Somapacitan 0.16 mg/kg/wk	14	13 (92.9)	1 (7.1)	0
	Somatropin 0.034 mg/kg/d	14	14 (100)	1 (7.1)	0
REAL 4	Somapacitan 0.16 mg/kg/wk	132	94 (71.2)	6 (4.5)	4 (3.0)
	Somatropin 0.034 mg/kg/d	68	41 (60.3)	2 (2.9)	1 (1.5)
Opko II	Somatrogon 0.66 mg/kg/wk	14	10 (71.4)	0	0
	Somatropin 0.034 mg/kg/d	11	8 (72.7)	0	0
Opko III	Somatrogon 0.66 mg/kg/wk	109	95 (87.2)	3 (2.8)	9 (8.3)
	Somatropin 0.034 mg/kg/d	115	97 (84.3)	2 (1.7)	6 (5.2)

Abbreviations: AE, adverse event; d, day; ITC, indirect treatment comparison; wk, week.

Injection site AEs

Injection site reactions, injection site pain, and other injection site-related AEs were reported variably. Across trials, injection site pain was reported by a considerably higher proportion of patients in the somatrogon trials compared with somapacitan trials (Table 31).

In REAL 3, no injection site reactions were reported with somapacitan 0.16 mg/kg/week or somatropin throughout the 52 weeks. In REAL 4, a similar proportion of patients treated with somapacitan 0.16 mg/kg/week and somatropin experienced injection site reactions (5.3% vs 5.9%) throughout the 52 weeks; the same proportion in each arm (1.5%) reported injection site pain that was mild and transient.

The somatrogon trials (Opko II, Opko III) reported injection pain using a Pain Assessment Scale ranging from 0 to 5, with 5 indicating greatest pain. A patient was considered to have injection site pain if they rated pain as 4 or 5. In these cases, an investigator subsequently classified the pain as mild, moderate, or severe. In Opko II, erythema, swelling, and hematoma were each reported in one (7.1%) patient treated with somatrogon 0.66 mg/kg/wk and no patients treated with somatropin. Patients reported little injection site pain (pain score 2–3), except for one patient treated with somatrogon 0.66 mg/kg/wk who experienced severe pain for four days. In Opko III, injection site pain (pain score ≥4) was reported by more patients treated with somatrogon 0.66 mg/kg/wk compared with somatropin (39.4% vs 25.2%); severe injection site pain was experienced by five (4.6%) patients treated with somatrogon 0.66 mg/kg/wk and three (2.6%) patients treated with somatropin.

In the somatrogon trials, injection site pain occurred more frequently with somatrogon compared with somatropin. Overall, injection site pain AEs were considerably higher for somatrogon compared with somapacitan. This could be due to larger volume injection with somatrogon compared with somapacitan, the needle size used in each device, or preservatives present in the respective buffer solutions (85, 86).

Table 31: Injection AEs through 52 weeks of treatment; ITC Part 1

Trial	Arm	N	Injection site AE, n (%)	Injection site pain, n (%)	Severe injection site pain, n (%)
REAL 3	Somapacitan 0.16 mg/kg/wk	14	0	0	0
	Somatropin 0.034 mg/kg/d	14	0	0	0
REAL 4	Somapacitan 0.16 mg/kg/wk	132	7 (5.3)	2 (1.5)	0
	Somatropin 0.034 mg/kg/d	68	4 (5.9)	1 (1.5)	0
Opko II	Somatrogon 0.66 mg/kg/wk	14	NR	NR	1 (7.1)
	Somatropin 0.034 mg/kg/d	11	NR	NR	0
Opko III	Somatrogon 0.66 mg/kg/wk	109	NR	43 (39.4)	5 (4.6)
	Somatropin 0.034 mg/kg/d	115	NR	29 (25.2)	3 (2.6)

Abbreviations: AE, adverse event; ITC, indirect treatment comparison; NR: not reported; wk, week.

Antibodies

The incidence of non-neutralising and neutralising antibodies was reported across trials. Overall, rates of non-neutralising antibodies varied up to 77% in a trial of somatrogon. However, rates of antibodies that neutralise and may inhibit the circulating GH were uncommon across all trials (87). Where reported, analyses from trials showed that the presence of antibodies did not have any considerable effect on efficacy or safety.

In REAL 3, one (7.1%) patient treated with somatropin had persistent non-neutralising anti-hGH antibodies of low titre, and two (14.2%) patients treated with somapacitan 0.16 mg/kg/week had one single transient measurement of low titre, non-neutralising, anti-somapacitan antibodies throughout 52 weeks. No neutralising anti-hGH or anti-somapacitan antibodies were observed. In REAL 4, two (1.5%) patients treated with somapacitan, and one patient treated with somatropin (1.5%) had ≥2 consecutive positive non-neutralising antibody samples throughout 52 weeks. No neutralising anti-hGH or anti-somapacitan antibodies were observed.

In Opko II, two (14.3%) patients treated with somatrogon 0.66 mg/kg/wk and one (9.1%) patient treated with somatropin had anti-drug antibodies. There was no incidence of anti-CTP antibodies. In Opko III, 84 (77.1%) patients treated with 0.66 mg/kg/week tested

positive for anti-drug antibodies compared with 18 (15.6%) patients treated with somatropin.

Overall, rates of antibodies varied considerably across the trials. Analyses showed children who were positive for antibodies did not experience reduced efficacy or safety issues compared with those without antibodies. The rates of antibodies were considerably high in the somatrogon trials; additionally, neutralising antibodies were observed with somatrogon but not with somapacitan.

B.3.9.6.2 Results for Part 2 (>52 weeks)

Four trials included evidence from an extension phase and were considered to inform analyses of Part 2 (>52 weeks). The evidence from these extensions was largely limited to single-arm trials; therefore, synthesis of outcomes consists of qualitative summaries of results only. For further details see the ITC report (80).

B.3.9.6.3 Conclusions

The comparative efficacy and safety of somapacitan and somatrogon for the treatment of GHD was summarised qualitatively and assessed using indirect analysis.

The Part 1 results (≤52 weeks) showed that there were no significant differences between somapacitan and somatrogon. The Part 2 results (>52 weeks) showed sustained efficacy with somapacitan and somatrogon during continued treatment (see the ITC report). Mean AHV showed a sustained growth rate and results for height SDS reflected height normalisation over time. This suggests that somapacitan and somatrogon address the clinical goals of GH treatment for patients with GHD and can be considered as equivalent in terms of efficacy outcomes.

Somapacitan and somatrogon were generally well-tolerated in the Part 1 analyses with most AEs reported as mild or moderate in severity. The rates of injection site pain and antibodies were considerably higher in the somatrogon trials compared with somapacitan; additionally, neutralising antibodies were observed with somatrogon but not with somapacitan. The cause of the higher injection site pain could be due to different needle sizes, or preservatives and buffer solution used.

Both somapacitan and somatrogon demonstrated equivalent efficacy and were non-inferior to somatropin with fewer injections per year; however, lower injection site pain rates compared with somatrogon suggest that somapacitan is the more favourable treatment as injection site pain is often cited as a reason for poor treatment adherence (discussed in Section B.1.3.4.2).

B.3.9.6.4 Heterogeneity and inconsistency

The main limitation of the network was the small number of relevant trials (as is expected for a rare disease such as GHD), and the lack of trial replication, which limited the information on heterogeneity in the network. In the case of the RE models, this necessitated the use of more informative priors for between-trial heterogeneity. An attempt was made to leverage the shared mode of action of the various GHs to calculate an appropriate prior, but it was potentially problematic that the same data were used to

both calculate the prior and update it, and the former was not taken from an external source instead.

Imbalance in prognostic factors (such as age, race and gender) between arms in the trials was limited and adjusted for by using them as covariates in the statistical analyses. However, there were differences between the trials when it comes to these prognostic factors. No effect modification was expected, so this is not considered a severe limitation. Furthermore, height SDS and HVSDS are standardised for age and gender.

In the safety data analysed, injection site pain and antibodies were reported by a considerably higher proportion of patients in the somatrogon trials. However, as noted by the EMA during their assessment of somatrogon, differences in how injection related AEs were recorded makes it difficult to compare rates across treatment arms. In a somatrogon trial, injection site pain was recorded weekly, therefore capturing the once-weekly somatrogon injection but only one of the seven daily somatropin injections. The same difficulty in comparing rates across arms within this trial should also be extended to comparing rates across trials. Nonetheless, the rate of injection site pain with somatrogon is considerably high and may be due to larger injection volumes, preservatives in buffer solution, needle size, or other needle features.

B.3.10 *Adverse reactions*

B.3.10.1 *Studies reported in Section B.3.2*

Adverse reactions were recorded throughout the somapacitan clinical development programme; the identification, study details, methodologies, and results of the somapacitan trials are presented in Section B.3.2 to Section B.3.6. Key safety evidence from the Phase II and III studies of somapacitan are presented below.

B.3.10.1.1 REAL 4 safety outcomes

Extent of exposure

Total exposure was approximately 2-fold higher for somapacitan (~133 patient years of exposure [PYE]) compared with somatropin (~69 PYE), reflecting the 2:1 randomisation ratio. The extent of exposure is summarised in Table 32.

Adherence

The majority of children received the planned treatment with a mean adherence among children on treatment (i.e., not counting exposure duration in one child after discontinuing treatment) of 95.8% for the somapacitan group and 88.3% for the somatropin group. Adherence is summarised in Table 33.

Table 32: Summary of exposure; SAS, REAL 4

	Somapacitan Week 0–52 n=132	Somatropin Week 0–52 n=68	Somapacitan/ somapacitan Week 52–104 n=131	Somatropin/ somapacitan Week 52–104 n=68	Somapacitan/ somapacitan Week 0–104 n=132	Somapacitan pooled n=200
Total exposure (days)	48,734	25,166	46,039	24,498	94,773	119,271
Exposure (days)						
N	132	68	131	68	132	200
Mean (SD)	369.2 (28.8)	370.1 (3.7)	351.4 (41.9)	360.3 (8.4)	718.0 (70.6)	596.4 (179.4)

Abbreviations: SAS, safety analysis set; SD, standard deviation.
Exposure days in the treatment period are calculated as time from first date on randomised treatment to last date on randomised treatment for somatropin and plus six days for somapacitan or to Visit 7 (Week 52), whichever comes first.

Table 33: Summary of adherence (%) until treatment discontinuation; FAS, REAL 4

	Somapacitan Week 0–52 n=132	Somatropin Week 0–52 n=68	Total Week 0–52 n=200	Somapacitan/ somapacitan Week 52–104 n=131	Somatropin/ somapacitan Week 52–104 n=68	Somapacitan/ somapacitan Week 0–104 n=132	Somapacitan pooled n=200
Number of reported dosings	6,708	23,710	30,418	6,209	3,263	12,917	16,180
Number of dosings in adherence	6,691	22,203	28,894	6,173	3,205	12,864	16,069
Adherence according to diary,† mean (SD)	95.8 (10.19)	88.3 (23.57)	93.3 (16.38)	88.8 (16.58)	88.8 (15.95)	92.7 (13.79)	91.4 (14.64)

Abbreviations: FAS, full analysis set; SD, standard deviation.
† Number of reported dosings from diary divided by number of planned dosings, multiplied by 100.

Adverse events

Main trial (Weeks 0–52)

The safety profile of once-weekly somapacitan was similar to the well-known safety profile of somatropin. In total, 135 (67.5%) children experienced 457 AEs during the 52 weeks of treatment, with 94 (71.2%) children reporting 310 AEs in the somapacitan group compared with 41 (60.3%) children reporting 147 AEs in the somatropin group.

The majority (98%) of AEs were mild (82%) or moderate (16%) and considered unlikely to be related to the trial product. No AEs in the somapacitan group led to discontinuation of trial product and no new safety issues or local tolerability issues were identified. The most frequent AEs (≥5%) in the somapacitan group were events commonly observed in children including (by proportion) headache, nasopharyngitis, pain in extremity and pyrexia (Table 34). Low SAE rates were observed (eight SAEs in six children in the somapacitan group, and three SAEs in two children in the somatropin group). All SAEs were resolved and were assessed by the investigator as unlikely related to trial product. No AEs led to discontinuation of trial product (Table 34).

Pain in extremities was reported more frequently for somapacitan (9.1%) than for somatropin (2.9%). In the somapacitan group, all 17 cases of pain in extremities were non-serious, 15 of 17 were mild and 13 of 17 were resolved. Growing pain is a well-known effect of GH treatment. Otherwise, there were no considerable differences in the type and frequency of frequent AEs between somapacitan and somatropin.

Safety extension (Weeks 52–104)

Lower AE reporting rates were observed in the second year of treatment (Weeks 52–104) compared with the first year (Weeks 0–52) both for the somapacitan/somapacitan group (166.6 AEs/100 PYE vs 245.0 AEs/100 PYE) and for the subjects switching from somatropin to somapacitan from Week 52 (125.3 AEs/100 PYE vs 217.1 AEs/100 PYE) (Table 34).

The most frequent AEs (≥5%) in the somapacitan/somapacitan (Weeks 0–104) group were events commonly observed in children including (by decreasing proportion) nasopharyngitis (15.9%), headache (14.4%), pain in extremity (11.4%) and pyrexia (10.6%). The type of the most frequent AEs (≥5%) was similar between somatropin (Weeks 0–52) and somatropin/somapacitan (Weeks 52–104) (Table 34). Low SAE rates were observed in the extension (four SAEs in three children in the somapacitan/somapacitan group, and no SAEs in the somatropin/somapacitan group). All SAEs were resolved and were assessed by the investigator as unlikely related to trial product. No AEs led to discontinuation of trial product.

AEs considered possibly or probably related to somapacitan were less frequently reported during the second year of treatment (somapacitan/somapacitan [Weeks 52–104] vs somapacitan [Weeks 0–52]) (Table 34). A lower rate of AEs considered possibly or probably related was also reported in the somatropin/somapacitan (Week 52–104) vs somatropin (Week 0–52) groups, though a similar proportion of subjects reported possibly or probably related AEs in these groups. Pain in extremity was reported less

frequently during the second year (Week 52–104) of treatment (somapacitan/ somapacitan 3.8%; somatropin/somapacitan 0.0%) compared with the first year.

Injection site reactions

Comparable low proportions of children experienced injection site reactions (reported as AEs) in the somapacitan group (5.3%) and the somatropin group (5.9%) (Table 35). In total, seven children experienced nine AEs in the somapacitan group compared with four children who experienced four AEs in the somatropin group. All cases were of mild severity, and 11 of 13 AEs were resolved. The frequency of injection site reactions was similar in the somapacitan and somatropin treatment groups (6.7 and 5.8 events per 100 patient years, respectively). Injection site pain was reported in one patient (1.5%) in the somatropin group, and two patients (1.5%) in the somapacitan group. None of the injection site reactions were considered SAEs. There were no injection site reactions linked to premature treatment discontinuation.

A lower proportion of subjects experienced injection site reactions in the trial extension (somapacitan/somapacitan, 2.3%; somatropin/somapacitan, 2.9%) compared with the 52-week main period (somapacitan group, 5.3%; and somatropin group, 5.9%). None of the injection site reactions were reported as SAEs. There were no injection site reactions linked to premature treatment discontinuation. All cases were of mild severity.

Table 34: Summary of AEs, REAL 4

Adverse events	Somapacitan Week 0–52 (n=132) (%)	Somatropin Week 0–52 (n=68) (%)	Somapacitan/ somapacitan Week 52–104 (n=131) (%)	Somatropin/ somapacitan Week 52–104 (n=68) (%)	Somapacitan/ somapacitan Week 0–104 (n=132) (%)
≥1 AE	94 (71.2)	41 (60.3)	82 (62.6)	29 (57.4)	114 (86.4)
≥1 AEs possibly or probably related to trial product	32 (42.3)	13 (19.1)	12 (9.2)	Somapacitan: 10 (14.7) Somatropin: 5 (7.4)	39 (29.5)
≥1 SAE	6 (4.5)	2 (2.9)	3 (2.3)	0 (0)	9 (6.8)
≥1 SAEs possibly or probably related to trial product	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Deaths	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Discontinuation due to AEs	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
AEs occurring in ≥5% of patients					
Headache	16 (12.1)	6 (8.8)	3 (2.3)	3 (4.4)	-
Nasopharyngitis	15 (11.4)	7 (10.3)	11 (8.4)	5 (7.4)	-
Pain in extremity	12 (9.1)	2 (2.9)	5 (3.8)	2 (2.9)	-
Pyrexia	10 (7.6)	7 (10.3)	11 (8.4)	5 (7.4)	-
Bronchitis	4 (3.0)	5 (7.4)	5 (3.8)	2 (2.9)	-
Vomiting	6 (4.5)	4 (5.9)	5 (3.8)	1 (1.5)	-

Abbreviations: AE, adverse event; SAE, serious adverse event.

Table 35: Summary of injection site reaction AEs by SOC and preferred term; SAS, REAL 4

	Somapacitan Week 0–52				Somatropin Week 0–52				Total Week 0–52				Somapacitan/ somapacitan Week 52–104				Somatropin/ somapacitan Week 52–104				Somapacitan/ somapacitan Week 0–104			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Total child years at risk	133.4				69.1				202.5				126.1				67.1				259.5			
General disorders and administration site conditions	7	(5.3)	9	6.7	4	(5.9)	4	5.8	11	(5.5)	13	6.4	3	(2.3)	6	4.8	2	(2.9)	2	3.0	10	(7.6)	15	5.8
Injection site bruising	2	(1.5)	2	1.5	2	(2.9)	2	2.9	4	(2.0)	4	2.0	1	(0.8)	3	2.4	0	-	-	-	3	(2.3)	5	1.9
Injection site pain	2	(1.5)	2	1.5	1	(1.5)	1	1.4	3	(1.5)	3	1.5	0	-	-	-	0	-	-	-	2	(1.5)	4	1.5
Injection site haematoma	2	(1.5)	4	3.0	0	-	-	-	2	(1.0)	4	2.0	0	-	-	-	0	-	-	-	2	(1.5)	2	0.8
Injection site hypersensitivity	0	-	-	-	1	(1.5)	1	1.4	1	(0.5)	1	0.5	0	-	-	-	1	(1.5)	1	1.5	0	-	-	-
Injection site swelling	1	(0.8)	1	0.7	0	-	-	-	1	(0.5)	1	0.5	0	-	-	-	0	-	-	-	1	(0.8)	1	0.4

Abbreviations: AE, adverse event; E, number of events; R, event rate per 100 patient years at risk; SAS, safety analysis set; SOC, standard of care.
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn children, and with an onset after the first administration of trial product and up until Visit 7 (Week 52) or 14 days after last trial drug administration, whichever comes first, for all other children, are included.
MedDRA version 24.1.

Antibodies

All antibody positive samples were negative for *in vitro* neutralising antibodies (Table 36). Low titre, non-neutralising antibodies were detected in 20 (15.2%) somapacitan-treated children and seven (10.3%) children treated with somatropin in the 52-week main trial period. Of these, two (1.5%) children in the somapacitan group and one (1.5%) child in the somatropin group had at least two consecutive positive antibody samples.

Anti-drug antibodies were detected in 25 (18.9%) subjects in the somapacitan/ somapacitan group from Weeks 0–104 (including four subjects with positive antibodies at baseline). Of these, four (3%) children in the somapacitan group and three (4.4%) children in the somatropin group had at least two consecutive positive antibody samples. No neutralising activity was detected for any positive antibody samples.

Table 36: Summary of GH antibodies by visit; SAS, REAL 4

	Somapacitan N=132	**Somatropin N=68**
Visit 2 (Week 0), n (%)	132 (100.0)	68 (100.0)
Positive antibodies	4 (3.0)	0 (0)
Cross reacting	0 (0)	NA
Neutralising	0 (0)	0 (0)
Visit 4 (Week 13)	123 (100.0)	64 (100.0)
Positive antibodies	10 (8.1)	5 (7.8)
Cross reacting	2 (1.6)	NA
Neutralising	0 (0)	0 (0)
Visit 7 (Week 52)	132 (100.0)	67 (100.0)
Positive antibodies	8 (6.1)	3 (4.5)
Cross reacting	4 (3.0)	NA
Neutralising	0 (0)	0 (0)
Visit 9 (Week 78)	123 (100)	66 (100.0)
Positive antibodies	7 (5.7)	4 (6.1)
Cross reacting	5 (4.1)	3 (4.5)
Neutralising	0 (0)	0 (0)
Visit 11 (Week 104)	127 (100.0)	67 (100.0)
Positive antibodies	5 (3.9)	4 (6.0)
Cross reacting	5 (3.9)	4 (6.0)
Neutralising	0 (0)	0 (0)

	Somapacitan N=132	Somatropin N=68
Children with positive antibody sample, Week 0–52	20 (15.2)	7 (10.3)
Children with two consecutive positive antibody samples, Week 0–52	2 (1.5)	1 (1.5)
Children with positive antibody sample, Week 52–104	9 (6.8)	5 (7.4)
Children with two consecutive positive antibody samples, Week 52–104	3 (2.3)	3 (4.4)
Children with positive antibody sample, Week 0–104	25 (18.9)	10 (14.7)
Children with two consecutive positive antibody samples, Week 0–104	4 (3.0)	3 (4.4)

Abbreviations: GH, growth hormone; NA, not applicable; SAS, safety analysis set.
Note: The four children with positive antibodies at baseline are most likely false positive findings as the children were naïve to GH treatment and did not have positive antibodies at the following visit.

Safety conclusions for REAL 4

The results of REAL 4 demonstrate the comparable safety profile of once-weekly somapacitan vs daily somatropin in children with GHD, with benefits maintained for up to 104 weeks of treatment:

- Somapacitan was well-tolerated with no new safety issues identified; the majority of AEs in the 52-week main trial and 52-week extension period were mild or moderate, and most AEs were associated with growing pains experienced by children. All SAEs in the main trial and extension were resolved and assessed by the investigator to be unlikely related to trial product
- Injection site pain was reported in one patient (1.5%) in the somatropin group, and two patients (1.5%) in the somapacitan group
- There were no discontinuations due to AEs and no deaths reported during the main trial or extension period
- Adherence was high in both treatment groups in the main trial period with 95.8% and 88.3% of patients taking scheduled dosages as reported by e-diary logs for somapacitan and somatropin, respectively
- No neutralising antibodies were detected in children on somapacitan treatment in the main trial or the extension period

B.3.10.1.2 REAL 3 safety outcomes

Extent of exposure (up to Week 52 and Week 156)

In total, 45 children with GHD were exposed to somapacitan, and 14 children with GHD were exposed to somatropin for up to 156 weeks. The median exposure was similar across treatment arms. Exposure during the trial is summarised in Table 37.

Table 37: Summary of exposure; SAS, REAL 3

	Somapacitan (0.04/0.16 mg/kg/week)	Somapacitan (0.08/0.16 mg/kg/week)	Somapacitan (0.16/0.16 mg/kg/week)	Somapacitan pooled	Somatropin (0.034 mg/kg/day)
N	16	15	14	45	14
Total exposure (days)	14,667	15,855	14,665	45,187	12,901
Exposure (days)					
N	16	15	14	45	14
Mean (SD)	916.7 (396.8)	1,057.0 (190.1)	1,047.5 (194.7)	1,004.2 (284.1)	921.5 (367.6)

Abbreviations: SAS, safety analysis set; SD, standard deviation.
Exposure days in the treatment period are calculated as time from first date on randomised treatment to last date on randomised treatment for somatropin and plus six days for somapacitan or to Week 156, whichever comes first. All subjects randomised to double-blind somapacitan 0.04, 0.08 or 0.16 mg/kg/week in Weeks 0–52 were allocated to open-label somapacitan 0.16 mg/kg/week in the safety extension (Weeks 52–156).

Adherence (up to Week 52 and Week 156)

The majority of children received the planned treatment; mean adherence among children on treatment (i.e. not counting exposure duration in two children after discontinuing treatment) was 92.2% for the somapacitan group and 87.2% for the somatropin group. Adherence is summarised in Table 38.

Table 38: Summary of adherence (%) until treatment discontinuation; FAS, REAL 3

	Somapacitan n=43	Somatropin n=14
Number of reported dosings	6,276	12,738
Number of dosings in adherence	6,264	12,735
Adherence according to diary,† mean (SD)	92.2 (17.35)	87.2 (29.87)

Abbreviations: FAS, full analysis set; SD, standard deviation.
† Number of reported dosings from diary in adherence divided by number of planned dosings multiplied by 100.
The two children discontinuing treatment prematurely in the somapacitan 0.04/0.16 mg/kg/week treatment arm were not included in this analysis as they were excluded from the FAS.

Adverse events (up to Week 52 and Week 156)

In total, 54 (91.5%) children experienced 413 AEs during the 156 weeks of the trial. AE rates were similar between the somapacitan treatment arms (somapacitan pooled, 258.1/100 PYE) and the somatropin treatment arm (267.7/100 PYE). The most common AEs observed in ≥10% of children (AEs observed in at least two children in ≥1 treatment arm) included pyrexia, influenza, nasopharyngitis, constipation, vomiting, rhinitis allergic and gastroenteritis (Table 39). The majority of AEs were of mild (87.2%) or moderate (12.1%) severity and three AEs were classified as severe.

The majority of AEs (93.9%) were considered unlikely related to trial product by the investigator. Of the 59 children included in the trial, 14 children across treatment groups had 25 AEs that were considered possibly (12 AEs) or probably (13 AEs) related to trial product. At the end of the 156-week trial period, the majority (90.6%) of AEs across treatment groups were reported as 'Recovered/Resolved'.

In total, six (10.2%) children had 11 SAEs during the 156 weeks of treatment. The event rates were similar for the somapacitan and somatropin treatment arms (6.5 SAEs/100 PYE and 8.5 SAEs/100 PYE, respectively). Between somapacitan treatment arms, the event rate was lowest for somapacitan 0.04/0.16 mg/kg/week (2.5 SAEs/100 PYE) followed by somapacitan 0.08/0.16 mg/kg/week (6.9 SAEs/100 PYE) and somapacitan 0.16/0.16 mg/kg/week (10 SAEs/100 PYE). Nine out of the 11 SAEs were evaluated as unlikely related to trial product. Two SAEs (generalised oedema and vomiting) in one child were evaluated as probably related to trial product.

No deaths occurred during the trial.

Table 39: Summary of AEs, REAL 3

Adverse events	Somapacitan (n=45)	Somatropin (n=14)
≥1 AE	40 (88.9)	14 (100.0)
≥1 AEs possibly or probably related to trial product	10 (22.2)	4 (28.6)
≥1 SAE	2 (14.3)	4 (8.9)
≥1 SAEs possibly or probably related to trial product	1 (2.2)	0 (0)
Deaths	0 (0)	0 (0)
Discontinuation due to AEs	0 (0)	1 (7.1)
AEs occurring in ≥10% of patients		
Pyrexia	18 (40.0)	2 (14.3)
Influenza	9 (20.0)	3 (21.4)
Nasopharyngitis	7 (15.6)	3 (21.4)
Constipation	5 (11.1)	0 (0)
Vomiting	6 (13.3)	1 (7.1)
Rhinitis allergic	5 (11.1)	3 (21.4)

Abbreviations: AE, adverse event; SAE, serious adverse event.

Injection site reactions (up to Week 52 and Week 156)

In total, five children experienced nine injection site-related AEs reported by the following preferred terms: 'Haemorrhage Subcutaneous', 'Haematoma' (two AEs), 'Injection Site Haematoma', 'lipoatrophy (two AEs)', 'Hip Deformity', 'Skin Atrophy' and 'Injection Site Reaction'. Eight injection site reactions were observed in the somapacitan treatment arms (somapacitan 0.04/0.16 mg/kg/week: five; somapacitan 0.08/0.16 mg/kg/week: two; somapacitan 0.16/0.16 mg/kg/week: one) and one in the somatropin treatment arm. Seven AEs were of mild severity and two were severe.

None of the injection site-related AEs were SAEs. Eight injection site reactions were considered possibly (seven)/probably (one) related to trial product and one was considered unlikely related.

Nine injection site reactions in four children were reported as AEs. Of these, seven AEs were considered as mild and two as severe. Eight injection site reactions were observed in the somapacitan treatment arms and one in the somatropin treatment arm.

Antibodies (up to Week 52 and Week 156)

During the 156 weeks of the trial, low titre non-neutralising antibodies were observed in 10 somapacitan-treated children. In seven children, somapacitan antibodies were observed at single time points (somapacitan 0.04/0.16 mg/kg/week: four children; somapacitan 0.08/0.16 mg/kg/week: two children; somapacitan 0.16/0.16 mg/kg/week: one child). In three children, positive samples were observed in two (somapacitan 0.16/0.16 mg/kg/week), three (somapacitan 0.04/0.16 mg/kg/week) and four (somapacitan 0.08/0.16 mg/kg/week) consecutive samples, respectively.

One child in the somatropin treatment arm had persistent anti-hGH antibodies of low titre from Visit 4 (Week 13) to Visit 16 (follow-up visit for the present trial period). All antibody positive samples were negative for *in vitro* neutralising antibodies.

Safety conclusions for REAL 3

- Somapacitan was well-tolerated at all doses investigated (0.04, 0.08 and 0.16 mg/kg/week), with no new clinically significant safety or local tolerability issues identified. After 156 weeks of treatment, 54 (91.5%) children experienced 413 AEs, the majority of which were classified as mild (87.1%) or moderate (12.1%). The majority of AEs (93.9%) were evaluated as unlikely related to trial product by the investigator
- Six (10.2%) children had 11 SAEs during the 156 weeks of treatment. No children withdrew from the trial due to AEs. No injection site reactions were reported as SAEs
- All antibody positive samples were negative for in vitro neutralising antibodies
- Overall, the safety data showed that somapacitan has a favourable long-term safety profile that is similar to daily GH treatment. The safety profile with somapacitan from Weeks 156–208 was consistent with the first 156 weeks of the trial (see Appendix J for results of the ongoing long-term safety extension). Data did not indicate any relevant differences in safety parameters from Week 156 to 208 between the

39 children who had received somapacitan at Week 0 compared with the 11 children on somapacitan who switched from somatropin to somapacitan at Week 156. For the children switching to somapacitan from somatropin, no injection site reactions and no medication errors were reported

- No new safety issues were identified in the children in cohorts I, II, and III during the long-term safety extension (Appendix J)

B.3.10.2 *Safety overview*

Overall, the available data show that treatment with once-weekly somapacitan is generally well-tolerated, with a similar safety profile to once-daily somatropin in the Phase III REAL 4 study (up to 52 weeks) and the Phase II REAL 3 study (up to 156 weeks). In REAL 4 and REAL 3, the majority of AEs were mild or moderate.

AEs considered to be possibly or probably related to trial product, such as pain in extremities, would be expected in children and are common when patients undergo accelerated growth. The frequency of injection site reactions was low, and no neutralising antibodies were detected.

The comparable safety profile of somapacitan vs somatropin is highly promising given that somapacitan therapy is administered in larger dosages per injection. No new safety issues were identified during the Phase II REAL 3 long-term safety extension in previously-treated (Cohort I) or treatment-naïve patients (Cohorts II and III) (Appendix J).

B.3.11 *Conclusions about comparable health benefit and safety*

In the Phase III REAL 4 trial, once-weekly somapacitan demonstrated similar HV after 52 weeks of treatment compared with once-daily somatropin (11.2 cm and 11.7 cm, respectively). Non-inferiority for somapacitan vs somatropin at Week 52 was confirmed for both the treatment policy and hypothetical estimands, indicating comparable efficacy. These results were supported by sensitivity and per protocol analyses. The continued efficacy of somapacitan was demonstrated in the REAL 4 extension, with increases in HV sustained to Week 104 in both the somatropin/somapacitan and somapacitan/ somapacitan groups.

Somapacitan demonstrated a similar safety profile to that of once-daily somatropin. Somapacitan was well-tolerated with no new safety issues identified. The majority of AEs were mild or moderate and most AEs were likely related to growing pains experienced by children. All SAEs were resolved and assessed by the investigator to be unlikely related to trial product. No neutralising antibodies were detected in the somapacitan treatment arm.

Data from REAL 4 also show the potential for improved treatment adherence with somapacitan vs daily GH; in the main trial phase (to Week 52), mean adherence according to diary[h] was 95.8% with somapacitan vs 88.3% with somatropin.

[h] Number of reported dosings divided by number of planned dosings, multiplied by 100.

In the ITC of somapacitan vs once-weekly somatrogon (conducted in the absence of head-to-head trials), somapacitan demonstrated similar HV compared with somatrogon after 52 weeks of treatment, indicating non-inferiority with the only other approved weekly GH therapy. The results from the ITC showed that somapacitan and somatrogon were generally well-tolerated and demonstrated similar safety to somatropin. Injection site pain was more commonly reportedly in the somatrogon trials compared with the somapacitan trials. In the somatrogon trials, injection site pain occurred more frequently with somatrogon compared with somatropin.

B.3.12 *Ongoing studies*

The long-term safety extensions to REAL 3 (please see Appendix J for available results up to Week 208) and REAL 4 are ongoing.

B.4. Cost-comparison analysis

B.4.1 *Changes in service provision and management*

Service provisions for the existing once-daily and once-weekly GH products have previously been outlined in TA188 and TA863, respectively (see Section B.2.2). The introduction of somapacitan is not expected to have an impact on service provision or management (29).

B.4.2 *Cost comparison analysis inputs and assumptions*

B.4.2.1 *Features of the cost comparison analysis*

Cost inputs considered in the analysis comprised of drug acquisition costs only; treatment costs per year per patient were estimated. Acquisition costs were sourced from British National Formulary (BNF) (88). As per the cost comparison methodology, healthcare resource use did not have an impact on the results because it is assumed to be the same between comparators.

Costs were calculated for the average age and weight of a patient for children with GHD. The average weight (40 kg) 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 database as part of the assumption used in TA188, the rounded midpoint age (13 years). The time horizon was 1 year, in line with TA188.

The per-milligram treatment dose was based on the REAL 4 Phase III clinical trial (see Section B.3.3) for both somapacitan and somatropin. The dosages applied to the model were 0.16 mg/kg/week and an equivalent dose of 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week) for somapacitan and somatropin, respectively. The dose of 0.034 mg/kg/day was the most appropriate dose given that in REAL 4, patients started the trial on this dose and ended with the same average dose. For somatrogon a dose of 0.66 mg/kg/week was used as per the cost comparison in TA863.

Due to the nature of a cost-comparison model, and because there is no difference in efficacy or treatment duration across the relevant comparators, discontinuation and discounting were not factored into the analysis. These were also not considered as part of the base case analysis for the assessment group model in TA188.

For simplicity, compliance (adherence) was not factored into the analysis. This is a conservative approach, since there is evidence to suggest that missing more than one injection per week leads to reduced HV compared with fully adherent patients (46, 48), and because somapacitan has the potential to improve treatment outcomes by reducing treatment burden and increasing compliance and adherence. Furthermore, there may be improvements in paediatric patients' QoL through reduced life interference and treatment burden. These additional benefits are not captured in the cost comparison analysis and therefore the analysis could be considered an underestimation of the value of somapacitan to the NHS. In a 2022 time trade-off (TTO) study, once-daily GH therapies were associated with a greater disutility compared with once-weekly GH therapies

among the general population evaluating health states as themselves with GHD, and as a parent of a child with GHD (54).

According to the pairwise ITC (see Section B.3.9), somapacitan demonstrated lower rates of injection site pain compared with somatrogon. In the TTO study above, avoiding injection pain was associated with significant utility gain from the perspective of a person with GHD (gain of 0.030 (95% CI; 0.026, 0.035; p<0.001)) and as a parent of a child with GHD (gain of 0.044 (95% CI; 0.038, 0.051; p<0.001) (54) (Section B.4.2.7).

B.4.2.2 *Intervention and comparators' acquisition costs*

Unit costs for each comparator and somapacitan are summarised in Table 40. The daily GH 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 settings for paediatric GHD and is in line with the posology licensed for its use. This was also the dose investigated in the pivotal study for somapacitan where non-inferiority to somatropin was demonstrated (71, 73). Dosing aligned with real-world practice administration used by HCPs in England (29).

The per mg/kg costs vary across the daily somatropin therapies, which were all previously deemed cost-effective as part of TA188 (2) and TA863 (1).

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

Table 40: Acquisition costs of the intervention and comparator technologies

	Somapacitan	Somatrogon	Humatrope®	Zomacton®	NutropinAq®	Norditropin®	Genotropin®	Omnitrope®	Saizen®
Pharmaceutical formulation	Solution for injection in a pre-filled pen	Solution for injection	Powder and solvent for solution for injection	Powder and solvent for solution for injection	Solution for injection	Solution for injection in a pre-filled pen	Powder and solvent for solution for injection	Solution for injection in a cartridge	Two pharmaceutical forms are available: Solution for injection in a cartridge 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	Primarily Hospital setting
Acquisition cost (excluding VAT)*	[redacted]	24 mg/1.2 ml, 1 = £166.08 60 mg/1.2 ml, 1 = £415.20	6 mg, 1 = £108.00 12 mg, 1 = £216.00 24 mg, 1 = £432.00	4 mg, 1 = £68.28	10 mg/2 ml, 1 = £203.00 3 = £609.00	FlexPro: 5 mg/1.5 ml, 1 = £106.35 10 mg/1.5 ml, 1 = £212.70 15 mg/1.5 ml, 1 = £319.05 NordiFlex: 5 mg/1.5 ml, 1 = £115.90 10 mg/1.5 ml, 1 = £231.80 15 mg/1.5 ml, 1 = £347.70	5.3 mg, 1 = £92.15 12 mg, 1 = £208.65	5 mg/1.5 ml, 5 = £368.74 10 mg/1.5 ml, 5 = £737.49 15 mg/1.5 ml, 5 = £1106.22	5.83 mg/ml, 1 x 1.03 ml (6 mg = £139.08) 8 mg/ml, 1 x 1.5 ml (12 mg = £278.8; 1 x 2.5ml) (20 mg = £463.60)
Method of administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Doses	0.16 mg/kg/ week	0.66 mg/kg/ week	0.034 mg/kg/ day	0.034 mg/kg/ day	0.034 mg/kg/ day	0.034 mg/kg/ day	0.034 mg/kg/ day	0.034 mg/kg/ day	0.034 mg/kg/ day
Dosing frequency	Once-weekly	Once-weekly	Once-daily	Once-daily	Once-daily	Once-daily	Once-daily	Once-daily	Once-daily

	Somapacitan	Somatrogon	Humatrope®	Zomacton®	NutropinAq®	Norditropin®	Genotropin®	Omnitrope®	Saizen®
Dose adjustments	Somapacitan dose may be individualised and adjusted based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor I (IGF-I) concentrations. If the IGF-I (SDS) is > 2, it should be reassessed after a subsequent somapacitan administration. If the value remains >2, reducing the dose by 0.04 mg/kg/week is recommended. More than one dose reduction may be required in some patients. In patients who have had the dose reduced but are not growing well, the dose may be gradually increased as tolerated up to a maximum dose of 0.16 mg/kg/week. Dose increments should not exceed 0.02 mg/kg per week.	In patients whose serum IGF-I 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.	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 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)	N/A	The dosage is individual and must always be adjusted in accordance with the individual's clinical and biochemical response to therapy.	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 recommended. Even higher doses have been used.	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 recommended. Even higher doses have been used.	N/A

	Somapacitan	Somatrogon	Humatrope®	Zomacton®	NutropinAq®	Norditropin®	Genotropin®	Omnitrope®	Saizen®
Average length of a course of treatment	Long-term; mean treatment length is 7 years. 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)	[redacted]	£6.92 per mg, £9,499.78 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	FlexPro: £21.27 per mg, £10,530 est. annual cost NordiFlex: £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	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-I, hormones, glucose, and lipid levels) and pubertal status. More frequent evaluations should be considered during puberty. Treatment should be discontinued in patients having achieved final height or near final height, i.e. an annualised height	Treatment should be discontinued when there is evidence of closure of the epiphyseal growth plates. 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 development including lean body mass and bone mineral accrual.	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.

	Somapacitan	Somatrogon	Humatrope®	Zomacton®	NutropinAq®	Norditropin®	Genotropin®	Omnitrope®	Saizen®
	velocity <2 cm/year and a bone age >14 years in girls or >16 years in boys which corresponds to the closure of the epiphyseal growth plates. Once the epiphyses are fused, patients should be clinically re-evaluated for the need for growth hormone treatment.								

*per mg cost taken from BNF; estimated annual cost based on daily dose of 0.034 mg/kg (converted to weekly) and weekly dose of 0.16 mg/kg/week (somapacitan) and average child weight of 40 kg. 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 (0.24 mg/kg/wk) worldwide in real world setting for paediatric GHD, and is in line with the posology licensed for its use. This was the dose investigated in the pivotal study for somapacitan. During interviews with clinicians based in England, 0.034 mg/kg/day was confirmed as the typical average dose provided to patients by two out of four interviewees (29).

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.

Abbreviations: BNF, British National Formulary; est., estimated; GHD, growth hormone deficiency; IGF-I, insulin like growth factor 1; N/A, not applicable; SDS, standard deviation score; SmPC, summary of product characteristics.

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

Costs in the model were based on NICE TA188, NICE TA863 and results from the SLR (1, 2). Overall, all once-daily and once-weekly GH treatments incurred identical treatment costs, with the only variable factor in overall costs being the acquisition cost of the medicine. The only costs deemed relevant for consideration in this submission are the medicine acquisition costs.

B.4.2.4 *Adverse reaction unit costs and resource use*

There was no significant difference in the AEs reported between somapacitan and somatropin in the Phase III clinical trial (REAL 4). As such, AE costs were not included in the cost comparison analysis.

B.4.2.5 *Miscellaneous unit costs and resource use*

None that are relevant.

B.4.2.6 *Clinical expert validation*

Clinical experts agreed that once-weekly GH therapies would not be expected to result in any changes to resource use compared with once-daily GHs (29).

B.4.2.7 *Uncertainties in the inputs and assumptions*

A recent (2022) TTO study, conducted in the UK and Canada, highlighted that avoiding injection pain and lower injection frequency result in significant utility gains (see Section B.4.2.1) (54). Somapacitan demonstrated lower rates of injection site pain compared with somatrogon (see the ITC results in Table 31) and results in fewer injections compared with daily GH given its less frequent administration regime. These benefits of somapacitan over its comparators have not been included in the economic analysis in line with the cost comparison methodology.

B.4.3 *Base case*

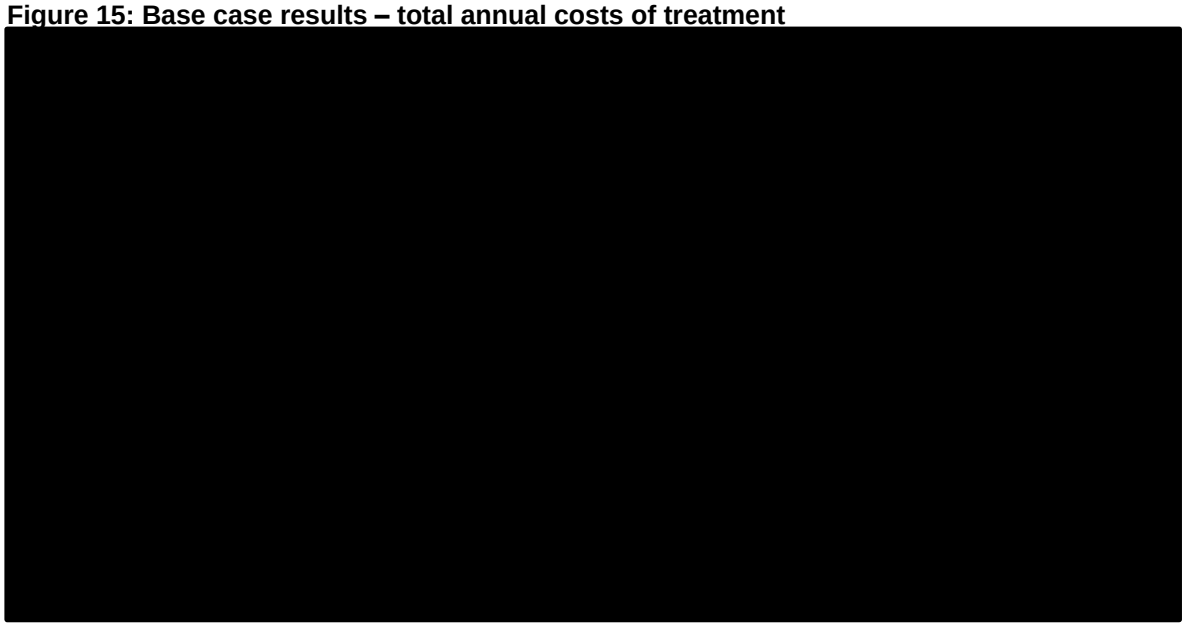
Annual treatment costs for somatropin brands, estimated per patient based on a simple cost acquisition model, range from £7,301.64 to £11,475.03, and somatrogon has an estimated annual cost of £9,499.78. The annual treatment cost of somapacitan is [redacted]. The results are summarised in Table 41 and Figure 15.

Table 41: Base case results

	Acquisition costs (£)	Resource/adverse event/other costs (£)	Total annual costs (£)	Market share
Somapacitan	[redacted]	N/A	[redacted]	[redacted]
Somatrogon	£9,499.78	N/A	£9,499.78	[redacted]
Norditropin	*FlexPro*: £10,529.50 *NordiFlex*: £11,475.03	N/A	*FlexPro*: £10,529.50 *NordiFlex*: £11,475.03	[redacted]
Saizen	£11,475.03	N/A	£11,475.03	[redacted]
NutropinAQ	£10,049.31	N/A	£10,049.31	[redacted]
Humatrope	£8,910.72	N/A	£8,910.72	[redacted]
Genotropin	£8,607.33	N/A	£8,607.33	[redacted]
Zomacton	£8,450.33	N/A	£8,450.33	[redacted]
Omnitrope	£7,301.64	N/A	£7,301.64	[redacted]

Abbreviations: N/A, not applicable.

Figure 15: Base case results – total annual costs of treatment



B.4.4 *Sensitivity and scenario analysis*

Most variables that impact the annual treatment costs are generally consistent across all available daily and weekly treatment options, and will result in proportional changes for all available treatment options, thus having little or no impact on the comparative treatment costs. The exceptions are acquisition costs and dose.

[redacted]. The dose used to estimate annual treatment costs for somatropin was deemed appropriate given that in REAL 4, patients started the trial on this dose and ended with the same average dose. It was therefore not required to include any sensitivity or scenario analysis.

B.4.5 *Subgroup analysis*

No subgroup analysis was conducted for this evaluation.

B.4.6 *Interpretation and conclusions of economic evidence*

Results of the cost comparison analysis show that the annual treatment cost of somapacitan [redacted]. Somapacitan will be the second once-weekly LAGH commercially available in the UK (MHRA marketing authorisation expected in August 2023), expanding the available treatment options for patients.

In summary, somapacitan clearly demonstrates adherence to crucial criteria that should allow for a proportionate review with a simple cost acquisition model:

1) Somapacitan has similar efficacy and safety to daily somatropin, demonstrated through direct head-to-head evidence in the Phase III REAL 4 clinical study

2) Somapacitan has similar efficacy and reduced injection site pain compared with once-weekly somatrogon, demonstrated through a pairwise ITC in the absence of head-to-head trials

3) Somapacitan is expected to be an alternative to daily somatropin offering a less frequent dosing schedule and is expected to have no difference in terms of costs (resource, administration, or adverse event costs)

The reduction in treatment burden and potential for increased utility experienced from reduced frequency of injections with somapacitan vs daily GH, and a reduced rate of injection site reactions vs somatrogon, have not been quantified or included within the analysis. Therefore, given the positive impact these benefits have on both patients and their caregivers, the use of a cost-comparison can be considered an underestimation of the true value of somapacitan to the NHS.

B.5. References

1. NICE. Somatrogon for treating growth disturbance in children and young people aged 3 years and over. Technology Appraisal TA863. Available at: https://www.nice.org.uk/guidance/ta863 Last accessed Feburary 2023. 2023.

2. NICE. Overview, Human growth hormone in children (review of NICE technology appraisal guidance 188). Available at: https://www.nice.org.uk/guidance/ta188/resources/human-growth-hormone-somatropin-for-the-treatment-of-growth-failure-in-children-pdf-82598502860485 (Last accessed: 25 July 2022). Data on file. 2022.

3. Hage C, Gan H-W, Ibba A, Patti G, Dattani M, Loche S, et al. Advances in differential diagnosis and management of growth hormone deficiency in children. Nature Reviews Endocrinology. 2021 2021/10/01;17(10):608-24.

4. Song K, Jin SL, Kwon AR, Chae HW, Ahn JM, Kim D-H, et al. Etiologies and characteristics of children with chief complaint of short stature. Annals of Pediatric Endocrinology & Metabolism. 2015;20:34 - 9.

5. Boot AM, de Ridder MA, Pols HA, Krenning EP, de Muinck Keizer-Schrama SM. Bone mineral density in children and adolescents: relation to puberty, calcium intake, and physical activity. J Clin Endocrinol Metab. 1997 Jan;82(1):57-62.

6. Boot AM, Engels MA, Boerma GJ, Krenning EP, De Muinck Keizer-Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. J Clin Endocrinol Metab. 1997 Aug;82(8):2423-8.

7. Møller N, Jørgensen JO. Effects of growth hormone on glucose, lipid, and protein metabolism in human subjects. Endocr Rev. 2009 Apr;30(2):152-77.

8. Kopchick JJ, Berryman DE, Puri V, Lee KY, Jorgensen JOL. The effects of growth hormone on adipose tissue: old observations, new mechanisms. Nature Reviews Endocrinology. 2020 2020/03/01;16(3):135-46.

9. Colao A, Di Somma C, Salerno M, Spinelli L, Orio F, Lombardi G. The cardiovascular risk of GH-deficient adolescents. J Clin Endocrinol Metab. 2002 Aug;87(8):3650-5.

10. Isaksson OG, Lindahl A, Nilsson A, Isgaard J. Mechanism of the stimulatory effect of growth hormone on longitudinal bone growth. Endocr Rev. 1987 Nov;8(4):426-38.

11. Jørgensen JO, Thuesen L, Müller J, Ovesen P, Skakkebaek NE, Christiansen JS. Three years of growth hormone treatment in growth hormone-deficient adults: near normalization of body composition and physical performance. Eur J Endocrinol. 1994 Mar;130(3):224-8.

12. LeRoith D, Yakar S. Mechanisms of disease: metabolic effects of growth hormone and insulin-like growth factor 1. Nat Clin Pract Endocrinol Metab. 2007 Mar;3(3):302-10.

13. Brooks AJ, Waters MJ. The growth hormone receptor: mechanism of activation and clinical implications. Nature Reviews Endocrinology. 2010 2010/09/01;6(9):515-25.

14. Clemmons DR. Metabolic actions of insulin-like growth factor-I in normal physiology and diabetes. Endocrinology and metabolism clinics of North America. 2012;41(2):425-viii.

15. Richmond E, Rogol AD. Treatment of growth hormone deficiency in children, adolescents and at the transitional age. Best Practice & Research Clinical Endocrinology & Metabolism. 2016 2016/12/01/;30(6):749-55.

16. Yuen K, Frystyk J, Umpleby M, Fryklund L, Dunger D. Changes in free rather than total insulin-like growth factor-I enhance insulin sensitivity and suppress endogenous peak growth hormone (GH) release following short-term low-dose GH administration in young healthy adults. J Clin Endocrinol Metab. 2004 Aug;89(8):3956-64.

17. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Frontiers in Endocrinology. 2021 2021-September-01;12(950).

18. Ranke MB, Wit JM. Growth hormone — past, present and future. Nature Reviews Endocrinology. 2018 2018/05/01;14(5):285-300.

19. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000 Nov;85(11):3990-3.

20. Webb EA, Dattani MT. Diagnosis of growth hormone deficiency. Endocr Dev. 2010;18:55-66.

21. Flavelle S, Cummings E. Case 2: An unusual case of delayed puberty. Paediatrics & child health. 2012;17(9):505-7.

22. Alatzoglou KS, Webb EA, Le Tissier P, Dattani MT. Isolated Growth Hormone Deficiency (GHD) in Childhood and Adolescence: Recent Advances. Endocrine Reviews. 2014;35(3):376-432.

23. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. Br Med J. 1977 Aug 13;2(6084):427-30.

24. Orso M, Polistena B, Granato S, Novelli G, Di Virgilio R, La Torre D, et al. Pediatric growth hormone treatment in Italy: A systematic review of epidemiology, quality of life, treatment adherence, and economic impact. PLoS One. 2022;17(2):e0264403.

25. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr. 1994 Jul;125(1):29-35.

26. Tanaka T, Soneda S, Sato N, Kishi K, Noda M, Ogasawara A, et al. The Boy:Girl Ratio of Children Diagnosed with Growth Hormone Deficiency-Induced Short Stature Is Associated with the Boy:Girl Ratio of Children Visiting Short Stature Clinics. Horm Res Paediatr. 2021;94(5-6):211-8.

27. Kirk J, Clayton P. Specialist services and transitional care in paediatric endocrinology in the UK and Ireland. Clin Endocrinol (Oxf). 2006 Jul;65(1):59-63.

28. British Society for Paediatric Endocrinology and Diabetes. Shared care guidelines: Paediatric use of Recombinant Human Growth Hormone (r-hGH). Available at: https://www.bsped.org.uk/media/1377/sharedcaregh_july2015.pdf LAst accessed November 2022. 2020.

29. Novo Nordisk. Clinical expert interviews to support a cost-comparison STA for NICE for somapactian in paediatric patients with GHD, Feburary 2023. Data on file. 2023.

30. National Organization for Rare Disorders. Growth hrmone deficiency, available at: https://rarediseases.org/rare-diseases/growth-hormone-deficiency/ last accessed Novermber 2022. 2016.

31. Norditropin SmPC. Norditropin Summary of Product Charateristics. Available at: https://www.ema.europa.eu/en/documents/referral/opinion-following-article-75-referral-norditropin-international-non-proprietary-name-inn-somatropin_en.pdf Last Acessed March 2023.

32. Reiter EO, Price DA, Wilton P, Albertsson-Wikland K, Ranke MB. Effect of growth hormone (GH) treatment on the near-final height of 1258 patients with idiopathic GH deficiency: analysis of a large international database. J Clin Endocrinol Metab. 2006 Jun;91(6):2047-54.

33. Polak M, Konrad D, Tønnes Pedersen B, Puras G, Šnajderová M. Still too little, too late? Ten years of growth hormone therapy baseline data from the NordiNet® International Outcome Study. J Pediatr Endocrinol Metab. 2018 Apr 25;31(5):521-32.

34. Sävendahl L, Polak M, Backeljauw P, Blair J, Miller BS, Rohrer TR, et al. Treatment of Children With GH in the United States and Europe: Long-Term Follow-Up From NordiNet® IOS and ANSWER Program. J Clin Endocrinol Metab. 2019 Oct 1;104(10):4730-42.

35. Ben-Ari T, Chodick G, Shalev V, Goldstein D, Gomez R, Landau Z. Real-World Treatment Patterns and Outcomes of Growth Hormone Treatment Among Children in Israel Over the Past Decade (2004–2015). Frontiers in Pediatrics. 2021 2021-August-20;9.

36. Brod M, Alolga SL, Beck JF, Wilkinson L, Højbjerre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. Qual Life Res. 2017 Jul;26(7):1673-86.

37. Kaplowitz P, Manjelievskaia J, Lopez-Gonzalez L, Morrow CD, Pitukcheewanont P, Smith A. Economic burden of growth hormone deficiency in a US pediatric population. J Manag Care Spec Pharm. 2021 Aug;27(8):1118-28.

38. Dunger D, Darendeliler F, Kandemir N, Harris M, Rabbani A, Kappelgaard AM. What is the evidence for beneficial effects of growth hormone treatment beyond height in short children born small for gestational age? A review of published literature. J Pediatr Endocrinol Metab. 2020 Jan 28;33(1):53-70.

39. Beshyah SA, Johnston DG. Cardiovascular disease and risk factors in adults with hypopituitarism. Clin Endocrinol (Oxf). 1999 Jan;50(1):1-15.

40. Colao A, Marzullo P, Di Somma C, Lombardi G. Growth hormone and the heart. Clin Endocrinol (Oxf). 2001 Feb;54(2):137-54.

41. Hansen MA, Overgaard K, Riis BJ, Christiansen C. Role of peak bone mass and bone loss in postmenopausal osteoporosis: 12 year study. BMJ (Clinical research ed.). 1991;303(6808):961-4.

42. Brod M, Højbjerre L, Alolga SL, Beck JF, Wilkinson L, Rasmussen MH. Understanding Treatment Burden for Children Treated for Growth Hormone Deficiency. Patient. 2017 Oct;10(5):653-66.

43. Tanaka T, Tai S, Morisaki Y, Tachibana K, Kambayashi Y, Chihara K, et al. Evaluation of Quality of Life in Children with GH Deficiency and Idiopathic Short Stature Using the Child Behavior Checklist. Clin Pediatr Endocrinol. 2009;18(1):15-22.

44. Voss LD, Mulligan J. Bullying in school: are short pupils at risk? Questionnaire study in a cohort. BMJ (Clinical research ed.). 2000;320(7235):612-3.

45. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PLoS One. 2011 Jan 31;6(1):e16223.

46. Hughes IP, Choong C, Rath S, Atkinson H, Cotterill A, Cutfield W, et al. Early cessation and non-response are important and possibly related problems in growth hormone therapy: An OZGROW analysis. Growth Hormone & IGF Research. 2016 2016/08/01/;29:63-70.

47. Fisher BG, Acerini CL. Understanding the growth hormone therapy adherence paradigm: a systematic review. Horm Res Paediatr. 2013;79(4):189-96.

48. Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, Ong KK, et al. Monitoring of concordance in growth hormone therapy. Archives of Disease in Childhood. 2008;93(2):147.

49. Farfel A, Shalitin S, Morag N, Meyerovitch J. Long-term adherence to growth hormone therapy in a large health maintenance organization cohort. Growth Horm IGF Res. 2019 Feb;44:1-5.

50. Koledova E, Stoyanov G, Ovbude L, Davies PSW. Adherence and long-term growth outcomes: results from the easypod(™) connect observational study (ECOS) in paediatric patients with growth disorders. Endocr Connect. 2018 Aug;7(8):914-23.

51. York Health Economics Consotrium and School of Pharmacy UoL. Evaluation of the Scale, Causes and Costs of Waste Medicines. Published 2020. Available at: https://discovery.ucl.ac.uk/id/eprint/1350234/1/Evaluation_of_NHS_Medicines_Waste_web_publication_version.pdf. Last accessed June 2022. 2020.

52. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018 Jan 21;8(1):e016982.

53. Novo Nordisk. Health state utility generation for growth hormone deficiency. Results. January 2023. Data on file.

54. Kirsch S, Butler G, Jensen L, Bøgelund M, Håkan-Bloch J. Pain-Free Injections for Growth Hormone Deficiency (GHD) Improve Quality of Life: A Time Trade-Off (TTO) Study in the UK and Canada. Poster presented at ISPOR, May 2023, Boston, MA, USA.

55. McNamara M, Turner-Bowker DM, Westhead H, Yaworsky A, Palladino A, Gross H, et al. Factors Driving Patient Preferences for Growth Hormone Deficiency (GHD) Injection Regimen and Injection Device Features: A Discrete Choice Experiment. Patient Prefer Adherence. 2020;14:781-93.

56. Shepherd S, Saraff V, Shaw N, Banerjee I, Patel L. Growth hormone prescribing patterns in the UK, 2013-2016. Arch Dis Child. 2019 Jun;104(6):583-7.

57. Ranke MB, Lindberg A, Tanaka T, Camacho-Hübner C, Dunger DB, Geffner ME. Baseline Characteristics and Gender Differences in Prepubertal Children Treated with Growth Hormone in Europe, USA, and Japan: 25 Years' KIGS® Experience (1987-2012) and Review. Hormone Research in Paediatrics. 2017;87(1):30-41.

58. Grimberg A, Lindberg A, Wajnrajch M, Cucchiara AJ, Camacho-Hübner C. Racial/Ethnic Disparities in US Pediatric Growth Hormone Treatment. Horm Res Paediatr. 2018;90(2):102-8.

59. Grimberg A, Kutikov JK, Cucchiara AJ. Sex differences in patients referred for evaluation of poor growth. The Journal of Pediatrics. 2005;146(2):212-6.

60. Grote FK, Oostdijk W, De Muinck Keizer-Schrama SM, van Dommelen P, van Buuren S, Dekker FW, et al. The diagnostic work up of growth failure in secondary health care; an evaluation of consensus guidelines. BMC Pediatr. 2008 May 13;8:21.

61. Graham S, Auyeung V, Weinman J. Exploring Potentially Modifiable Factors That Influence Treatment Non-Adherence Amongst Pediatric Growth Hormone Deficiency: A Qualitative Study. Patient Prefer Adherence. 2020;14:1889-99.

62. Hartmann K, Ittner J, Müller-Rossberg E, Schönau E, Stephan R, Ullrich KP, et al. Growth hormone treatment adherence in prepubertal and pubertal children with different growth disorders. Horm Res Paediatr. 2013;80(1):1-5.

63. Haverkamp F, Gasteyger C. A review of biopsychosocial strategies to prevent and overcome early-recognized poor adherence in growth hormone therapy of children. J Med Econ. 2011;14(4):448-57.

64. NICE. Technology Assessment Report commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence, Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. Available at: https://www.nice.org.uk/guidance/ta188/documents/assessment-group-report-recombinant-human-growth-hormone-for-the-treatment-of-growth-disorders-in-children-a-systematic-review-and-economic-evaluation2 Last accessed December 2022. 2009.

65. Takeda A, Cooper K, Bird A, Baxter L, Frampton GK, Gospodarevskaya E, et al. Recombinant human growth hormone for the treatment of growth disorders in children: a systematic review and economic evaluation. Health Technol Assess. 2010 Sep;14(42):1-209, iii-iv.

66. Curtis L. Unit costs of health and social care. University of Kent, Canterbury: Personal Social Services Research Unit. 2008.

67. Department of Health. NHS Reference Costs, UK. 2006.

68. Contracting Unit SUHT. Unit costs (unpublished database). 2008.

69. Jones SA, McGovern M, Lidove O, Giugliani R, Mistry PK, Dionisi-Vici C, et al. Clinical relevance of endpoints in clinical trials for acid sphingomyelinase deficiency enzyme replacement therapy. Mol Genet Metab. 2020 Sep-Oct;131(1-2):116-23.

70. Novo Nordisk. SLR to assess the effectiveness and safety of long-acting growth hormones in pediatric growth hormone deficiency (GHD). Data on file. 2023.

71. Novo Nordisk. REAL 4: A trial comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin® in children with growth hormone deficiency, Phase 3a. Data on file. 2022.

72. Novo Nordisk. REAL 4: A trial comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin® in children with growth hormone deficiency, Phase 3a. Main and extension period (up to Week 104). Data on file. 2023.

73. Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, et al. Weekly Somapacitan is Effective and Well Tolerated in Children with GH Deficiency: The Randomized Phase 3 REAL4 Trial. J Clin Endocrinol Metab. 2022 Sep 5.

74. Novo Nordisk. REAL 3, A randomised, multinational, active-controlled, (open-labelled), dose finding, (double-blinded), parallel group trial investigating efficacy and safety of once-weekly somapacitan treatment compared to daily growth hormone

treatment (Norditropin® FlexPro®) in growth hormone treatment naïve pre-pubertal children with growth hormone deficiency. Data on file. 2021.

75. Sävendahl L, Battelino T, Brod M, Højby Rasmussen M, Horikawa R, Juul RV, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. The Journal of clinical endocrinology and metabolism. 2020;105(4):e1847-e61.

76. Sävendahl L, Battelino T, Højby Rasmussen M, Brod M, Saenger P, Horikawa R. Effective GH Replacement With Once-weekly Somapacitan vs Daily GH in Children with GHD: 3-year Results From REAL 3. J Clin Endocrinol Metab. 2022 Apr 19;107(5):1357-67.

77. Sävendahl L, Battelino T, Rasmussen MH, Brod M, Röhrich S, Saenger P, et al. Weekly Somapacitan in GH Deficiency: 4-Year Efficacy, Safety and Treatment/Disease Burden Results from REAL 3. J Clin Endocrinol Metab. 2023 Mar 30.

78. Deal CL, Steelman J, Vlachopapadopoulou E, Stawerska R, Silverman LA, Phillip M, et al. Efficacy and Safety of Weekly Somatrogon vs Daily Somatropin in Children With Growth Hormone Deficiency: A Phase 3 Study. J Clin Endocrinol Metab. 2022 Jun 16;107(7):e2717-e28.

79. Zelinska N, Iotova V, Skorodok J, Malievsky O, Peterkova V, Samsonova L, et al. Long-Acting C-Terminal Peptide-Modified hGH (MOD-4023): Results of a Safety and Dose-Finding Study in GHD Children. J Clin Endocrinol Metab. 2017 May 1;102(5):1578-87.

80. Novo Nordisk. Comparative efficacy and safety of somapacitan and somatrogon in paediatric growth hormone deficiency. Data on File. 2023.

81. Zelinska NS YM, O; Iotova, V; Rosenfeld, R; Zadik, Z; et al.,. Long-Term Safety of a Once-Weekly Somatrogon (hGH-CTP): 4-Year Results of a Phase 2 Extension Study in Children with Growth Hormone Deficiency. Presented at ESPE. 2019.

82. Horikawa R, Tanaka T, Hasegawa Y, Yorifuji T, Ng D, Rosenfeld RG, 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. Horm Res Paediatr. 2022;95(3):275-85.

83. Philippo D. R package multinma: Bayesian Network Meta-Analysis of Individual and Aggregate Data. Documentation available at: https://cran.r-project.org/web/packages/multinma/multinma.pdf. Accessed Jun 2022. 2022.

84. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE Decision Support Unit Technical Support Documents. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. London: National Institute for Health and Care Excellence (NICE) Copyright © 2014 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.; 2014.

85. Kappelgaard AM, Bojesen A, Skydsgaard K, Sjögren I, Laursen T. Liquid growth hormone: preservatives and buffers. Horm Res. 2004;62 Suppl 3:98-103.

86. Laursen T, Hansen B, Fisker S. Pain perception after subcutaneous injections of media containing different buffers. Basic Clin Pharmacol Toxicol. 2006 Feb;98(2):218-21.

87. Ahangari G, Ostadali MR, Rabani A, Rashidian J, Sanati MH, Zarindast MR. Growth hormone antibodies formation in patients treated with recombinant human growth hormone. Int J Immunopathol Pharmacol. 2004 Jan-Apr;17(1):33-8.

88. BNF. Somatropin Medicinal Forms 2022 [2022 Jul 12]. Available from: https://bnf.nice.org.uk/medicinal-forms/somatropin.html. Last accessed Feburary 2023. 2022.

89. Novo Nordisk. SLR to assess the effectiveness and safety of long-acting growth hormones in pediatric growth hormone deficiency (GHD): List of publications excluded at full-text review. Data on file. 2023.

90. Novo Nordisk. Comparative efficacy and safety of long-acting growth hormones in paediatric growth hormone deficiency, Data on file. 2022.

91. Centonze C, Foo J, Vlachaki I, Novelli P. PDB60 - COST-CONSEQUENCE ANALYSIS FOR RECOMBINANT HUMAN GROWTH HORMONE TREATMENT ADMINISTERED VIA DIFFERENT DEVICES IN CHILDREN WITH GROWTH HORMONE DEFICIENCY IN ITALY. Value in Health. 2018;21:S128.

92. Chevreul K, Berg Brigham K, Clément M-C, Poitou C, Tauber M, Appendix MotB-RRNlitO. Economic burden and health-related quality of life associated with Prader–Willi syndrome in France. Journal of Intellectual Disability Research. 2016;60(9):879-90.

93. Flodmark CE, Lilja K, Woehling H, Järvholm K. Switching From Originator to Biosimilar Human Growth Hormone Using Dialogue Teamwork: Single-Center Experience From Sweden. Biol Ther. 2013;3(1):35-43.

94. Hauspurg A, Albright C, Rouse D, Werner E. 570: Third trimester fetal growth ultrasound: a cost-benefit analysis. American Journal of Obstetrics & Gynecology. 2015;212(1):S285.

95. Lee JM, Davis MM, Clark SJ, Hofer TP, Kemper AR. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. Arch Pediatr Adolesc Med. 2006 Mar;160(3):263-9.

96. Al Khalifah RA, Alhakami A, AlRuthia Y, Al Sarraj HZ, Abulqasim J, Al-Rasheedi A, et al. The long-term growth, cost-effectiveness, and glycemic effects of growth hormone therapy on children born small for gestational age over 10 years: a retrospective cohort study. J Pediatr Endocrinol Metab. 2022 Nov 25;35(11):1357-68.

97. Grimberg A, Kanter GP. US Growth Hormone Use in the Idiopathic Short Stature Era: Trends in Insurer Payments and Patient Financial Burden. J Endocr Soc. 2019 Nov 1;3(11):2023-31.

98. Marzouk A, Filipovic-Pierucci A, Baud O, Tsatsaris V, Ego A, Charles M-A, et al. Prenatal and post-natal cost of small for gestational age infants: a national study. BMC Health Services Research. 2017 2017/03/21;17(1):221.

99. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003 Dec;112(6 Pt 1):1290-7.

100. Joshi AV, Munro V, Russell MW. Cost-utility of somatropin (rDNA origin) in the treatment of growth hormone deficiency in children. Curr Med Res Opin. 2006 Feb;22(2):351-7.

101. Souza PV, Biglia LV, Zanini FE. Cost-Minimization of Somatropin for GH Deficiency and Turner Syndrome Treatment from SUS Perspective. Value in Health. 2017;20(9):A919-A20.

102. Foo J, Maghnie M, Colao A, Vlachaki I, Colombo G. Cost-consequence analysis for human recombinant growth hormone (r-hGH) treatment administered via different devices in children with growth hormone deficiency in Italy. Clinicoecon Outcomes Res. 2019;11:525-37.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technology appraisal

Somapacitan for treating growth hormone deficiency in children [ID6178]

Summary of Information for Patients (SIP)

June 2023

File name	Version	Contains confidential information	Date
ID6178_Somapacitan_SIP	1.0	Yes	23 June 2023

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Somapacitan Brand name: Sogroya®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Children and adolescents (aged 3 years and over) with growth failure due to growth hormone deficiency (GHD)

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Somapacitan does not currently have UK marketing authorisation for the population in this submission (Table 2, Section B.1.2. of submission document B). A new marketing authorisation application for somapacitan was submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) in May 2023. Regulatory approval for somapacitan for children for and adolescents (aged 3 years and over) is expected in August 2023 via the European Commission Decision Reliance Procedure. It is anticipated that somapacitan will be indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above, and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

There are no existing collaborations between Novo Nordisk UK and UK patient groups relevant to somapacitan. In the recent past, Novo Nordisk has partnered with patient groups such as the Child Growth Foundation and the Pituitary Foundation. Details of these collaborations can be provided upon request.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is GHD?

Growth hormone (GH) is produced by the pituitary gland in the brain and is responsible for the growth of bone and other tissues in children and adolescents. Growth hormone deficiency (GHD) is a rare disease characterised by insufficient amounts of GH (1), and is one of the most common hormone-related causes of short stature (2).

Children with GHD most commonly present with growth failure and maturation delays (1, 3). Other clinical features include delayed dentition (development of teeth), facial abnormalities, a high-pitched voice, increased fat mass (predominantly around the abdomen), decreased muscle mass, and delayed puberty (1, 4, 5).

The clinical presentation of GHD depends on the age of disease onset; for example, infants may initially have non-specific signs and symptoms such as lethargy and poor weight gain (1). GHD in childhood is associated with persistent growth failure and short stature, while in adolescents the most common presentation is growth retardation and delayed puberty (1, 6). Children with GHD typically have normal body proportions, but they are often shorter, chubbier, and may be perceived to be younger, compared with children of a similar age without GHD (7). Notably, very few (4%) children with GHD cite short stature as the only disease-related symptom (7); other symptoms, reported in up to half of those with GHD, include poor appetite, reduced strength or poor muscle development, poor energy levels, and poor sleep (7).

In the UK, GHD affects approximately 1 in 4,000 to 1 in 3,500 children (8, 9). It is therefore estimated that, of all children born in the UK each year, approximately 175 to 200 are born with GHD or develop it later in life (9, 10). Boys are more frequently diagnosed with GHD than girls (ratio of 1.58 to 1) (11). According to a survey published in 2006 by the British Society for Paediatric Endocrinology and Diabetes (BSPED), 4,758 patients have been receiving GH therapy in the UK, of which 4,168 were in England and Wales (12).

What causes GHD?

In most cases, the cause of GHD cannot be identified (referred to as 'idiopathic' GHD). However, the disease can be present at birth due to mutations in certain genes, or it can develop later in

childhood as a result of damage to the pituitary gland (1, 3). GHD can occur in isolation, or may develop alongside other hormone conditions (1, 13).

What is the impact of GHD on people living with the condition and their families?
The clinical impact of GHD is described briefly above (see What is GHD?). In addition to these symptoms, children with GHD are more likely to develop other medical conditions, including cardiovascular disease and metabolic conditions (14-18), and to have lower bone mineral density (19), compared with children without GHD.

GHD significantly impacts the quality of life (QoL) of children living with the condition (20-22). The three main areas of daily life known to be affected by symptoms of GHD are physical aspects, social wellbeing, and emotional wellbeing (7) (see Section 2d below). A UK study also found that children with short stature in junior and secondary school are significantly more likely to be bullied than their taller peers, and that short pupils report a greater degree of isolation (spending break time alone) (22).

The parents of children with GHD have an increased caregiver burden compared with those of normal height children, with a reduced QoL due to the stress caused by caring for a child with GHD and the frequent worry about their child's lack of height and how it will affect them throughout their life (7, 23, 24).

The burden of daily GH injections also negatively impacts the QoL of children with GHD and their parents/caregivers (see 2d below).

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Children with GHD are typically diagnosed by a paediatric endocrinologist (doctor specialising in children's hormones), using GH stimulatory tests. However, other measurements such as height, bone density, and magnetic resonance imaging (MRI) are also used.

In the UK, children with GHD are generally diagnosed during one of two age ranges: at 5–6 years (at the beginning of schooling); and at 10–13 years in girls and 12–16 years in boys, when the disease is associated with delayed puberty (25).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatments are currently used?

GHD is treated by the administration of synthetic GH (produced in a laboratory) that is identical to the human GH that is naturally produced by the pituitary gland. Most currently available GH treatments are administered once a day by injection under the skin in the thigh or abdomen; all once-daily preparations are identical (8). In total, there are eight treatments available: seven once-daily GH therapies (**Table 1**) and one once-weekly GH therapy recently recommended by the National Institute of Health and Care Excellence (NICE) (Ngenla® [somatrogon], produced by Pfizer). The choice of GH treatment should be made on an individual basis after discussion between the patient/carer and their clinician (8).

Table 1: Available growth hormone (somatropin) preparations for daily injection

Treatment name	Manufacturer
Norditropin®	Novo Nordisk
NutropinAQ®	Genentech + Ipsen
Genotropin®	Pfizer
Humatrope®	Eli Lilly
Saizen®	Merck Serono
Zomacton®	Ferring
Omnitrope®	Sandoz

Somapacitan

Somapacitan is a long-acting GH treatment for once-weekly injection in patients with GHD. It is expected to reduce the treatment burden and improve the QoL of people with GHD, compared with current once-daily GH treatments.

Somapacitan is delivered in a storage-flexible, easy-to-use pen injector device. The device is ready to use as it comes prefilled with liquid somapacitan (no reconstitution is required) (26). The pen is portable and can be stored at temperatures of up to 30°C for up to a total of 72 hours (3 days) over 6 weeks' usage (26). Injection pain is minimal when using somapacitan, partly due to the ultra-thin and ultra-short needle used (26-28).

Switching to once-weekly somapacitan from once-daily GH would result in a decrease in the number of injections from 365 per year to 52 per year (i.e. a reduction of 313 injections). Switching patients from a once-daily GH to once-weekly somapacitan is not expected to require a change in service provision or management (29).

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Several studies have reported the negative impact of GHD on health-related QoL (20-22). In a 2017 international study to examine the burden of GHD on children and adolescents, Brod and colleagues conducted interviews and focus groups in the UK, Germany and the US (7). Three key aspects of daily life that are affected by symptoms of GHD were identified by patients and parents

in this study: 1) physical aspects, such as reduced physical/sporting ability (reported by 59% of respondents) and difficulty reaching things (44% of respondents); 2) social wellbeing due to the child's visibly smaller size; and 3) emotional wellbeing, most commonly the child disliking or feeling bothered by their height or size (7).

The burden of daily GH injections is also associated with reduced QoL in people with GHD and in parents of children with GHD. A recent (2022) time trade off (TTO) study, conducted in the UK and Canada, highlighted the burden of injection pain in terms of its impact on health-related QoL (30). Two surveys were conducted, using eight health states (defined in collaboration with two clinical experts and one health economics expert). Of all the health states, the 'injection pain' health state was associated with the highest 'disutility' (reduction in QoL) in both the UK and Canada from the perspective of a person with a hormone deficiency (values of 0.030 and 0.030, respectively [survey 1]) and as a parent of a child with GHD (0.039 and 0.050, respectively [survey 2]). Once-daily GH therapies were also associated with a greater disutility compared with once-weekly GH therapies among the general population evaluating health states as themselves with GHD, and as a parent of a child with GHD (30).

The burden of treatment administration is one of the most commonly reported reasons for patients not adhering to their daily GH treatment (20, 31). Other factors reported to adversely affect adherence to current once-daily GH therapies are a lack of storage flexibility, lack of choice of device, and low device ease of use. A recent study demonstrated that patient preference is for a less frequent injection regimen for treating GHD (32). Despite the recognised benefits of GH therapy in children with GHD, poor adherence to once-daily GH therapy is common (3, 33) and is associated with reductions in treatment efficacy, and worsened clinical outcomes compared with compliant patients (3, 31, 33, 34). In a UK study including children aged 9–15 years with GHD, patients who missed more than two injections per week had a significantly lower height velocity (the rate of growth over time) compared with those who missed none (−41%, $p<0.05$) (35). In interviews with paediatric endocrinologists based in England, three out of four experts stated that patients report missing doses of daily GH (29).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Somapacitan is a growth hormone (GH) replacement that is 99% identical in structure to naturally occurring human GH (somatropin). It has been designed to replace the GH that is lacking in children with growth hormone deficiency (GHD). The somapacitan molecule contains a modification that increases its stability in the blood, meaning that it is long acting and can therefore be injected once a week instead of once a day (26).

Somapacitan is a new medicine that provides a comparable treatment effect and safety profile to once-daily GH, but with fewer injections each week/year. An indirect analysis of data from clinical

trials has found that somapacitan showed a comparable clinical treatment effect to the other once-weekly GH, somatrogon, with a lower rate of injection site pain (36).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes/No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Somapacitan is not intended to be used in combination with any other medicines.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Somapacitan is administered once weekly as an injection under the skin using a small needle. The recommended dosage of somapacitan is 0.16 mg/kg body weight/week. Treatment should be taken until the final height or near final height has been achieved i.e., height velocity decreases to below 2 cm/year and a bone age is higher than 14 years in girls or 16 years in boys. Patients should be trained in administration and can then carry out the process at home by themselves once they feel comfortable (26).

The administration method for somapacitan is the same as existing GH therapies so no new training would be required. However, the treatment burden is expected to be lower for patients and caregivers due to the reduced frequency of injections compared with current once-daily GH treatments, and reduced injection pain compared with the other available once-weekly GH treatment (36).

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

The clinical efficacy (how well somapacitan works) and safety of somapacitan have been evaluated for the treatment of GHD in one Phase III clinical trial (REAL 4 [NCT03811535]) (37), and a Phase II dose-finding study (REAL 3 [NCT02616562]) (38-40), both of which compared once-weekly somapacitan with daily GH (Norditropin®). Details of the design and methodology of REAL 4 and REAL 3 can be found in Section B 3.3. of the submission document B.

REAL 4

Patients were enrolled at 86 sites in 20 countries across Europe (including the UK), Asia, and North America. Patients were eligible for the study if they were prepubertal with a confirmed diagnosis

of GHD (determined by two different GH stimulation tests) and with impaired height, impaired height velocity, insulin-like growth factor-1 (IGF-1) <–1.0 below standard deviation score (SDS) compared with age and gender normalised range, and no prior exposure to GH therapy.

In total, 200 children were randomised to receive somapacitan 0.16 mg/kg/week (n=132) or Norditropin® 0.034 mg/kg/week (n=68). Participants received the treatment for 52 weeks in the main trial period to determine the effect of somapacitan compared with Norditropin®. Patients completing the main trial could continue to receive somapacitan, or switch from Norditropin® to somapacitan, in the ongoing 3-year safety extension (results are currently available for Week 52 to Week 104) (37).

REAL 3

Patients were enrolled at 29 sites in 11 countries across Europe, Asia, and North America. Eligibility for the study included all patients who were prepubertal with a confirmed diagnosis of GHD, impaired height, and no prior exposure to GH therapy.

In total, 57 children were randomised to receive somapacitan 0.04 mg/kg/week (n=14), somapacitan 0.08 mg/kg/week (n=15), somapacitan 0.16 mg/kg/week (n-14), and Norditropin® 0.034 mg/kg/week (n=14). Participants received the treatment for 26 weeks to determine the effect of somapacitan compared with Norditropin®. The 26-week main trial period was followed by a 26-week extension trial period, a 104-week safety extension, and a 208-week long-term safety extension (38-40).

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

REAL 4

In the REAL 4 study, the clinical efficacy of somapacitan was measured by improvements in height velocity after 52 weeks of treatment. The results of the REAL 4 study showed that:

- Treatment with somapacitan resulted in a similar (statistically non-inferior) increase in height velocity compared with once-daily somatropin at Week 52
- Somapacitan was also statistically non-inferior for all other height- and biomarker-related outcomes, compared with somatropin, after 52 weeks of treatment
- Mean treatment adherence was higher with somapacitan (95.8%) vs somatropin (88.3%) to Week 52

For further information please see Section B.3.6.1. of the submission document B.

REAL 3

In REAL 3, the clinical efficacy of somapacitan was measured according to its impact on height velocity. The main objective was to find the optimum dose and establish how safe the treatment is for patients. The results of the REAL 3 study showed that:

- Treatment with somapacitan 0.16 or 0.08 mg/kg/week resulted in a similar difference in height velocity compared with somatropin at Week 26

- Patients treated with somapacitan had a significant increase in height velocity after 52 weeks of treatment compared with somatropin

For further information please see Section B.3.6.2. of the submission document B.

Ongoing studies
The long-term safety extensions to REAL4 and REAL 3 are ongoing.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The health-related QoL of patients in the REAL 4 trial was measured using the following patient questionnaires:

- **Growth hormone deficiency – child impact measure (GHD-CIM):** Similar improvements in all domains of the GHD-CIM (physical functioning, emotional well-being, social well-being, and total score) were observed at Week 52 for the somapacitan and daily GH treatment groups.
- **Growth hormone deficiency – child treatment burden (GHD-CTB):** Treatment burden scores were similar between somatropin and daily GH for the four domains (physical, emotional well-being, interference, and total) at Week 52. This questionnaire was completed by non-biased 'observers' (clinicians or healthcare professionals).
- **Growth hormone deficiency – parent treatment burden (GHD-PTB):** Treatment burden scores were significantly improved (lowered) with somapacitan vs daily GH after 52 weeks for the emotional domain, for the interference domain, and for total score. This questionnaire was completed by parents.
- **Growth hormone device assessment tool (G-DAT**): Both the somapacitan and daily GH injection devices were evaluated as 'very easy' or 'easy' to use by 96% of patients.

Further information is provided in Section B.3.6. of submission document B.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Somapacitan is generally well-tolerated, with no evidence of side effects associated with treatment (treatment-emergent adverse events) that would lead to treatment discontinuation or study withdrawal. No deaths occurred in any of the studies.

In REAL 4 and REAL 3, all side effects were mild or moderate in severity, and there were few side effects associated with the injection of the treatment, for example bruising and needle pain. In

the REAL 3 long-term safety extension, no new safety issues were identified, and no issues were identified in patients switching from once-daily somatropin to once-weekly somapacitan.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The current standard of care for patients with GHD is GH replacement therapy (as discussed in Section 2c). However, the majority of currently available GH treatments require daily injection which can be burdensome for patients and their families (3, 20, 33).

Somapacitan provides children with GHD with a treatment that will target the underlying cause of the disease by replacing the missing GH. Evidence from clinical trials shows that somapacitan provides similar clinical efficacy (such as improvements in height velocity) as daily GH, with a comparable safety profile. However, somapacitan provides the additional benefit of 313 fewer injections each year (52 vs 365 injections) compared with once-daily treatment, which is may improve patient adherence and outcomes.

Patient adherence may also be improved as a result of the portability and storage flexibility of the somapacitan device, allowing patients to travel with their medicine. Somapacitan is also expected, based on an indirect analysis of clinical trial data, to result in reduced injection pain compared with the only other available once-weekly GH treatment (Ngenla® - somatrogon) (36).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

There are no disadvantages to note for patients or caregivers.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)

- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Despite the benefits of currently available GH therapies for children with GHD, poor adherence to daily GH therapy is common due to the burden of daily administration (35, 41). Somapacitan addresses the need for GH therapies with a reduced administration burden, including less frequent dosing in an easy-to-use, storage-flexible device with minimal injection pain.

The results of the somapacitan clinical trials in children with GHD show that somapacitan provides similar clinical benefits (efficacy and safety) to currently available once-daily GH treatments. However, somapacitan provides the added benefit of a reduction in the number of injections compared with daily treatment options (52 vs 365 injections per year), which is expected to reduce the burden of treatment for patients and their families. Indeed, in the pivotal Phase III trial (REAL 4), treatment burden scores (as measured by the GHD-PTB questionnaire) were significantly improved (lowered) with somapacitan compared with daily somatropin, and adherence was higher with somapacitan (95.8%) vs somatropin (88.3%), after 52 weeks of treatment.

Based on the evidence available, the company's economic analysis, and additional benefits not captured in the economic analysis, somapacitan treatment for children with GHD would be considered as offering a good use of National Health Service (NHS) resources.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.
If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Despite the recognised benefits of GH therapy in children with GHD, poor adherence to once-daily GH therapy is common (3, 33). Overall, there is a considerable need to reduce the treatment burden of GH therapies and improve adherence.

The main reasons for reduced adherence reported by patients are the frequency of injections and injection pain. Somapacitan is the second once-weekly GH to be available in the UK and addresses both these issues; treatment with weekly somapacitan requires 313 fewer injections per year compared with daily GH (52 vs 365 injections), and is associated with a lower rate of injection site pain vs once-weekly somatrogon (36), while producing a similar clinical effect.

Patient adherence may also be improved as a result of the portability and storage flexibility of the somapacitan device, allowing patients to travel with their medicine. The majority of patients in REAL 4 described the somapacitan device as 'very easy' or 'easy' to learn to use and to store.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
An awareness of potential gender biases is important for the adequate care of girls with short stature. In the UK, a higher frequency of boys than girls has been noted among children with GHD treated with GH replacement therapy (42), an observation that is consistent globally (43, 44). Boys are also over-represented among hospital referrals for short stature (45, 46). The effects of socioeconomic status on adherence to GH therapy in children should also be considered, a topic on which several studies have been published (47-49). In a 2011 literature review, key factors identified in relation to poor adherence to GH therapy were psychological/emotional problems, socioeconomic/everyday problems, and issues with technical handling of the drug delivery device. The authors emphasised the need for healthcare professionals to be sensitive to socioeconomic factors that can affect adherence (49). As poor adherence to GH treatment is associated with poorer clinical outcomes compared with compliant patients (31, 33, 34), disadvantaged children are at risk of poorer health outcomes than those living in more favourable socioeconomic circumstances.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

Clinical trial publications
• REAL 3 publications:
  ○ Effective GH Replacement With Once-weekly Somapacitan vs Daily GH in Children with GHD: 3-year Results From REAL 3 - PubMed (nih.gov)
  ○ Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial - PubMed (nih.gov)
  ○ Weekly Somapacitan in GH Deficiency: 4-Year Efficacy, Safety and Treatment/Disease Burden Results from REAL 3 (nih.gov)
• REAL 4 publication:
  ○ Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial - PMC (nih.gov)
 	
Further information on NICE and the role of patients:
• Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
• NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
• EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

A

Adverse event/Side effect: An unexpected medical problem that arises during treatment with a drug or other therapy. Adverse events may be mild, moderate, or severe (50)

B

C

Clinical trial: A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis, or treatment of a disease. Also called clinical study (50)

D

E

Eligibility: In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance (50)

EMA (European Medicines Agency): The regulatory body that evaluates, approves, and supervises medicines throughout the European Union (50)

F

G

H

HTA (Health Technology Assessment) (bodies): Bodies that make recommendations groups regarding the financing and reimbursing of new medicines and medical products based on the added value (efficacy, safety, medical resources saving) of a therapy compared to existing ones.

I

J

K

L

M

MHRA (Medicines and Healthcare products Regulatory Agency): The body that regulates medicines, medical devices and blood components for transfusion in the UK (51)

N

O

P

Paediatric: Having to do with children (50)

Q

Quality of life: The overall enjoyment of life. Many clinical trials assess it to measure aspects of an individual's sense of wellbeing and ability to carry out activities of daily living (50)

R

S

Symptom: A physical or mental problem that a person experiences that may indicate a disease or condition. Symptoms cannot be seen and do not show up on medical tests. Some examples of symptoms are headache, fatigue, nausea, and pain (50)

T

U

V

W

X

Y

Z

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

1. Hage C, Gan H-W, Ibba A, Patti G, Dattani M, Loche S, et al. Advances in differential diagnosis and management of growth hormone deficiency in children. Nature Reviews Endocrinology. 2021 2021/10/01;17(10):608-24.
2. Song K, Jin SL, Kwon AR, Chae HW, Ahn JM, Kim D-H, et al. Etiologies and characteristics of children with chief complaint of short stature. Annals of Pediatric Endocrinology & Metabolism. 2015;20:34 - 9.
3. Ranke MB. Short and Long-Term Effects of Growth Hormone in Children and Adolescents With GH Deficiency. Frontiers in Endocrinology. 2021 2021-September-01;12(950).
4. Growth Hormone Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. GH Research Society. J Clin Endocrinol Metab. 2000 Nov;85(11):3990-3.
5. Webb EA, Dattani MT. Diagnosis of growth hormone deficiency. Endocr Dev. 2010;18:55-66.
6. Flavelle S, Cummings E. Case 2: An unusual case of delayed puberty. Paediatrics & child health. 2012;17(9):505-7.
7. Brod M, Alolga SL, Beck JF, Wilkinson L, Højbjerre L, Rasmussen MH. Understanding burden of illness for child growth hormone deficiency. Qual Life Res. 2017 Jul;26(7):1673-86.
8. NICE. Overview, Human growth hormone in children (review of NICE technology appraisal guidance 188). Available at: https://www.nice.org.uk/guidance/ta188/resources/human-growth-hormone-somatropin-for-the-treatment-of-growth-failure-in-children-pdf-82598502860485 (Last accessed: 25 July 2022). Data on file. 2022.
9. Vimpani GV, Vimpani AF, Lidgard GP, Cameron EH, Farquhar JW. Prevalence of severe growth hormone deficiency. Br Med J. 1977 Aug 13;2(6084):427-30.
10. Lindsay R, Feldkamp M, Harris D, Robertson J, Rallison M. Utah Growth Study: growth standards and the prevalence of growth hormone deficiency. J Pediatr. 1994 Jul;125(1):29-35.
11. Tanaka T, Soneda S, Sato N, Kishi K, Noda M, Ogasawara A, et al. The Boy:Girl Ratio of Children Diagnosed with Growth Hormone Deficiency-Induced Short Stature Is Associated with the Boy:Girl Ratio of Children Visiting Short Stature Clinics. Horm Res Paediatr. 2021;94(5-6):211-8.
12. Kirk J, Clayton P. Specialist services and transitional care in paediatric endocrinology in the UK and Ireland. Clin Endocrinol (Oxf). 2006 Jul;65(1):59-63.

13. Alatzoglou KS, Webb EA, Le Tissier P, Dattani MT. Isolated Growth Hormone Deficiency (GHD) in Childhood and Adolescence: Recent Advances. Endocrine Reviews. 2014;35(3):376-432.
14. Dunger D, Darendeliler F, Kandemir N, Harris M, Rabbani A, Kappelgaard AM. What is the evidence for beneficial effects of growth hormone treatment beyond height in short children born small for gestational age? A review of published literature. J Pediatr Endocrinol Metab. 2020 Jan 28;33(1):53-70.
15. Kaplowitz P, Manjelievskaia J, Lopez-Gonzalez L, Morrow CD, Pitukcheewanont P, Smith A. Economic burden of growth hormone deficiency in a US pediatric population. J Manag Care Spec Pharm. 2021 Aug;27(8):1118-28.
16. Kopchick JJ, Berryman DE, Puri V, Lee KY, Jorgensen JOL. The effects of growth hormone on adipose tissue: old observations, new mechanisms. Nature Reviews Endocrinology. 2020 2020/03/01;16(3):135-46.
17. Beshyah SA, Johnston DG. Cardiovascular disease and risk factors in adults with hypopituitarism. Clin Endocrinol (Oxf). 1999 Jan;50(1):1-15.
18. Colao A, Marzullo P, Di Somma C, Lombardi G. Growth hormone and the heart. Clin Endocrinol (Oxf). 2001 Feb;54(2):137-54.
19. Boot AM, Engels MA, Boerma GJ, Krenning EP, De Muinck Keizer-Schrama SM. Changes in bone mineral density, body composition, and lipid metabolism during growth hormone (GH) treatment in children with GH deficiency. J Clin Endocrinol Metab. 1997 Aug;82(8):2423-8.
20. Brod M, Højbjerre L, Alolga SL, Beck JF, Wilkinson L, Rasmussen MH. Understanding Treatment Burden for Children Treated for Growth Hormone Deficiency. Patient. 2017 Oct;10(5):653-66.
21. Tanaka T, Tai S, Morisaki Y, Tachibana K, Kambayashi Y, Chihara K, et al. Evaluation of Quality of Life in Children with GH Deficiency and Idiopathic Short Stature Using the Child Behavior Checklist. Clin Pediatr Endocrinol. 2009;18(1):15-22.
22. Voss LD, Mulligan J. Bullying in school: are short pupils at risk? Questionnaire study in a cohort. BMJ (Clinical research ed.). 2000;320(7235):612-3.
23. Backeljauw P, Cappa M, Kiess W, Law L, Cookson C, Sert C, et al. Impact of short stature on quality of life: A systematic literature review. Growth Horm IGF Res. 2021 Apr-Jun;57-58:101392.
24. Silva N, Bullinger M, Sommer R, Rohenkohl A, Witt S, Quitmann J. Children's psychosocial functioning and parents' quality of life in paediatric short stature: The mediating role of caregiving stress. Clin Psychol Psychother. 2018 Jan;25(1):e107-e18.
25. National Organization for Rare Disorders. Growth hrmone deficiency, available at: https://rarediseases.org/rare-diseases/growth-hormone-deficiency/ last accessed Novermber 2022. 2016.
26. EMA. Sogroya SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/sogroya-epar-product-information_en.pdf (Last accessed: 25 May 2022). 2018.
27. Laursen T, Hansen B, Fisker S. Pain perception after subcutaneous injections of media containing different buffers. Basic Clin Pharmacol Toxicol. 2006 Feb;98(2):218-21.
28. Kappelgaard AM, Bojesen A, Skydsgaard K, Sjögren I, Laursen T. Liquid growth hormone: preservatives and buffers. Horm Res. 2004;62 Suppl 3:98-103.
29. Novo Nordisk. Clinical expert interviews to support a cost-comparison STA for NICE for somapactian in paediatric patients with GHD, Feburary 2023. Data on file. 2023.
30. Kirsch S, Butler G, Jensen L, Bøgelund M, Håkan-Bloch J. Pain-Free Injections for Growth Hormone Deficiency (GHD) Improve Quality of Life: A Time Trade-Off (TTO) Study in the UK and Canada. ISPOR Poster. Data on file. 2023.

31. Fisher BG, Acerini CL. Understanding the growth hormone therapy adherence paradigm: a systematic review. Horm Res Paediatr. 2013;79(4):189-96.
32. McNamara M, Turner-Bowker DM, Westhead H, Yaworsky A, Palladino A, Gross H, et al. Factors Driving Patient Preferences for Growth Hormone Deficiency (GHD) Injection Regimen and Injection Device Features: A Discrete Choice Experiment. Patient Prefer Adherence. 2020;14:781-93.
33. Cutfield WS, Derraik JG, Gunn AJ, Reid K, Delany T, Robinson E, et al. Non-compliance with growth hormone treatment in children is common and impairs linear growth. PLoS One. 2011 Jan 31;6(1):e16223.
34. Hughes IP, Choong C, Rath S, Atkinson H, Cotterill A, Cutfield W, et al. Early cessation and non-response are important and possibly related problems in growth hormone therapy: An OZGROW analysis. Growth Hormone & IGF Research. 2016 2016/08/01/;29:63-70.
35. Kapoor RR, Burke SA, Sparrow SE, Hughes IA, Dunger DB, Ong KK, et al. Monitoring of concordance in growth hormone therapy. Archives of Disease in Childhood. 2008;93(2):147.
36. Novo Nordisk. Comparative efficacy and safety of long-acting growth hormones in paediatric growth hormone deficiency, Data on file. 2022.
37. Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, et al. Weekly Somapacitan is Effective and Well Tolerated in Children with GH Deficiency: The Randomized Phase 3 REAL4 Trial. J Clin Endocrinol Metab. 2022 Sep 5.
38. Sävendahl L, Battelino T, Brod M, Højby Rasmussen M, Horikawa R, Juul RV, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. The Journal of clinical endocrinology and metabolism. 2020;105(4):e1847-e61.
39. Sävendahl L, Battelino T, Højby Rasmussen M, Brod M, Saenger P, Horikawa R. Effective GH Replacement With Once-weekly Somapacitan vs Daily GH in Children with GHD: 3-year Results From REAL 3. J Clin Endocrinol Metab. 2022 Apr 19;107(5):1357-67.
40. Sävendahl L, Battelino T, Rasmussen MH, Brod M, Röhrich S, Saenger P, et al. Weekly Somapacitan in GH Deficiency: 4-Year Efficacy, Safety and Treatment/Disease Burden Results from REAL 3. J Clin Endocrinol Metab. 2023 Mar 30.
41. Graham S, Weinman J, Auyeung V. Identifying Potentially Modifiable Factors Associated with Treatment Non-Adherence in Paediatric Growth Hormone Deficiency: A Systematic Review. Hormone Research in Paediatrics. 2018;90(4):221-7.
42. Shepherd S, Saraff V, Shaw N, Banerjee I, Patel L. Growth hormone prescribing patterns in the UK, 2013-2016. Arch Dis Child. 2019 Jun;104(6):583-7.
43. Ranke MB, Lindberg A, Tanaka T, Camacho-Hübner C, Dunger DB, Geffner ME. Baseline Characteristics and Gender Differences in Prepubertal Children Treated with Growth Hormone in Europe, USA, and Japan: 25 Years' KIGS® Experience (1987-2012) and Review. Hormone Research in Paediatrics. 2017;87(1):30-41.
44. Grimberg A, Lindberg A, Wajnrajch M, Cucchiara AJ, Camacho-Hübner C. Racial/Ethnic Disparities in US Pediatric Growth Hormone Treatment. Horm Res Paediatr. 2018;90(2):102-8.
45. Grimberg A, Kutikov JK, Cucchiara AJ. Sex differences in patients referred for evaluation of poor growth. The Journal of Pediatrics. 2005;146(2):212-6.
46. Grote FK, Oostdijk W, De Muinck Keizer-Schrama SM, van Dommelen P, van Buuren S, Dekker FW, et al. The diagnostic work up of growth failure in secondary health care; an evaluation of consensus guidelines. BMC Pediatr. 2008 May 13;8:21.
47. Graham S, Auyeung V, Weinman J. Exploring Potentially Modifiable Factors That Influence Treatment Non-Adherence Amongst Pediatric Growth Hormone Deficiency: A Qualitative Study. Patient Prefer Adherence. 2020;14:1889-99.

48. Hartmann K, Ittner J, Müller-Rossberg E, Schönau E, Stephan R, Ullrich KP, et al. Growth hormone treatment adherence in prepubertal and pubertal children with different growth disorders. Horm Res Paediatr. 2013;80(1):1-5.
49. Haverkamp F, Gasteyger C. A review of biopsychosocial strategies to prevent and overcome early-recognized poor adherence in growth hormone therapy of children. J Med Econ. 2011;14(4):448-57.
50. National Cancer Insitute. NCI Cancer Dictionary. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms. Last accessed April 2023.
51. GOV.UK. MHRA. Available at: https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency. Last accessed July 2022.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Somapacitan for treating growth hormone deficiency in children [ID6178]

Clarification questions

July 2023

File name	Version	Contains confidential information	Date
ID6178 Somapacitan EAG clarification questions and company responses	1.0	Yes	13 July 2023

Abbreviations

CHMP	Committee for Medicinal Products for Human Use
ECDRP	European Commission Decision Reliance Procedure
EMA	European Medicines Agency
GH	Growth hormone
GHD	Growth hormone deficiency
HV	Height velocity
ITC	Indirect treatment comparison
MHRA	Medicines and Healthcare products Regulatory Agency
RCT	Randomised controlled trial
RE	Random effects
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SDS	Standard deviation score
SIGN	Scottish Intercollegiate Guidelines Network

Section A: Clarification on effectiveness data

Literature searches

A1. Appendix D, Tables 1-9 (p.10-27): The company searches report the use of an RCT study design filter and observational study design filter. Please provide the citation information for each study design filter utilised or confirm these study design filters were constructed in-house as part of the search strategy development.

The search filters used for both RCTs and observational studies were the "Expert Searches" as recommended by Ovid (https://tools.ovid.com/ovidtools/expertsearches.html). These searches are based on the validated search filters published by the Scottish Intercollegiate Guidelines Network (SIGN; https://www.sign.ac.uk/what-we-do/methodology/search-filters/), which are routinely used, including for submissions to NICE.

Clinical effectiveness evidence

A2. Section B.4.2.1 (P. 93) The reference population used in the cost comparison has an estimated age of 13 years old, while the clinical evidence comes from trials with mean patient ages of 5.9 years old in REAL 3 (1), and 6.4 years old in REAL 4 (2). The EAG acknowledges the safety extension of REAL 3 provides some data on the effects of somapacitan for older children with growth hormone deficiency (GHD); however, the sample sizes are small and there's no assessment of relative efficacy using the comparators from the NICE scope (3). Please provide further evidence that the effectiveness evidence observed in younger children cohorts focused on in the clinical trials is maintained in the older teenage cohorts of patients focused on in the cost comparison.

The literature suggests that first-year growth is indicative of the growth outcomes of patients with growth hormone deficiency (GHD) throughout the course of their treatment. This is confirmed by a validated growth prediction model constructed from the Swedish National Growth Hormone Registry which uses early growth data as

one of its variables (4). The total duration of the somapacitan trials to the end of the safety extensions will be 4 years (REAL 4) and 7 years (REAL 3). Currently available results to Year 2 and Year 4, although not comparative, demonstrate the sustained efficacy of somapacitan (please see Section B.3.6.1 of the submission for REAL 4 extension results, and Appendix J for REAL 3 extension results).

These two trials, REAL 4 and REAL 3, were used as the evidence base for the positive EMA CHMP opinion recommending an extension to the somapacitan marketing authorisation to include the entire paediatric indication (children aged 3 years and above, and adolescents with growth failure due to GHD) (5). The same indication is expected to be licensed by the MHRA using the European Commission Decision Reliance Procedure (ECDRP).

It is also worth noting that the mean baseline age of patients in the somapacitan clinical trials is broadly in line with the baseline age in the trials of somatrogon, the only weekly GH treatment currently approved by NICE. Mean baseline ages were 6.4 and 5.9 years in the somapacitan arms in REAL 4 and REAL 3 [pooled somapacitan group], respectively, and 6.1 and 7.8 in the somatrogon arms in the Opko II and Opko III studies, respectively.

ITC analysis

A3. The study by Horikawa et al (2022) was excluded from the base-case ITC analyses because they used a different dosage to the Opko II and Opko III trials (6). Please could you clarify why you thought this was grounds for exclusion when the dose was within the recommended range?

In the pairwise ITC report sent to NICE with the somapacitan submission, an alternative evidence network including Opko JPN is presented. Results from that alternative analysis are in line with the results of the base-case network analysis presented in the submission.

The Opko JPN trial was excluded from the base-case network analysis in the ITC as it differed in several aspects to the other eligible trials. One of those was the six-week somatrogon dose escalation period in Opko JPN in which patients received

somatrogon in three escalating doses (0.25, 0.48, and 0.66 mg/kg/week; two weeks at each dose) before receiving a weekly dose of 0.66 mg/kg/week for 46 weeks, unlike in other somatrogon trials.

Secondly, somatropin dose used in the Opko JPN trial was lower (0.025 mg/kg/day) compared with the somatropin dose in the other somatrogon trials and the somapacitan trials (0.034 mg/kg/day). A recently published analysis of registry (ANSWER and NordiNet® IOS) data from paediatric patients receiving long-term GH therapy (including 12,683 with GHD) provides evidence of a dose response relationship with somatropin (7). In this study, higher GH dose in the previous year was associated with greater increases in height SDS among patients with GHD. Specifically, an increase in GH dose of 0.01 mg/kg/day was estimated to increase height SDS by 0.03 and 0.02 in females and males with GHD, respectively ($p<0.0001$). Additionally a model constructed from the KIGS database shows that GH dose can be used to predict growth (4).

Finally, all patients in the Opko JPN study were Asian (N=44; as noted in the EAG report for the somatrogon appraisal) and therefore the trial population is not expected to be reflective of the general population of children with GHD in the UK.

A4. We were unable to find R code and data included in the ITC analyses. Please could you provide all data needed to replicate the base-case and alternative-evidence analyses in the ITC report?

Please see the statistical analysis plan (SAP) that has been sent to NICE with this response document (8). Data included in the ITC analyses are provided in Appendix 1 of the SAP; R code is provided in Appendix 2.

A5. Section 4.3.5 of the ITC report states that priors for the between-trial SD were calculated "through a class-level meta-analysis with fixed effects, for each endpoint." Please could you provide a) the prior for between-trial SD used in base-case and alternative-evidence analyses and b) the data and code

used to calculate those values for the prior, in a format that can be replicated by the EAG?

a) Priors for the between-trial SD used in the base case and alternative network analyses can be found in Appendix 1 of the SAP (file: z_re_priors_pairwise.csv) and are provided in Table 1.

Table 1: Priors for the random effects model

Variable	Timepoint	prior_tau_sd
Annualised HV	52	0.221872217
Height SDS	52	0.042705347
HVSDS	52	0.338631915
Annualised HV	26	0.295724555
Height SDS	26	0.030556262

Abbreviations: HV, height velocity; SDS, standard deviation score.

b) Data used to calculate the values for the prior are provided in Appendix 1 of the SAP (A1.1 Analysis ready data set [file: ads_alt.csv]). The R code is provided in Appendix 2 of the SAP (A2.1 Script: estimate SE from class model to use as priors in the RE model).

Section B: Clarification on cost-comparison data

Cost-comparison analysis

B1. Section B.4.2.1 (p. 93): There is very little description of the process of delivering the drug to the patients. Can the company clarify whether somapacitan is likely to involve different drug delivery costs relative to the comparator interventions? If the answer is yes, can the company specify which if any resource use would be different in terms of NHS services, medical staff and/or equipment?

Somapacitan is administered as a weekly subcutaneous injection using the same ready-to-use, prefilled PDS290 pen device as for once-daily Norditropin® FlexPro®, with no reconstitution required (9-11). No difference in drug delivery costs, or in service provision or management, between somapacitan and comparators is expected. In the survey of clinicians in England, experts agreed that resource use would be similar for somapacitan and once-daily GH therapies (12).

B2. Section B.4.2.1 (P. 93): The cost-comparison analysis presented makes the assumption that either: (i) there is no differences in wastage are expected across intervention and comparators, or that (ii) there is no wastage is expected. Both somapacitan and somatrogon are delivered to patients through pre-filled pens, while the delivery of somatropin depends on the brand of preparation used.

a) Does the company have any evidence that drug wastage is equivalent across all interventions?

In line with the assumptions in the somatropin (TA188) and somatrogon (TA863) appraisals (13, 14), the cost comparison analysis assumes no wastage for somapacitan or the comparator preparations, since wastage is not expected to have a notable impact on cost differences between treatments. Indeed, in the EAG's critique of cost evidence submitted for the somatrogon appraisal, it was concluded that "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."

b) Are there any factors that are likely to increase or reduce wastage from the use of somapacitan compared with the other interventions? Does the company have any further evidence or data collected around wastage?

We do not anticipate that there are any factors that impact wastage from the use of somapacitan compared with other interventions. Somapacitan is delivered using the same ready-to-use, prefilled PDS290 pen device as Norditropin® FlexPro®, with no reconstitution required. The pen is portable and may be kept temporarily out of the fridge (e.g. while travelling) at temperatures of up to 30°C for up to a total of 72 hours (3 days) over 6 weeks' usage (9-11). In a web-based survey of patients (n=48) and caregivers (n=98) administering GH, storage-flexible products were found to be associated with significantly lower wastage ($p<0.01$), greater adherence (43% reported missing at least one injection per month vs 24%, respectively; $p<0.05$), and shorter mean injection times (20.5 min vs 10.9 min; $p<0.001$), compared with refrigeration-only products (15).

B3. Section B.4.2.2 (p. 94): NICE guidelines for somatropin to treat GHD in children recommend dosages between 23-29 micrograms (0.023-0.029 mg/kg/day) for the treatment of growth hormone deficiency in children, and doses of up to 35 micrograms (0.035 mg/kg/day) for children with growth disturbance born too small at gestational age (13). The somatropin dose of 34 micrograms (0.034 mg/kg/day) was presented in the company submission for TA863 (14) but this does not align with the dosage assumptions of TA188 (13); moreover, the then EAG explored cost-comparison scenarios at the upper and lower ends of the range proposed by NICE and suggested a dose of 25 micrograms (0.025 mg/kg/day) was more reflective of clinical practice in the NHS.

Please can the company provide a justification for not considering the suggested dose of 25 micrograms (0.025 mg/kg/day) and the absence of a sensitivity analysis and discussion on the dose ranges of somatropin in their submission. Alternatively, please can the company provide the deterministic

analysis based on the above suggested dose and sensitivity analysis exploring the dose range of somatropin?

The somatropin dose used in the base case analysis was 0.034 mg/kg/day (equivalent to 0.24 mg/kg/week), as this was the average dose in the somapacitan REAL 4 clinical trial. A summary of average weekly dose by visit in REAL 4 is provided in Table 2.

In cost comparison analysis, the annual treatment cost of somapacitan is [redacted] and in TA863, NICE has stated that using the 0.023 to 0.039 mg/kg/day dosages of somatropin, the costs of somatrogon are similar to the once daily somatropin preparations. A scenario analysis is provided in Table 3, in which the dose of daily somatropins was assumed to be 0.025 mg/kg (to align with the assumptions in TA188 and the sensitivity analysis conducted in the somatrogon submission for TA863). The base case and a scenario analysis using somatropin 0.034 mg/kg/day and 0.039 mg/kg/day (the higher end of the dosing range for daily GH) respectively are also provided for completeness.

Table 2: Somatropin and somapacitan dose by visit in REAL 4 – SAS

Average weekly dose (mg/kg/week)	Somatropin (n=68)
Visit 3 (Week 4)	
N	68
Mean (SD)	0.234 (0.021)
Visit 4 (Week 13)	
N	66
Mean (SD)	0.234 (0.023)
Visit 5 (Week 26)	
N	64
Mean (SD)	0.237 (0.013)
Visit 6 (Week 39)	
N	67
Mean (SD)	0.241 (0.014)
Visit 7 (Week 52)	
N	67
Mean (SD)	0.239 (0.012)

Abbreviations: N, number of patients; SAS, safety analysis set; SD, standard deviation.

Table 3: Annual cost comparison using low and high daily somatropin doses

	Total annual costs (£)		
	Somatropin low dose (0.025 mg/kg/day) scenario	**Somatropin base case (0.034 mg/kg/day) scenario**	**Somatropin high dose (0.039 mg/kg/day) scenario**
Somapacitan	[redacted]	[redacted]	[redacted]
Somatrogon	£9,499.78	£9,499.78	£9,499.78
Norditropin	FlexPro: £7,742.28 NordiFlex: £8,437.52	FlexPro: £10,529.50 NordiFlex: £11,475.03	FlexPro: £12,077.96 NordiFlex: £13,162.53
Saizen	£8,437.52	£11,475.03	£13,162.53
NutropinAQ	£7,389.20	£10,049.31	£11,527.15
Humatrope	£6,552.00	£8,910.72	£10,221.12
Genotropin	£6,328.92	£8,607.33	£9,873.12
Zomacton	£6,213.48	£8,450.33	£9,693.03
OMnitrope	£5,368.85	£7,301.64	£8,375.41

References

1. Sävendahl L, Battelino T, Brod M, Højby Rasmussen M, Horikawa R, Juul RV, et al. Once-Weekly Somapacitan vs Daily GH in Children With GH Deficiency: Results From a Randomized Phase 2 Trial. J Clin Endocrinol Metab. 2020 Apr 1;105(4):e1847-61.
2. Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, et al. Weekly Somapacitan is Effective and Well Tolerated in Children With GH Deficiency: The Randomized Phase 3 REAL4 Trial. J Clin Endocrinol Metab. 2022 Nov 25;107(12):3378-88.
3. Sävendahl L, Battelino T, Rasmussen MH, Brod M, Röhrich S, Saenger P, et al. Weekly Somapacitan in GH Deficiency: 4-Year Efficacy, Safety and Treatment/Disease Burden Results from REAL 3. J Clin Endocrinol Metab. 2023 Mar 30.
4. Ly HJ, Lindberg A, Fors H, Dahlgren J. Comparison of two prediction models in a clinical setting to predict growth in prepubertal children on recombinant growth hormone. Growth Horm IGF Res. 2023 Feb;68:101523.
5. European Medicines Agency (EMA). CHMP post-authorisation summary of positive opinion for Sogroya. Available at: https://www.ema.europa.eu/en/medicines/human/summaries-opinion/sogroya-0 (last accessed: July 2023). 2023.
6. Horikawa R, Tanaka T, Hasegawa Y, Yorifuji T, Ng D, Rosenfeld RG, 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. Horm Res Paediatr. 2022;95(3):275-85.
7. Ross J, Fridman M, Kelepouris N, Murray K, Krone N, Polak M, et al. Factors Associated With Response to Growth Hormone in Pediatric Growth Disorders: Results of a 5-year Registry Analysis. J Endocr Soc. 2023 Mar 6;7(5):bvad026.
8. Novo Nordisk. Statistical analysis plan for an indirect analysis assessing the relative efficacy and safety of somapacitan compared to somatrogon in children with growth hormone disorder. Data on file. 2023.
9. Novo Nordisk. Somapacitan 5 mg/1.5 mL draft Summary of Product Characteristics. 2023.
10. Novo Nordisk. Somapacitan 10 mg/1.5 mL draft Summary of Product Characteristics. 2023.
11. Novo Nordisk. Somapacitan 15 mg/1.5 mL draft Summary of Product Characteristics. 2023.
12. Novo Nordisk. Clinical expert interviews to support a cost-comparison STA for NICE for somapactian in paediatric patients with GHD, Feburary 2023. Data on file. 2023.
13. National Institute for Health and Care Excellence (NICE). Human growth hormone (somatropin) for the treatment of growth failure in children [TA188]. Available at: https://www.nice.org.uk/guidance/ta188 (last accessed: July 2023). 2010.
14. National Institute for Health and Care Excellence (NICE). Somatrogon for treating growth disturbance in children and young people aged 3 years and over [TA863]. Available at: https://www.nice.org.uk/guidance/ta863 (last accessed: July 2023). 2023.

15. Kappelgaard AM, Metzinger CP, Schnabel D. A web-based survey assessing the impact of storage flexibility on the daily life of patients and caregivers administering growth hormone. Expert Rev Med Devices. 2015;12(5):517-27.

Somapacitan for treating growth hormone deficiency in children [ID6178]

Produced by Newcastle University

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Commercial in confidence (CiC) data are highlighted in blue throughout the report.

Confidential comparator prices are highlighted in green throughout the report.

Any de-personalised data are highlighted in pink throughout the report.

Rider on responsibility for report

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Contributions of authors

Luke Vale acted as project lead. Nick Meader acted as lead effectiveness reviewer. Giovany Orozco-Leal acted as lead health economist. Fiona Beyer acted as lead reviewer of the literature search methods. Negar Yousefzadeh and Chizoba Oparah acted as assistant effectiveness reviewers. Diarmuid Coughlan, Najmeh Moradi, Elena Olariu acted as assistant health economics reviewers. Claire Eastaugh assisted in reviewing the literature search methods. Eugenie Evelynne Johnson provided critical comments during the project and on the final report. Tim Cheetham provided clinical advice.

Abbreviations

AE	Adverse event
AHV	Annualised height velocity
BNF	British National Formulary
CDSR	Cochrane Database of Systematic Reviews or Cochrane Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CrI	Credible interval
CS	Company submission
DARE	Database of Abstracts of Reviews of Effects
DIC	Deviance Information Criterion
EAG	Evidence Assessment Group
G-DAT	Growth hormone device assessment tool
GH	Growth hormone
GHD	Growth hormone deficiency
GHD-CIM	Growth hormone deficiency–child impact measure
GHD-CTB	Growth hormone deficiency – child treatment burden
GH-PPQ	Growth Hormone Patient Questionnaire-Parent/Guardian
GHD-PTB	Growth hormone deficiency – parent treatment burden
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
IGF	Insulin-like growth factor-I
ITC	Indirect treatment comparison
KIGS	Pfizer International Growth Database
kg	Kilogram
MD	Mean difference
mg	Milligram
ml	millilitre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
PfC	Points for clarification
PRESS	Peer Review of Electronic Search Strategies
PROs	Participant-reported outcomes
PSS	Personal Social Services
RCT	Randomised controlled trial
rhGH	Recombinant human growth hormone
SD	Standard deviation
SDS	Standard deviation score
SLR	Systematic literature review
TA	Technology assessment
TBCGHD-O	Treatment burden measure – child growth hormone deficiency – observer
TBCGHDP	Treatment burden measure – child growth hormone deficiency – parent
UK	United Kingdom

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1 EXECUTIVE SUMMARY

1.1 Summary of the evidence

The efficacy and safety of somapacitan versus somatropin in the company submission (CS) was informed by two company trials: REAL 4, a phase III trial of 200 participants; and REAL 3, a phase II dose-finding study of 57 participants.[1,2] Outcomes were consistent with the National Institute for Health and Care Excellence (NICE) scope.

The company conducted indirect treatment comparison (ITC) analyses to evaluate somapacitan with somatrogon, focusing on four randomised controlled trials (RCTs): REAL 3, REAL 4, Opko II and Opko III.[1-4] The cost-comparison approach presented by the company was informed by two NICE technology appraisals: the multiple technology appraisal for somatropin and the technology appraisal of somatrogon.[5,6] In line with both appraisals, this CS focused on acquisition costs only. Costs and resource use were estimated per patient per year, based on the average weekly or daily dose for a patient weighting 40 kg using list prices. The dose used for daily somatropin was 0.034 mg/kg/day, based on the doses used in the REAL 3 and REAL 4 trials.[1,2]

1.2 Does this topic meet the criteria for the cost comparison approach?

The Evidence Assessment Group (EAG) believe there is sufficient evidence to conclude that somapacitan and somatropin are clinically similar in terms of annualised height velocity (AHV), with no evidence of differences in other outcomes. Somatropin was taken as the main comparator.

The rationale behind this relates to the use of ITC analyses to evaluate somapacitan against somatropin (as well as somatrogon) in terms of AHV. The company excluded one RCT from their base-case ITC analyses;[7] the EAG disagree with this decision. This exclusion had limited impact on ITC results but has implications for the cost-comparison analyses.

The trial data are sparse and imprecise, thus the ITC results are uncertain and depend on which heterogeneity priors are used in the analyses. Heterogeneity priors are a 'first guess' before the analysis of how likely we think effects will differ between studies. As the trial data are imprecise, the choice of prior affects the estimated first guess (the prior) about heterogeneity and has an important impact on final estimates (posterior estimates).

The EAG consider the heterogeneity priors used by the company to be inappropriate. Priors were derived from fixed effect models of the same trials but these analyses had poor fit (particularly for 52 weeks), so these 'empirical priors' are of doubtful validity. When the EAG used expert elicited priors or modified empirical priors, somapacitan no longer met the criteria for non-inferiority with somatrogon, although remained non-inferior to somatropin in terms of AHV.

1.3 Critical issues

- ***Effect of dosage assumption on cost difference estimates***

The daily dose used for somatropin of 0.034 mg/kg/day used in the CS was based on dosages from the REAL 3 and REAL 4 trials.[1,2] These dosages were within the recommended British National Formulary (BNF) range of 0.023 to 0.039 mg/kg/day. However, evidence from the NICE guidance on somatropin and somatrogon,[5,6] along with clinical expert opinion consulted by the EAG, suggest a daily somatropin dose of 0.025 mg/kg/day is more appropriate as it aligns more closely with National Health Service (NHS) clinical practice. An EAG sensitivity analysis for somatropin using doses from 0.025 to 0.039

mg/kg/day showed that, depending upon the dose used, somapacitan could be either cost-saving or cost-incurring relative to somatropin.

- ***Impact of wastage on cost differences***

The CS assumed that no cost differences would result from differential wastage. The EAG felt this was not realistic, as there might be differences in the cost of wastage between the weekly and the daily formulations of growth hormone (GH) therapy; that had not been explored in previous submissions. Based on expert clinical opinion, the EAG is particularly concerned with wastage from the disposal of injection pens/cartridges containing less than a complete dose to minimise the number of injections per dose, which can increase the relative costs for weekly GH therapy formulations.

The EAG presents an analysis for a recommended dose daily somatropin of 0.025 mg/kg/day, assuming that GH therapies delivered through injection pens/cartridges lead to the disposal of pens/cartridges containing less than a complete dose. Sensitivity analyses explored an alternative scenario where only cartridges with less than 75% of a complete dose are disposed, and the wastage costs associated with higher and lower patient weights. Results from the EAG base-case shows that the annual costs of somapacitan can be higher than the annual costs of somatrogon and the average annual costs of somatropin formulations available to the NHS, with the estimated cost differences being highly uncertain depending on the dose of somatropin used and the assumptions made around drug wastage.

Overall, the EAG considers that somapacitan is clinically similar to somatropin but, depending upon assumptions around the weight of the patient and the possibility of wastage, it may be cost incurring. The magnitude of any additional costs is uncertain. The EAG further note that there is a likely small probability that somapacitan may be slightly more effective in terms of AHV than somatropin (see Table 4.4 – the EAG analysis estimated a MD of -0.49 95% CrI -2.75 to 1.56). Assuming the same non-inferiority margin for somatropin vs somapacitan then the lower limit of -2.75cm (i.e. somapacitan results in a higher AHV than somatropin) suggests there is some chance that somapacitan is superior to somatropin. Should somapacitan be judged cost incurring then this suggests that a cost-utility analysis would be a more appropriate approach to evaluate the two treatments.

2 BACKGROUND

Paediatric growth hormone deficiency (GHD) is a rare disorder associated with growth failure and short stature in children.[8,9] It is caused by insufficient production of GH by the anterior pituitary gland. It can be congenital, acquired later in life or idiopathic. In the United Kingdom (UK), current approximate prevalence ranges from 1 in 3500 to 1 in 4000 children.[5]

The current standard of care for growth failure in children with GHD is through subcutaneous injections of human recombinant (or synthetic) GH.[5] Treatment pathways vary according to the child's particular condition and their age at diagnosis.

The EAG considers that the company has provided an acceptable description of the disease area (CS Section B.1.3.1) and of the treatment pathway (CS Section B.1.3.3).[10] It provided a detailed description of the role, physiology and biological effects of GH and of the clinical manifestations of GHD in children (CS Section B.1.3.1). The company included up-to-date details on prevalence estimates of the disease in the UK (CS Section B.1.3.2) and adequately captured the burden of the disease by underlining its impact on the physical, emotional and social wellbeing of the affected children (CS Section B.1.3.4). It also provided evidence that reduced dosing frequency and injection pain of GH therapies could potentially improve treatment adherence and outcomes (CS Section B.1.3.4.2). Treatment pathways were clearly described, with details provided on healthcare resource use at treatment initiation, discontinuation and follow-up visits (CS Section B.1.3.3).[10]

Somapacitan is a long-acting recombinant human GH derivative and, due to its albumin-binding capacity, it has a longer in-vivo half-life than other human GH derivatives (CS Section B.1.2, Table 2). Somapacitan acts in the same way as human GH by binding to GH receptors and by producing Insulin-like Growth Factor-I (IGF) in tissues throughout the body (CS Section B.1.2, Table 2). It is currently also indicated for the replacement of endogenous GH in adults with GHD (CS Section B.1.2, Table 2). If approved, somapacitan will be indicated for the replacement of endogenous GH in children aged 3 years and above, and adolescents with GHD.[10]

Based on the conclusions of the European Public Assessment Report,[11] the EAG considers that somapacitan has a similar mechanism of action to both somatrogon and the different commercial formulations of somatropin, with somapacitan and somatrogon requiring weekly administrations, and somatropin requiring daily administrations. Moreover, NICE guidance suggests that the effectiveness of different formulations of somatropin may be considered equivalent.[5]

This cost comparison considers whether we can conclude that somapacitan is clinically similar to somatropin, as the index comparator and somatrogon as a secondary comparator. It then considers if a cost comparison approach is appropriate and, if so, whether the technology had a similar or lower cost compared with other technologies recommended in published NICE guidance for the same condition.

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

3.1 Population

At the time of receiving the submission, somapacitan did not have marketing authorisation in the UK. The company reported that somapacitan would be indicated in children aged three years old and above, adolescents, and adults with GHD. This submission focused on children and adolescents aged three years old and above with GHD, in line with the final NICE scope.

The clinical effectiveness evidence was underpinned by two pivotal trials comparing somapacitan with somatropin: REAL 4 and REAL 3.[1,2] The data in these clinical trials also informed the ITC between somapacitan and somatrogon. However, the inclusion criteria in both REAL 3 and REAL 4 limited eligibility to pre-pubertal patients.[1,2] This diverges from the NICE scope, which includes a wider population of both children and adolescents and may limit the generalisability of the trials to an adolescent patient population.

In Appendix J of the CS, the company report the results of a safety extension of REAL 3; cohort III of the extension focuses on nine participants with ages ranging between 10.2 and 16.1 years. Two of these participants received somapacitan as their first GH therapy, while the other seven participants switched from somatropin to somapacitan.[12] Although the results in this cohort suggested the effect of somapacitan on AHV was maintained in older children, it was still not possible to assess the relative effectiveness of somapacitan versus somatropin and somatrogon. This could potentially be a generalisability issue, as the evidence available for comparative effectiveness is only available for only a proportion of the patient population the company expects to cover in its marketing authorisation. This also has implications for the cost-comparison analysis, as the dose estimates are modelled for a population of patients around 13 years old.[10]

A previous NICE appraisal has also highlighted that adherence may decrease once patients reach adolescence.[6] Given the data in the CS, it was not possible to estimate changes in adherence across the age groups and between intervention and comparators for adolescent patients. As treatment adherence is related to treatment effectiveness, it is possible that the effectiveness seen in younger patients may not be equivalent across adolescent patients. However, the EAG would expect similar patterns of adherence across the treatment arms.

3.2 Comparators

The two comparators of interest in the NICE scope are both recombinant human GH (rhGH) therapies: daily somatropin and weekly somatrogon.

All seven combinations of somatropin available in the UK were considered relevant comparators for analysis in the CS.[13] While all the variations of somatropin are considered as the same biological formulation, it is worth noting they differ in the method of drug delivery, as some are administered via injection vials, or injection cartridges for pre-filled pens. Pre-filled injection pens are the most common method of drug delivery for daily somatropin. Both weekly somatrogon and weekly somapacitan are delivered through pre-filled injection pens. Administration methods can also include shielded needle technologies to address fears of needles in experienced by some patients.[6] The EAG considers the method of drug delivery may impact drug wastage across interventions, as dose adjustments for individual patients can be a common occurrence in this population (see sections 5.3.2.1, 6.12 and 6.2.1.2).

The included comparators were in line with previous NICE technology appraisals, TA188 and TA863,[5,6] where despite the poor quality of evidence, no significant differences were found in the effectiveness across the daily somatropin indications and, more recently, for weekly somatrogon for treating GHD.

The market shares across the comparator interventions were based on sales volume data in the UK from the company, with five-year projections for the budget impact analysis based on internal company assumptions, and therefore could not be independently verified by the EAG. [redacted] Given the dominant market share enjoyed by somatropin brands the main comparison focused by the EAG has been between somapacitan and somatropin, although consideration has also been given to the comparison between somapacitan and somatrogon.

3.3 Outcomes

Health-related quality of life (HRQoL) using preference-based outcomes measures was not reported, as these measures were not collected in the pivotal REAL 4 clinical trial. Instead, they used disease-specific questionnaires to assess the impact of GHD on physical functioning and social and emotional well-being of children with GHD and child and parent treatment burden.

The cost-comparison approach chosen requires similar outcomes across all the interventions. This was in line with the previous NICE technology assessments (TAs) for somatropin and somatrogon.[5,6]

The EAG considers the outcomes reported in the CS to be reasonable and in line with the NICE scope. The EAG also acknowledges there is a paucity in evidence translating the clinical benefits of GH therapy into HRQoL benefits that could capture, for example, differences in treatment burden to patients. Furthermore, clinical advice to the EAG highlighted the need to use final height achieved as the primary measure for treatment success in future studies, as there is a risk that seemingly small clinical differences in outcomes such as AHV observed over short time intervals can cumulatively result into large differences once patients reach adulthood.

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

4.1 Critique of the methods of review(s)

The company carried out a systematic literature review (SLR) that was later updated twice to identify clinical evidence for the safety and efficacy of long acting GH for the treatment of GHD in a paediatric population. The SLR methods are reported in Appendix D of the CS.[12]

4.1.1 Searches

The search strategy consisted of concepts pertaining to the population combined with interventions, restricted by several search filters for the inclusion of certain study types. The company conducted the original clinical effectiveness searches on 13th October 2021, with updated searches conducted on 19th May 2022 and 20th March 2023. The company searched for RCTs and observational studies in a range of electronic bibliographic databases including Embase, MEDLINE, and the Cochrane Library. The company provided search strategies for each of the searches conducted in all the databases listed.[12] The company imposed no date limitations on the search, though limited to the English language with no rationale provided. Relevant conferences, clinical trials, government/international bodies, Health Technology Assessment (HTA) websites and additional sources were identified and listed by the company as having been hand searched.[12]

EAG comment: The EAG appraised the searches presented in the CS using the Peer Review of Electronic Search Strategies (PRESS) checklist and the latest NICE methods manual and have no serious concerns.[14,15] The EAG notes the search may have benefited from including the term 'somatropin' in the comparator search string. The company reported two study design filters, one for RCTs and one for observational studies, but provided no source documentation in the submission. This was queried in the points for clarification (PfC) and the company confirmed validated study designs were used.[16] The company reported that the search was carried out in the Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Reviews (CDSR) and Database of Abstracts of Reviews of Effects (DARE). However, according to the search strategies reported in Tables 3, 6 and 9 in CS Appendix D,[12] searches of CENTRAL, CDSR and DARE were carried out in EBM Review on OVID.

4.1.2 Inclusion criteria

The pivotal REAL 4 trial included pre-pubertal boys aged ≥ 2.5 <11.0 years and girls aged ≥ 2.5 < 10.0 years, while the dose finding REAL 3 trial included pre-pubertal boys aged ≥ 2.5 ≤10.0 years and girls aged ≥ 2.5 ≤9.0 years at screening (CS Section B.3.3.1, Table 8).).[1,2,10] In both REAL 4 and REAL 3, patients had to have a confirmed diagnosis of GHD and no prior exposure to GHD therapy, excluding participants with any clinically significant abnormality likely to affect growth or the ability to evaluate growth criteria (CS Section B.3.3.1, Table 8).[1,2,10] Similar inclusion criteria were used in trials assessing the effectiveness of somatrogon.

EAG comments: The EAG agrees that all parameters of the study design were considered as per NICE scope. However, the EAG notes that the eligible age for included trials was narrower than the population set out in the NICE scope, which includes a wider age range of children and adolescents (see section 3.1 of the EAG report above for further discussion). Therefore, participants in the trial may not be representative of all children and adolescents with GHD receiving NHS treatment.

4.1.3 Quality assessment

Critical appraisal of the two RCTs conducted by the company (REAL 3 and REAL 4) are reported in CS Section B.3.5.[10] Both trials were open-label and compared weekly somapacitan and daily somatropin.

Baseline characteristics of comparator groups were generally similar, with no clinically relevant differences between them. Rates of discontinuation were also relatively similar.

EAG comment: The EAG agree that REAL 3 and REAL 4 are useful for decision-making. Differences in treatment regimen mean it would be difficult to blind participants and treatment providers for this comparison. Although this potentially impacts on risk of bias, most outcomes included in the CS were objective, so a lack of blinding is unlikely to have an important impact.[10]

A potential limitation of REAL 4 was the inclusion of 14 children who violated the trial's eligibility criteria. However, the company argued these were mainly minor deviations in criteria related to height or body mass index or deviations due to children having one or two GH stimulation tests performed more than the maximum of 12 months prior to randomisation.[10] Per protocol analyses were included in the CS excluding these 14 children, see CS Section 3.6.1. For further details about the company's trials, see CS Section B.3.3.[10]

4.1.4 Outcome measures

The focus of the EAG report is on AHV, as this was the primary outcome in the trials and the only outcome for which the company provided a non-inferiority margin. As ITC analyses are key for interpreting the non-inferiority of somapacitan with somatropin and somatrogon, the EAG focuses on these results which are reported in sections 4.2 and 4.3 below.

The company's phase III trial (REAL 4) reported that somapacitan was non-inferior to somatropin (Norditropin) for the primary outcome: AHV at week 52 (-0.5, 95% confidence interval (CI) -1.1 to 0.2). Section B.3.6.1.2[10] of the CS also reports the following outcomes without a pre-defined non-inferiority margin: height velocity standard deviation score (SDS; adjusted for age and sex); height SDS (adjusted for age and sex) bone age; and IGF-I SDS and IGFBP-3 SDS. Results from the company's dose finding phase II trial (REAL 3) are found in section B.3.6.2 of the CS.

EAG comment: The EAG's clinical expert agreed that the outcomes included in the CS were appropriate and there were no important omissions.[10] The EAG agreed results from REAL 4 support the company's conclusion that somapacitan is non-inferior to somatropin.

4.1.4.1 Participant-reported outcomes

Data from participant-reported outcomes (PROs) were reported in CS Section 3.6.1.3 for the following scales, using disease specific questionnaires:[10]

- Growth hormone deficiency–child impact measure (GHD-CIM)
- Treatment burden measure – child growth hormone deficiency – observer (TBCGHD-O). Also called the growth hormone deficiency – child treatment burden (GHD-CTB)
- Treatment burden measure – child growth hormone deficiency – parent (TBCGHDP). Also called the growth hormone deficiency – parent treatment burden (GHD-PTB)
- Growth hormone device assessment tool (G-DAT)
- Growth Hormone Patient Questionnaire-Parent/Guardian (GH-PPQ)

The GHD-CIM, GHD-CTB, GHD-PTB suggested that somapacitan was associated with similar or greater reductions in treatment burden and improved well-being compared with somatropin at 52 weeks (endpoint of trial).[10] The G-DAT questionnaire also found both somapacitan and somatropin were rated as "easy" or "very easy" to use by the vast majority of patients (96% for both).[10]

EAG comment: The EAG acknowledge that PROs in the CS were reasonable and aligned with the NICE scope. However, there was a lack of evidence regarding the translation of clinical benefits of GH therapy into improvements in HRQoL. In addition, it was not possible to assess non-inferiority as minimally important differences were not available for these scales.

4.1.4.2 Adverse events

Adverse events (AEs) for the two included RCTs were reported in CS Section B.3.10, indicating that the safety profile of once weekly somapacitan was similar to the safety profile of somatropin. Most AEs reported in REAL 3 and REAL 4 were mild or moderate. For further details, see CS Tables 34 and 39.[10]

EAG comment: Overall, the EAG notes that treatment with once-weekly somapacitan was generally well tolerated, with a similar safety profile to once-daily somatropin in the REAL 4 (up to 104 weeks) and REAL 3 (up to 156 weeks) trials. The majority of AEs experienced were mild or moderate, with none leading to death or complete discontinuation from the study. All injection site AEs were mild in severity.

4.1.4.3 Adherence

A summary of adherence data for REAL 3 and REAL 4 is reported in CS Section B.3.10.[10] Adherence rates were high for somatropin (ranging from 87.2% to 88.3%) and somapacitan (ranging from 92.2% to 95.8%).

EAG comment: The EAG consider that treatment adherence for weekly somapacitan was likely to be at least as high, and possibly higher, than for daily somatropin based on data from the REAL 4 trial (up to 104 weeks) and the REAL 3 trial (up to 156 weeks). The previous NICE appraisal for somatrogon highlighted adherence may decrease once patients reach adolescence, which may affect the effectiveness of the treatment.[6] Based on the provided evidence in the CS, it was not possible to estimate changes in adherence and effectiveness across age groups and between intervention and comparators for adolescent patients.

4.2 Critique of trials identified and included in the network meta-analysis

Five trials identified through the company's SLR were included in the company's indirect comparison analyses, see section B.3.9 of the CS.[10] and a brief summary below in Table 4.1. Three trials (Opko II, Opko III and Horikawa) compared somatropin with somatrogon.[7] Two trials compared somapacitan with somatropin (REAL 3, REAL 4).

Table 4.1 Summary characteristics of studies included in ITC analyses

	REAL 3 (N = 57)	REAL 4 (N = 200)	Opko II (N = 25)	Opko III (N = 224)	Horikawa (N = 44)
Study design	Phase II RCT: open label	Phase III RCT: open label	Phase II RCT: open label	Phase III RCT: open label	Phase III RCT: open label
Population	Mean age: 6 years Race: White 46% Asian 50%	Mean age: 6 years Race: White 57% Asian 37%	Mean age: 6 years Race: White 96%	Mean age: 8 years Race: White 75% Asian 20%	Mean: 6 years Race: Asian 100%
Intervention	Somapacitan 0.16 mg/kg/week	Somapacitan 0.16 mg/kg/week	Somatrogon 0.66 mg/kg/week	Somatrogon 0.66 mg/kg/week	Somatrogon 0.66 mg/kg/week*
Comparator	Somatropin 0.034 mg/kg/day	Somatropin 0.034 mg/kg/day	Somatropin 0.034 mg/kg/day	Somatropin 0.034 mg/kg/day	Somatropin 0.025 mg/kg/day

Source: CS Table 21[10]
* Escalating dose up to 0.66 mg/kg/week up to week 6, then 46 weeks at full dose
Abbreviations: kg = kilogram; mg = milligram; RCT = randomised controlled trial

There were no direct comparisons between somapacitan and somatrogon. However, these trials formed a connected network and it was therefore possible to compare them based on indirect evidence. The company base-case analyses excluded the Horikawa trial because the dosage for somatropin (0.025 mg/kg/day) was lower than in the company trials (REAL 3 and REAL 4: 0.034 mg/kg/day).[7] However, they conducted additional 'alternative network' ITC analyses that included this trial (see sections 4.4 and 4.5 of the company ITC report for further details).[17]

EAG comment: The EAG requested clarification on the company's rationale for excluding the Horikawa trial.[7] The company responded by stating:

- dosage is an important predictor of growth;
- somatrogon was received in escalated doses, which differed from the treatment regimen in other trials; and
- the trial was conducted in an Asian population (as pointed out in the EAG report for the somatrogon NICE appraisal[6]), therefore findings are not expected to be reflective of the UK population.[16]

The EAG agrees with the company that the Horikawa trial increases heterogeneity in the ITC analyses and there are limitations for its applicability to a UK population.[7] Nonetheless, the EAG disagree with the company base-case analyses excluding this trial. The NICE decision problem states that the comparison is between somapacitan and comparators across the range of recommended doses for these treatments. Since the trial dose for somatropin (0.025 mg/kg/day) was within the BNF recommended range, in common with TA863,[6] the EAG considers these data relevant to the decision problem, albeit with the caveats identified by the company. Therefore, the EAG considers the data from the Horikawa trial should have been included in the base-case.[7]

4.2.1 Results

4.2.1.1 Annualised height velocity: company analyses

The company set an a priori non-inferiority margin of 1.8 cm/year for AHV. In other words, somapacitan is non-inferior if the AHV for this treatment is, at a maximum, no more than 1.8 cm/year less than comparator treatments. This equates to the upper limit of the 95% credible interval (CrI) not exceeding 1.8 cm/year compared with reference treatment. In the CS, all treatments were compared with somapacitan as the reference treatment.

The company's base-case analysis found somapacitan was non-inferior to both comparators (see Table 8, Company ITC report):[17]

- 26 weeks (somatrogon: mean difference (MD) 0.40, 95% CrI -1.09 to 1.77; somatropin: MD 0.04, 95% CrI -0.97 to 0.99)
- 52 weeks (somatrogon: MD 0.09, 95% CrI -1.23 to 1.18; somatropin: MD -0.11, 95% CrI -1.00 to 0.62).

There were issues with model fit, particularly at 52 weeks (total residual deviance = 13.04, from 8 data points). The mean total residual deviance of a well-fitting model is similar to the number of data points in an ITC analysis. These problems with model fit mean there are important uncertainties regarding the company's ITC estimates.

The company's alternative network (including the Horikawa trial) also found somapacitan was non-inferior to somatrogon, somatropin 0.025mg/kg/d, and somatropin 0.034 mg/kg/d (see Tables 8 and 9 in the company ITC report).[7,17]

EAG comment:

Horikawa trial: MDs comparing the three treatments were mainly small. The EAG agree that company analyses were consistent with the non-inferiority of somapacitan with somatrogon and somatropin. However, as discussed in Section 4.2 above, the EAG disagreed with the exclusion of the Horikawa trial from the base-case analyses.[7]

Heterogeneity priors: The EAG agree that random-effects ITC models and the use of informative heterogeneity priors were appropriate. The EAG were largely able to replicate the company analyses and estimation of informative priors (within minor variations likely due to differences in rounding) after clarification from the company.

However, the company's heterogeneity priors were a key source of uncertainty. This may partly explain evidence of poor fit in the company ITC models. The EAG consider the fixed effect model estimates used to estimate the heterogeneity priors inappropriate for the following reasons.

- The company's fixed effect meta-analyses do not provide a relevant estimate of heterogeneity (between-study standard deviation (SD)). Their informative priors were based on an estimate of precision (within-study SD) of the pooled mean-difference in effects between short-acting and long-acting GH treatments, rather than between-study heterogeneity.
- Random-effects models, but not fixed effect models, allow estimation of between-study SDs (more relevant to a heterogeneity prior). The sensitivity of results to the choice of heterogeneity priors is explored below.

- Goodness of fit for fixed effect models estimating heterogeneity prior: for example, AHV at 52 weeks: a random-effects model (with non-informative prior (e.g. half-normal, SD = 3)) fitted the data better (total residual deviance = 8.4, from 8 data points; number of effective parameters = 7.6, Deviance Information Criterion (DIC) = 16) than the company's fixed effect model (total residual deviance = 15.8, from 8 data points; number of effective parameters = 5, DIC = 20.8).Therefore, the EAG conducted alternative base-case and sensitivity analyses to explore their impact on effect estimates in section 4.3.

4.2.1.2 Height velocity SDS and height SDS

CS Section B.3.9.6.1 summarises the ITC analyses for height velocity SDS and height SDS at 26 weeks and 52 weeks. Findings from these outcomes were similar to those for AHV. MDs were close to zero. However, since the company did not provide a non-inferiority margin, it was not possible for the EAG to assess if somapacitan met the criteria for non-inferiority for these outcomes.

Table compares the goodness of fit using the company's priors (a within-study SD of the pooled effect, using a fixed effect model) and a modified prior using the between-study SD (a more relevant estimate of heterogeneity) from a random-effects model. EAG modifications to the prior were calculated using R code and data provided by the company.[16] To simplify comparisons with the company analyses, the Horikawa trial was excluded.[7]

As with the AHV analyses, company analyses did not fit the data well. When random-effects models were used, this substantially increased the heterogeneity prior and improved the fit of the model. Suggesting the heterogeneity priors (between-study SDs) used by the company were too low.

Table 4.2 Goodness of fit for models using fixed effect and random-effects estimated priors

	Height velocity SDS		Height SDS	
	Company fixed effect prior	**Random-effects prior*** **	**Company fixed effect prior**	**Random-effects prior**** **
26 weeks	-	-	Estimated prior=0.03 Goodness of fit of final model: Total residual deviance=10.38** DIC=16.65	Estimated prior=0.16 Goodness of fit of final model: Total residual deviance=8.3** DIC=15.3
52 weeks	Estimated prior: 0.34 Goodness of fit for final model: Total residual deviance=9.34* DIC=14.8	Estimated prior=1.77 Goodness of fit for final model: Total residual deviance=6.5* DIC=12.7	Estimated prior=0.04 Goodness of fit for final model: Total residual deviance=11.35** DIC=17.74	Estimated prior=0.22 Goodness of fit for final model: Total residual deviance=8.7** DIC=15.7

Source: Company response to PfC, clinical expert opinion[16,18]
* From 6 data points (total residual deviance similar to number of data points indicates the model has an acceptable fit with the data)
** From 8 data points
*** The random-effect models for estimating priors at 26 and 52 weeks included a prior half-normal distribution, SD = 2.5
**** The random-effect models for estimating priors at 26 weeks included included a prior half-normal distribution, SD = 2.5
Abbreviations: DIC = deviance information criterion; PfC = points for clarification; SD = standard deviation

4.3 *EAG Base-case analyses*

The EAG base-case ITC analysis used the R code and data provided by the company but included the following three changes to the company base-case.[16]

- Inclusion of the Horikawa trial[7]
- Single node for somatropin (the company used a separate node for 0.025 mg/kg/day in the alternative network ITC analyses). EAG analyses found a simpler model with a single node had a lower total residual deviance at 26 weeks (10.8 from 10 data points) and 52 weeks (10.4 from 10 data points). The company alternative network model did not fit these data as well (total residual deviance 26 weeks: 12.30; 52 weeks: 14.96).
- Informative priors for heterogeneity (between-study SD) were elicited from a single clinical expert (Prof Cheetham) based on methods proposed by Ren and Alhussain.[19,20] The EAG base-case for AHV included a between-study SD approximately 2.5 times greater in magnitude than the company's base-case (see Table 4.3). For further details on the assumptions of this prior see EAG report Appendix section 10.1.

Table 4.3 AHV heterogeneity (between-study SD) priors

	Between-study SD	Distribution
Company heterogeneity priors	26 weeks: 0.30 52 weeks: 0.22	Half-normal
EAG heterogeneity prior base-case: expert elicited	26 and 52 weeks: 0.74 (95% CI 0.47 to 1.49)	Log-normal
EAG heterogeneity priors sensitivity analyses: calculated from random-effects models	26 weeks: 1.13 52 weeks: 1.37	Half-normal

Source: Company response to PfC, clinical expert opinion[16,18]
Abbreviations: AHV = annualised height velocity; CI = confidence interval; EAG = Evidence Assessment Group; PfC = points for clarification; SD = standard deviation

The EAG ITC analyses supported the company's conclusion that somapacitan was non-inferior to somatropin. But there was substantial uncertainty surrounding whether somapacitan was non-inferior to somatrogon for AHV (see Table 4.4). Heterogeneity priors were the key determinant of uncertainty.

- AHV estimates crossed the non-inferiority margin in comparisons with somatrogon at both 26 and 52 weeks when using an expert elicited prior (see Table 4.4) and EAG modified empirical priors (using a random-effects model instead of the company's fixed effect model; see Table 10.1 of the EAG report).
- AHV estimates were consistent with the non-inferiority of somapacitan with somatropin (upper CrI < 1.8 cm/year)
- Inclusion or exclusion of the Horikawa trial did not impact conclusions substantially (for ITC results excluding the Horikawa trial see Table 10.1).[7]

Table 4.4 Summary of AHV results from EAG base-case ITC analyses and sensitivity analyses versus somapacitan

	Somatrogon 26 weeks: MD (95% CrI)	Somatrogon 52 weeks: MD (95% CrI)	Somatropin 26 weeks: MD (95% CrI)	Somatropin 52 weeks: MD (95% CrI)
EAG base-case (expert elicited heterogeneity prior)	0.46 (-2.45 to 2.93) Total residual deviance = 10.8,* DIC = 19.9	0.20 (-2.76 to 2.91) Total residual deviance = 10.4,* DIC = 19.9	-0.29 (-2.44 to 1.64) Total residual deviance = 10.8,* DIC = 19.9	-0.49 (-2.75 to 1.56) Total residual deviance = 10.4,* DIC = 19.9
Sensitivity analyses: upper and lower 95% CI for EAG base-case heterogeneity prior				
Upper 95% CI	0.52 (-2.81 to 3.12) Total residual deviance = 10.8,* DIC = 19.9	Not estimated: problems with convergence	-0.24 (-2.68 to 1.79) Total residual deviance = 11.5,* DIC = 20.8	Not estimated: problems with convergence
Lower 95% CI	0.50 (-2.18 to 2.89) Total residual deviance = 10.8,* DIC = 19.7	0.18 (-2.41 to 2.54) Total residual deviance = 10.3,* DIC = 19.6	-0.27 (-2.28 to 1.61) Total residual deviance = 10.8,* DIC = 19.7	-0.52 (-2.45 to 1.28) Total residual deviance = 10.8,* DIC = 19.7

Source: Data and R code provided in the company response to PfC, EAG clinical expert opinion[16,18]
* From 10 data points
Abbreviations: MD = mean difference; CI = confidence interval; CrI = credible interval; DIC = deviance information criterion; PfC = points for clarification

4.4 Conclusions of the clinical effectiveness section

The efficacy and safety of somapacitan versus somatropin in the CS was informed by phase II (REAL 3) and phase III (REAL 4) open-label RCTs. The open-label nature of the trials selected were not considered a major threat to the risk of bias since primary outcomes were collected on objective measures.

The company conducted ITC analyses to evaluate somapacitan with somatrogon, constructing the evidence network around four studies: REAL 3, REAL 4, Opko II and Opko III.[1-4]

The CS base-case excluded a trial by Horikawa et al from the ITC on the grounds that it evaluated daily somatropin at a 0.025 mg/kg/day dose, which was lower than the 0.034 mg/kg/day average dose reported in the pivotal REAL 4 trial.[2,7] The EAG disagrees with this exclusion, since the somatropin dose in Horikawa et al is within the dose range recommended by the BNF of 0.023 to 0.039 mg/kg/day, and in line with previous NICE appraisals for GH therapy.[5-7]

The EAG's clinical advisor considered it clinically plausible that somapacitan is non-inferior to somatrogon and somatropin. However, trial data are relatively sparse and imprecise and ITC results were therefore uncertain and depended on which heterogeneity priors were used in the analyses.

The EAG consider the heterogeneity priors used by the company inappropriate. Priors were derived from fixed effect models of the same trials, but these analyses had poor fit (particularly for 52 weeks), so these 'empirical priors' are of doubtful validity. When the EAG used expert elicited priors or modified empirical priors, somapacitan no longer met the criteria for non-inferiority with somatrogon, although remained non-inferior to somatropin.

Analyses on safety outcomes suggested somapacitan had a similar safety profile to somatropin and potentially lower rates of injection site reactions relative to somatrogon. However, differences in AE definitions across studies made this comparison difficult. There was also similar, or potentially slightly higher, levels of adherence for weekly somapacitan compared with daily somatropin.

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

5.1 Critique of the methods of review(s)

The company carried out a SLR that was later updated to identify cost and resource data The search strategies are provided in Appendix D of the CS.[12]

5.1.1 Searches

The company conducted the original searches on 28th October 2019 and an updated search 31st January 2023. The search strategy consisted of concepts from the population combined with interventions and terms for economic and social costs, and health care resource utilisation. The searches were conducted in the bibliographic databases Embase, MEDLINE, the Cochrane Library and EconLit. The company provided search strategies for each of the searches conducted. The company imposed no date limitations on the search, limiting to human and English language but no rationale for these restrictions was included in the search statement. Relevant conferences, clinical trials, government/international bodies, HTA websites and additional sources were identified and listed by the company as being hand searched.[12]

EAG Comment: The EAG appraised the searches presented in the CS using the PRESS checklist and the latest NICE methods manual.[14,15] The EAG have no substantive concerns about these searches.

5.2 Summary of model assumptions

5.2.1 Model parameters

5.2.1.1 Patient characteristics

The CS model presented annual costs for an average patient with GHD weighing 40 kg. The weight value corresponded to the model input for weight used previously in TA863,[6] which was calculated from the average weight of children between 9 and 16 years old (midpoint age of 13 years old) in the western cohort of the Kabi/Pfizer International Growth Database (KIGS) as reported in TA188.[5,21]

5.2.1.2 Intervention and comparators

The recombinant GH therapy somapacitan was delivered as a weekly 0.16 mg/kg/week dose, which was assumed to have an equivalent efficacy to a weekly 0.66 mg/kg dose of somatrogon and the seven brands of somatropin available in the UK (Humatrope®, Zomacton®, NutropinAq®, Norditropin®, Genotropin®, Omnitrope®, and Saizen®) delivered as 0.034 mg/kg daily doses. Currently, rhGH therapy is delivered as a subcutaneous injection across all interventions, with injection pens using pre-filled cartridges as the most popular method of delivery. No further differences in the care setting were assumed across the interventions.

5.2.1.3 Perspective, time horizon and discounting

The base-case cost-comparison analysis only considered acquisition costs. Although monitoring costs were assumed to be equivalent across all interventions, an option to include further NHS and Personal Social Services (PSS) costs related to monitoring was included in the company model. Treatment duration was reported in the CS to be the same across all interventions, with a mean length of seven years.[10] However, costs for the average patient were estimated for the first year only, as variable parameters were assumed to be consistent across all treatment arms for the subsequent years of treatment. The EAG notes this is consistent with the assumptions of similar effects made in the CS.

However, given the differences estimated in the EAG analyses (see Section 4.4), the EAG suggests that a more sophisticated analysis would be required balancing cumulative costs and effects.

5.2.1.4 Adverse effects

Based on the results from the REAL 4 trial reported in Section 4.2.1.3 suggesting no significant differences in the AEs between somapacitan and somatropin,[2] the health-related impact of AEs was not included as part of the company model. The EAG considers this assumption consistent with the cost-comparison approach and the data on AE presented in the CS.[10] The company economic model included the costs of AEs but AE costs were not part of the base-case analysis, focusing only on acquisition costs.

5.2.1.5 Resource use and costs

5.2.1.5.1 Intervention and comparator acquisition costs

Information on acquisition costs was presented in CS Section B.4.2.2, Table 40.[10] Although both somatropin and somatrogon are available across multiple formulas, the cost per mg was assumed to be equivalent across all formulas available for each brand. As such, intervention costs varied by brand only and not by the formula selected.

As no wastage assumptions were implemented in the CS model, the formula selected did not have a further impact on acquisition costs. The EAG considers that including assumptions about potential wastage can make the selection of a particular formula more or less costly within each brand.

5.2.1.5.2 Dose and dose intensity

The dosage of all GH treatments was based on average patient body weight, such that a change in body weight in the company model had a proportionate change across all technologies and would not have an impact on relative costs, although it would change the absolute difference in costs estimated.[10] Somapacitan and somatropin doses were modelled, using data from the REAL 4 trial, at 0.16 mg/kg/week and at 0.238 mg/kg weekly (corresponding to a daily dose of 0.034 mg/kg/day), respectively.[2] The dose of weekly somatrogon was 0.66 mg/kg/week, corresponding with the values used in its respective cost-comparison with somatropin NICE TA863.[6] Although the dose of somatropin is consistent with the REAL 4 trial, the NICE guidance for somatropin recommends a daily dose between 0.023 and 0.039 mg/kg/day, since dose adjustments are common in GHD therapies.[13] The company provided a sensitivity analysis for both a 0.025 mg/kg/day and a 0.039 mg/kg/day dose of daily somatropin as a response to the PfCs;[16] the EAG reproduced the company sensitivity analysis.

No wastage assumptions were implemented in the CS model, implying that wastage differences were expected to have little differential impact across the interventions regardless of the brands, formulations or modes of injection administration presented. Although this assumption made in the CS was in line with assumptions made in the base-case of TA863, the EAG has explored alternative wastage assumptions based on expert clinical opinion to better reflect NHS practice (see Table 6.2).[6]

Some formulations of somatropin in the format of pre-filled disposable pen solutions present different concentrations of somatropin per 1 ml.[13] This was assumed to have no impact on costs as the focus was on the total mg content of somatropin; the EAG considers this a reasonable assumption.

5.2.1.5.3 Monitoring and disease management costs

The costs of monitoring were not included as part of the company base-case results, as the CS assumes that the disease monitoring resource use and costs were the same across all comparison treatments.

Annual resource use and costs from monitoring were included as a scenario in the company model based on resource use assumptions from TA188.[5] Although clinical advice sought by the EAG suggested minor changes to the disease monitoring process have occurred since the publication of TA188, the EAG does not expect meaningful differences in disease monitoring between the intervention and its comparators.

5.2.1.5.4 Adverse events costs

The model presented in the CS includes an analysis adding the cost of AEs to the base-case analysis for acquisition costs alone. The AE costs in the model correspond to treating injection-site pain based on annual incidence from the REAL 4 trial for somapacitan and somatropin, and Opko III for somatrogon.[2,4] As injection pain is managed through standard pain relief medication, the impact on cost-savings in this scenario is minimal. The EAG does not expect further meaningful differences in AE costs.

5.3 EAG critique

5.3.1 Dose

The somatropin dose was in line with the dose used in the REAL 4 trial.[2] However, while the somatropin dose fell within the range indicated by the BNF for the treatment of GHD in children, it lay closer to the upper range of the dose interval currently recommended (0.023 to 0.039 mg/kg daily, alternatively 0.7 to 1 mg/m^2 daily).[13]

The company stated in its CS that a dose of somatropin of 0.034 mg/kg/daily is the most used dose worldwide in real world settings for paediatric GHD and, based on a survey with four clinical experts from England, aligned with real world practice administration in England.[22] However, evidence from the Pfizer International Growth Database (KIGS) database shows that for Europe, in real world settings, median doses at the start of the therapy were estimated at 0.21 mg/kg/week (0.15 to 0.28) for prepubertal children with idiopathic GHD and at 0.21 mg/kg/week (0.14 to 0.26) for pubertal children with idiopathic GHD.[23] Hence, the KIGS reported doses are closer to 0.030 mg/kg daily than to the dose the company used in its economic analysis. The EAG acknowledge that the percentage of patients residing in the UK from the KIGS database is unknown, and also that doses reported there are the doses used at the start of the therapy and not the average dose after titration as are reported in the CS.[10]

The EAG considers the dose of somatropin to be a key driver in the cost-comparison with somapacitan and, due to the uncertainty surrounding what is real world practice in the UK, the EAG considers that a sensitivity analysis using the recommended BNF dosage interval for somatropin formulations (0.023 to 0.039 mg/kg daily) is informative. In the response to the PfCs,[16] the company provided a sensitivity analysis changing the daily dose of somatropin to 0.025 mg/kg/day and 0.039 mg/kg/day. These scenarios were also reproduced by the EAG in Section 6.

In line with clinical advice the EAG received, following the dose used in the cost-effectiveness model presented in TA188, and previous EAG advice from TA863, the EAG set their preferred base-case of the cost-comparison model to a dose of somatropin formulations of 0.025 mg/kg/daily.[5,6]

5.3.1.1 Dose adjustment

The company assumed equivalence in drug adjustment doses across somapacitan, somatrogon, and the different brands of somatropin. This was a pragmatic assumption that has been applied in the previous NICE TAs for this population, since adjustments are tailored to individual patient needs.[5,6] The EAG is

satisfied with this assumption under the current lack of evidence. However, since annual costs are sensitive to the dose used (see Section 6.1.1), this remains an area of outstanding uncertainty as differences in dose adjustments across therapies will feed directly into their estimated cost differences.

5.3.2 Drug delivery

All drugs considered in this submission are delivered subcutaneously by self-administration (or by a parent/guardian) using a pre-filled injection pen. Administration training and healthcare professional monitoring of patients/parents is not considered to differ between once-weekly and once-daily preparations by the company.[10,16] The EAG considers this an appropriate assumption.

5.3.2.1 Wastage

The EAG considers wastage is an important issue, as was previously highlighted in TA863 and elsewhere.[6,24] Although TA188 for somatropin considers that wastage might occur during drug delivery, differences across daily interventions were felt to be minor in this TA.[5] However, the EAG considers that, for weekly interventions of GH (i.e. somatrogon and somapacitan), wastage may be of greater importance at the current cost per mg they are being offered at.

The EAG is concerned that wastage from the delivery of GH may exist. For example, wastage may occur from the disposal of injection pens/cartridges containing less than a full dose. Based on responses from the clinical experts, the EAG felt it was possible that cartridges with less than a full dose could be disposed of in order to minimise the number of injections patients receive to one per dose. The EAG explores the impact of this assumption in a sensitivity analysis (see section 6.2.1.2 Cartridge wastage).

5.3.2.2 Injection-pen waste and multiple doses

Though not explicitly stated, the company assumes that patients would receive multiple injections (i.e., two injections per complete daily/weekly dose) to ensure there is no drug wastage. Clinical advice to the EAG suggested that this may not be the case. However, further details on this practice, particularly for one-weekly preparations, and at what age (if any) this is encouraged were not available and so the EAG are unable to comment further.

5.3.3 Additional comments

In accordance with the clinical expert opinion received and previous NICE TAs, the EAG acknowledges the lack of evidence around the impact of rhGH therapies on HRQoL.[5,6] Although the cost-comparison approach chosen by the company assumed an equivalence in health outcomes, it is possible that weekly therapies have an impact on the HRQoL of this population over daily GH therapies in terms of reduced number of injections, differences in treatment burden and adherence, differences in injection pain and other AEs, etc. As such, this continues to be an area of uncertainty in the appraisal of treatments for GHD.

The average acquisition cost of somatropin per year was estimated as a weighted average of list prices for the seven somatropin formulations available in the UK market. Weights were assigned according to future market share projections over five years reported in CS Section 5 (Table 7) budget impact analysis.[25] Market shares and market share projections are based on company data and assumptions, and therefore could not be verified by the EAG. However, the projected market share distribution of somatropin treatments varies little from the current market share estimates reported in CS Section B.4.3 (Table 41). [redacted].[10]

Although the average patient weight of 40 kg inputted in the model is consistent with NICE TA863,[6] the EAG notes that the median age for this weight was 13 years old. Meanwhile, the eligibility criteria in the pivotal REAL 4 trial selected pre-pubertal patients only.[2] The EAG acknowledge that extensions to the REAL 3 study provide evidence of the effects of somapacitan on adolescent patients.[26] However, this is not comparative evidence against the interventions in the scope and so the relative efficacy of somapacitan in adolescent populations is still uncertain.

Regarding the source of uncertainty and plausibility of assumptions in the cost comparison model, the EAG identified adherence as an uncertainty that could not be implemented. Since non-adherence in paediatric GHD is a critical issue in the treatment pathway,[27] and studies have demonstrated that discomfort and pain from the injection is a key factor affecting adherence,[28] the EAG considers that differences in injection pain can drive differences in adherence and that differences in adherence across GH therapies remain uncertain, particularly for adolescent patients.

5.4 Model check

The EAG checked that input values in the cost-comparison analysis matched the estimates reported in the CS. The model utilises the NHS indicative price for the 12 mg solution for injection cartridges of Humatrope® quoted in the BNF. However, since the drug tariff price is lower than the NHS indicative price, the EAG used the lower drug tariff price for the cost comparison.[13]

6 COMPANY AND EAG COST-COMPARISON RESULTS

6.1 Company's cost-comparison results

[redacted] The cost of weekly somatrogon was estimated annually at £9499.78. The cost of weekly somapacitan was estimated annually at [redacted] Annual cost estimates and respective market shares for the treatment and comparator interventions are presented in CS Section B.4.3 (Table 41 and Figure 15).[10] No further scenarios were presented by the company beyond the base-case. The company considered that most variables were consistent across daily and weekly treatment options and therefore had little to no impact on comparative costs. No subgroup analyses were requested for this submission.

6.1.1 Sensitivity analysis: somatropin dose

In response to the PfCs,[16] the company explored the impact on annual treatment costs of replacing the company's chosen dose of daily somatropin to a dose of 0.025 mg/kg/day and 0.039 mg/kg/day in a sensitivity analysis. The EAG reproduced this sensitivity analysis (see Table 6.1 and Table 6.3).

By changing the daily somatropin dose to 0.039 mg/kg/day, the top end of the BNF range, the average acquisition costs of somatropin increased [redacted] from the CS base-case values to [redacted]. This increased the cost-saving estimates of both somatrogon and somapacitan to an average of [redacted] per year relative to daily somatropin from the annual [redacted] cost-saving estimate in the CS base-case.

Table 6.1 EAG sensitivity analysis on annual treatment costs using somatropin at a dose of 0.039 mg/kg/day

	Company base-case dose (0.034 mg/kg/day)	Cost difference (versus somapacitan)	Somatropin dose 0.039 mg/kg/day	% change from baseline	Cost difference (versus somapacitan)
Somapacitan*	[redacted]		[redacted]	[redacted]	
Somatrogon	**£9499.78**	[redacted]	**£9499.78**	**0.00%**	[redacted]
Somatropin (weighted average)*	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Norditropin FlexPro	£10,529.50	[redacted]	£12,077.96	14.71%	[redacted]
Norditropin Nordiflex	£11,475.03	[redacted]	£13,162.53	14.71%	[redacted]
Saizen	£11,475.03	[redacted]	£13,162.53	14.71%	[redacted]
Omnitrope	£7301.64	[redacted]	£8375.41	14.71%	[redacted]
NutropinAQ	£10,049.31	[redacted]	£11,527.15	14.71%	[redacted]
Genotropin	£8607.33	[redacted]	£9873.12	14.71%	[redacted]
Zomacton	£8450.33	[redacted]	£9693.03	14.71%	[redacted]
Humatrope	£8910.72	[redacted]	£10,221.12	14.71%	[redacted]
Abbreviations: mg = milligram; kg= kilogram					

6.1.2 Sensitivity analysis: cartridge/pen related wastage

The EAG has proposed a wastage scenario using the CS model that includes all formulations for each brand of somatropin and somatrogon available in the UK. A limit in the number of doses per cartridge/pen was set at 28 days, beyond which the cartridge/pen needs to be replaced, except for somapacitan where the limit was set at six weeks following information from the PfC.[16] This scenario assumes that cartridges/pens are disposed once there is less than a full (daily or weekly) dose left so that patients receive no more than one injection per dose. This assumption is in line with the clinical expert opinion sought by the EAG.

Results from the wastage scenario analysis are presented in Table 6.2. The wastage of cartridges with less than a full dose increases costs across all interventions but has a stronger impact on weekly therapies, as annual costs for these can increase up to [redacted] £1295.42 for somatrogon, whereas annual cost increases due to cartridge/pen wastage for somatropin range from £19.52 (Omnitrope®) to £578.57 (Saizen®). [redacted]

Table 6.2 EAG wastage scenario analysis

	Company base-case	Cartridge waste	% change from baseline	Cost difference (versus somapacitan)
Somapacitan	[redacted]	[redacted]	[redacted]	
Somatrogon	**£9499.78**	**£10,795.20**	**13.64%**	[redacted]
Somatropin (weighted average)	[redacted]	[redacted]	[redacted]	[redacted]
Norditropin FlexPro	£10,529.50	£10,557.65	0.27%	[redacted]
Norditropin Nordiflex	£11,475.03	£11,505.71	0.27%	[redacted]
Saizen	£11,475.03	£12,053.60	5.04%	[redacted]
Omnitrope	£7301.64	£7321.17	0.27%	[redacted]
NutropinAQ	£10,049.31	£10,556.00	5.04%	[redacted]
Genotropin	£8607.33	£8860.28	2.94%	[redacted]
Zomacton*	£8450.33	£8450.33	0.00%	[redacted]
Humatrope	£8910.72	£9249.88	3.81%	[redacted]
*Zomacton is delivered through vials and therefore has no cartridge/pen wastage associated.				

The EAG acknowledge the assumption of patients receiving only one injection per dose and that disposing injection cartridges/pens with less a full dose might not occur in all settings. However, the EAG also notes that issues with cartridge wastage have been raised in the literature.[29] Furthermore, since the clinical experience of weekly treatments such as somatrogon is currently limited in the UK, the EAG considers this an informative scenario and considers the assumption of no wastage in the CS base-case to be unrealistic. The true amount of wastage from injection pen/cartridge use is unknown

and the EAG believe that the true estimate of annual acquisition costs is likely to lie between the scenario of no wastage, as adopted in the CS, and wastage, as explored by the EAG.

6.2 EAG's cost-comparison results

6.2.1 EAG base-case

6.2.1.1 Somatropin dose

Based on the clinical advice to the EAG and in line with previous NICE appraisals (TA188 and TA863),[5,6] the EAG considers a 0.025 mg/kg/daily dose of somatropin to be more representative of the NHS context. Table 6.3 presents the cost-comparison results using a 0.025 mg/kg daily dose of somatropin and the differences in costs compared with the company's base case. At a 0.025 mg/kg/daily dose of somatropin, [redacted]

Table 6.3 Comparison between the EAG preferred base case and the company's base case

	CS base-case (somatropin 0.034 mg/kg/daily)	EAG preferred dose (somatropin 0.025 mg/kg/daily)	% change from base case	Cost difference (versus somapacitan)
Somapacitan	[redacted]	[redacted]	[redacted]	[redacted]
Somatrogon	**£9499.78**	**£9499.78**	**0.00%**	[redacted]
Somatropin (weighted average)	[redacted]	[redacted]	[redacted]	[redacted]
Norditropin FlexPro	£10,529.50	£7742.28	-26.47%	[redacted]
Norditropin Nordiflex	£11,475.03	£8437.52	-26.47%	[redacted]
Saizen	£11,475.03	£8437.52	-26.47%	[redacted]
Omnitrope	£7301.64	£5368.85	-26.47%	[redacted]
NutropinAQ	£10,049.31	£7389.20	-26.47%	[redacted]
Genotropin	£8607.33	£6328.92	-26.47%	[redacted]
Zomacton	£8450.33	£6213.48	-26.47%	[redacted]
Humatrope	£8910.72	£6552.00	-26.47%	[redacted]
Abbreviations: mg = milligram; kg= kilogram				

6.2.1.2 Cartridge wastage

Implementing the assumption that cartridges with less than a full (weekly or daily) dose remaining are always disposed has little impact on the acquisition cost estimates of somatropin at a 0.025 mg/kg/daily dose. This is a consequence of the dose selected minimising wastage at an average paediatric patient weight of 40 kg. In contrast, this assumption increases the annual costs of weekly somapacitan and weekly somatrogon by [redacted] and [redacted] respectively. Although cartridge waste will vary depending on the total dose and formula selected, the EAG analysis suggests that annual acquisition costs of

weekly somapacitan are on average [redacted] higher than somatropin and [redacted] higher than somatrogon under this assumption. The results of the EAG base-case are reported in Table 6.4.

Table 6.4 EAG final base-case

	CS base-case	EAG final base-case	% difference from baseline	Cost difference (versus somapacitan)
Somapacitan	[redacted]	[redacted]	[redacted]	
Somatrogon	**£9499.78**	**£10,795.20**	**13.64%**	[redacted]
Somatropin (weighted average)	[redacted]	[redacted]	[redacted]	[redacted]
Norditropin FlexPro	£10,529.50	£7742.28	-26.47%	[redacted]
Norditropin Nordiflex	£11,475.03	£8437.52	-26.47%	[redacted]
Saizen	£11,475.03	£8437.52	-26.47%	[redacted]
Omnitrope	£7301.64	£5368.85	-26.47%	[redacted]
NutropinAQ	£10,049.31	£7389.20	-26.47%	[redacted]
Genotropin	£8607.33	£6328.92	-26.47%	[redacted]
Zomacton	£8450.33	£6213.48	-26.47%	[redacted]
Humatrope	£8910.72	£6329.05	-28.97%	[redacted]

6.2.2 EAG scenario analysis

6.2.2.1 Cartridge disposal below 75% of a dose

To address the extreme scenario where cartridges are disposed of when there is less than a full dose remaining in the cartridge, other studies focusing on daily somatropin have assumed that cartridges containing 75% or more of the prescribed dose can be used to deliver a full dose administration.[29,30] Under the current evidence, it is uncertain whether occasionally receiving less than 25% of a full dose will have an impact on the effectiveness of weekly compared with daily therapies. Cost-comparison results suggest this assumption has little impact on acquisition costs compared with the EAG base-case, beyond a 1.55% reduction in the average cost of somatropin due to less waste.

6.2.2.2 Average patient weight

The EAG notes that although average patient weight is likely to have a proportional effect across the interventions in the CS base-case assuming no waste, the addition of the cartridge wastage assumption is likely to lead to differences in the acquisition cost estimated depending on the total dose and formula used. Results from the EAG analysis suggest that for patients with an average weight of [redacted] more versus somatropin, and [redacted] more than somatrogon per year. For patients weighing 50 kg, somapacitan increases annual costs by [redacted] more than somatropin on average, while somapacitan decreases annual costs by [redacted] versus somatrogon (see Table 6.5).

Table 6.5 EAG average weight patient scenario

	EAG base-case (40 kg)	Cost difference versus somapacitan	Patient weight 16.5 kg	% change from baseline	Cost difference versus somapacitan	Patient weight 50 kg	% Change from baseline	Cost difference (versus somapacitan)
Somapacitan	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	
Somatrogon	**£10,795.20**	[redacted]	**£4318.08**	**-60.00%**	[redacted]	**£21,590.40**	**100.00%**	[redacted]
Somatropin (weighted average)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Norditropin FlexPro	£7742.28	[redacted]	£3225.95	-58.33%	[redacted]	£9677.85	25.00%	[redacted]
Norditropin Nordiflex	£8437.52	[redacted]	£3515.63	-58.33%	[redacted]	£10,546.90	25.00%	[redacted]
Saizen	£8437.52	[redacted]	£3616.08	-57.14%	[redacted]	£10,546.90	25.00%	[redacted]
Omnitrope	£5368.85	[redacted]	£2237.02	-58.33%	[redacted]	£6711.07	25.00%	[redacted]
NutropinAQ	£7389.20	[redacted]	£3078.83	-58.33%	[redacted]	£9236.50	25.00%	[redacted]
Genotropin	£6328.92	[redacted]	£2712.45	-57.14%	[redacted]	£8385.65	32.50%	[redacted]
Zomacton	£6213.48	[redacted]	£2761.55	-55.56%	[redacted]	£8284.64	33.33%	[redacted]
Humatrope	£6329.05	[redacted]	£2712.45	-57.14%	[redacted]	£8276.21	30.77%	[redacted]

6.3 Summary: EAG critique of the cost-comparison analysis and results

The EAG has highlighted the dose of somatropin and differences in wastage at drug delivery as key determinants of the cost-comparison results of somapacitan versus somatropin and somatrogon for the treatment of GHD in the NHS. The EAG acknowledges the use of an average daily dose of 0.034 mg/kg/day for somatropin in the REAL 4 study, which is within the range of the BNF guidance. However, based on precedence from previous TAs (TA188 and TA863) and clinical expert opinion received, the EAG considers the average daily somatropin dose of 0.025 mg/kg/day to better reflect clinical practice.[5,6] At this dosage, somapacitan is no longer a cost-saving option compared to the average annual costs of daily somatropin brands available.

The disposal of cartridges/injection pens with less than a full dose was identified as a potential source of wastage, which has a major impact in the cost-differences between weekly and daily GHD therapies. The EAG explored a scenario where all cartridges containing less than a full dose are always disposed of. This led to weekly somapacitan no longer being cost saving compared with the average daily somatropin therapy. The EAG recognises this is an extreme scenario, but clinical expert opinion sought by the EAG confirmed the likelihood of this being a source of waste. Hence, the EAG considers the assumption of no differences in drug wastage adopted in the CS to be unrealistic.

To explore this further, the EAG also explored a scenario where cartridges with at least 75% of a full dose were still delivered. Here, average daily somatropin costs remained lower than weekly somapacitan. Further sensitivity analyses conducted by the EAG show that wastage costs are dependent on the number of complete doses as a proportion of vial size and therefore may vary depending on the dose required, the size of the vial used, and any further brand-specific delivery instructions.

The EAG believes that adherence is one of the key issues not considered in the company model. Non-adherence in paediatric GHD is a critical issue in the treatment pathway. According to a 2018 SLR, adherence can vary between 7% and 71%.[27] A qualitative study on non-adherence factors in GHD treatment in the UK in 2020 stated that discomfort and pain from the injection are key factors affecting adherence.[28] If the evidence shows more pain from weekly injections, then adherence and, hence, effectiveness may be reduced. Further information on adherence in routine practice in the longer term is needed.

A final area of uncertainty affecting costs is age. Boys eligible to participate in REAL 3 and REAL 4 were aged up to 10 and 11 years old, respectively. For girls, the corresponding ages were 9 and 10, respectively. Age at the start of treatment is a key factor affecting the cost model's inputs, such as weight, dosage needed, wastage and, potentially, adherence.

7 EQUALITIES AND INNOVATION

Somapacitan does not raise any innovation considerations.

With respect to equality consideration issues were raised in Section B1.4 of the CS[10] but no consideration was given as to how somapacitan would address these. The EAG notes that weekly dose regimens may help ensure treatments for children and young people with a phobia against injections (as they require fewer injections per week) or with other circumstances making daily administration difficult.

8 EAG COMMENTARY ON THE ROBUSTNESS OF EVIDENCE SUBMITTED BY THE COMPANY

8.1 Summary and critique of the clinical effect evidence

Overall, and as summarised below, the EAG identified no critical issues that would deter NICE from proceeding with the cost-comparison approach for the comparison of somapacitan and somatropin (though potentially not with the far less commonly used somatrogon).

The efficacy and safety of somapacitan versus somatropin in the CS [10]was informed by two trials: REAL 4, a phase III trial of 200 participants; and REAL 3, a phase II dose-finding study of 57 participants. Outcomes were consistent with the NICE scope.

The company conducted ITC analyses to evaluate somapacitan with somatrogon, focusing on four RCTs: REAL 3, REAL 4, Opko II and Opko III.[1-4] The company excluded one RCT from their base-case ITC analyses; the EAG disagreed with this decision.[7] This exclusion had limited impact on the ITC results but has implications for the cost-comparison analyses. The open-label nature of all included trials was not considered an important risk of bias since most outcomes included in the CS were objective.[10]

The EAG's clinical advisor considered it clinically plausible that somapacitan is non-inferior to somatrogon and somatropin. However, trial data are relatively sparse and imprecise, therefore the ITC results were uncertain and depended on which heterogeneity priors were used in the analyses.

The EAG consider the heterogeneity priors used by the company to be inappropriate. Priors were derived from fixed effect models of the same trials. However, these analyses had poor fit (particularly for 52 weeks), so these 'empirical priors' are of doubtful validity. When the EAG used expert elicited priors or modified empirical priors, somapacitan no longer met the criteria for non-inferiority with somatrogon, although remained non-inferior to somatropin.

Somapacitan had a similar safety profile to somatropin and potentially lower rates of injection site reactions relative to somatrogon. However, differences in AE definitions across the studies made this comparison difficult. There were also similar, or potentially higher, levels of adherence for weekly somapacitan compared to daily somatropin.

8.2 Summary and critique of the cost-comparison approach

The cost-comparison approach presented by the company was informed by two NICE technology appraisals: the multiple technology appraisal for somatropin and the technology appraisal of somatrogon.[5,6] In line with these appraisals, this CS focused on acquisition costs only. Costs and resource use were estimated per patient per year, based on the average weekly or daily dose for a patient weighting 40 kg using list prices. The dose used for daily somatropin was 0.034 mg/kg/day, based on the doses used in the REAL 3 and REAL 4 trials.[1,2]

Several critical issues were identified, affecting claims that somapacitan would be cost saving compared with daily somatropin.

- ***Effect of dosage assumption on cost difference estimates***

The daily dose used in the CS for somatropin of 0.034 mg/kg/day was based on dosages from the REAL 3 and REAL 4 trials.[1,2] These dosages were within the recommended BNF range of 0.023 to 0.039 mg/kg/day. However, evidence from NICE guidance on somatropin and somatrogon,[5,6] along with

clinical expert opinion consulted by the EAG, suggest a daily somatropin dose of 0.025 mg/kg/day is more appropriate as it aligns more closely with NHS clinical practice. An EAG sensitivity analysis for somatropin using doses from 0.025 to 0.039 suggested that, depending upon the dose used, somapacitan could be either cost-saving or cost-incurring relative to somatropin.

- ***Impact of wastage on cost differences***

The CS base-case assumed that no cost differences would result from differential wastage. The EAG feels this was not realistic as there might be differences in the cost of wastage between the weekly and the daily formulations of GH therapy, which has not been explored in previous submissions. Based on expert clinical opinion, the EAG is particularly concerned with wastage from the disposal of injection pens/cartridges containing less than a complete dose to minimise the number of injections per dose, which can increase the relative costs for weekly GH therapy formulations.

The EAG base-case presents an analysis for a recommended dose daily somatropin of 0.025 mg/kg/day, and assuming that GH therapies delivered through injection pens/cartridges lead to the disposal of pens/cartridges containing less than a complete dose. Sensitivity analyses explored an alternative scenario where only cartridges with less than 75% of a complete dose are disposed, and the wastage costs associated with higher and lower patient weights. Results from the EAG base-case show that the annual costs of somapacitan can be higher than the annual costs of somatrogon and the average annual costs of somatropin formulations available to the NHS, with the estimated cost differences being highly uncertain depending on the dose of somatropin used and the assumptions made around drug wastage.

Overall, the EAG considers that somapacitan is clinically similar to somatropin but, depending upon assumptions around the weight of the patient and the possibility of wastage, it may be cost incurring. The magnitude of any additional costs is uncertain. The EAG further note that there is a likely small probability that somapacitan may be slightly more effective in terms of AHV than somatropin (see Table 4.4 – the EAG analysis estimated a MD of -0.49 95% CrI -2.75 to 1.56). Assuming the same non-inferiority margin for somatropin vs somapacitan then the lower limit of -2.75cm (i.e. somapacitan results in a higher AHV than somatropin) suggests there is some chance that somapacitan is superior to somatropin. Should somapacitan be judged cost incurring then this suggests that a cost-utility analysis would be a more appropriate approach to evaluate the two treatments.

9 REFERENCES

1 Sävendahl L, Battelino T, Brod M, Højby Rasmussen M, Horikawa R, Juul RV, et al. Once-weekly somapacitan vs daily GH in children with GH deficiency: results from a randomized phase 2 trial. The Journal of Clinical Endocrinology and Metabolism. 2020;105(4):e1847-e61. Available from: https://doi.org/10.1210/clinem/dgz310.

2 Miller BS, Blair JC, Rasmussen MH, Maniatis A, Kildemoes RJ, Mori J, et al. Weekly somapacitan is effective and well tolerated in children with GH deficiency: the randomized phase 3 REAL4 trial. The Journal of Clinical Endocrinology and Metabolism. 2022;107(12):3378-88. Available from: https://doi.org/10.1210/clinem/dgac513.

3 Zelinska N, Iotova V, Skorodok J, Malievsky O, Peterkova V, Samsonova L, et al. Long-acting C-terminal peptide–modified hGH (MOD-4023): results of a safety and dose-finding study in GHD children. The Journal of Clinical Endocrinology and Metabolism. 2017;102(5):1578-87. Available from: https://doi.org/10.1210/jc.2016-3547.

4 Deal CL, Steelman J, Vlachopapadopoulou E, Stawerska R, Silverman LA, Phillip M, et al. Efficacy and safety of weekly somatrogon vs daily somatropin in children with growth hormone deficiency: a phase 3 study. The Journal of Clinical Endocrinology and Metabolism. 2022;107(7):e2717-e28. Available from: https://doi.org/10.1210/clinem/dgac220.

5 National Institute for Health and Care Excellence (NICE). Human growth hormone (somatropin) for the treatment of growth failure in children [TA188]. Technology Appraisal Guidance National Institute for Health and Care Excellence (NICE); 2010. Available from: https://www.nice.org.uk/guidance/ta188.

6 National Institute for Health and Care Excellence (NICE). Somatrogon for treating growth disturbance in children and young people aged 3 years and over [TA863]. Technology Appraisal Guidance National Institute for Health and Care Excellence (NICE); 2023. Available from: https://www.nice.org.uk/guidance/ta863.

7 Horikawa R, Tanaka T, Hasegawa Y, Yorifuji T, Ng D, Rosenfeld RG, 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. Hormone Research in Paediatrics. 2022;95(3):275-85. Available from: https://doi.org/10.1159/000524600.

8 Chinoy A, Murray PG. Diagnosis of growth hormone deficiency in the paediatric and transitional age. Best Practice and Research Clinical Endocrinology and Metabolism. 2016;30(6):737-47. Available from: https://doi.org/https://doi.org/10.1016/j.beem.2016.11.002.

9 Dattani M, Preece M. Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment. The Lancet. 2004;363(9425):1977-87. Available from: https://doi.org/https://doi.org/10.1016/S0140-6736(04)16413-1.

10 Novo Nordisk. Somapacitan for treating growth hormone deficiency in children [ID6178]. Document B. Company evidence submission Single technology appraisal (STA): Cost-comparison appraisal. Novo Nordisk; 2023.

11 Committee for Medicinal Products for Human Use (CHMP). Sogroya. International non-proprietary name: somapacitan. Assessment report Procedure No EMEA/H/C/005030/0000. European

Medicines Agency; 2021. Available from: https://www.ema.europa.eu/en/documents/assessment-report/sogroya-epar-public-assessment-report_en.pdf.

12 Novo Nordisk. Somapacitan for treating growth hormone deficiency in children [ID6178]. Appendices Single technology appraisal (STA): Cost-comparison appraisal. Novo Nordisk; 2023.

13 British National Formulary for Children (BNFC). Somatropin. Indications and dose. National Institute for Health and Care Excellence (NICE); 2023. Available from: https://bnfc.nice.org.uk/drugs/somatropin/#indications-and-dose.

14 McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. Journal of Clinical Epidemiology. 2016;75:40-6. Available from: https://doi.org/https://doi.org/10.1016/j.jclinepi.2016.01.021.

15 National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual [PMG36]. Process and Methods. National Institute for Health and Care Excellence (NICE); 2022. Available from: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

16 Novo Nordisk. Somapacitan for treating growth hormone deficiency in children [ID6178]. Clarification questions Single technology appraisal (STA): Cost-comparison appraisal. Novo Nordisk; 2023.

17 Novo Nordisk. Comparative efficacy and safety of somapacitan and somatrogon in paediatric growth hormone deficiency. Version 3.0. ITC Report. Novo Nordisk; 2022.

18 Evidence Assessment Group (EAG). Additional clinical questions: Somapacitan for treating growth hormone deficiency in children. Single technology appraisal (STA): Cost-comparison appraisal. Evidence Assessment Group (EAG); 2023.

19 Ren S, Oakley JE, Stevens JW. Incorporating genuine prior information about between-study heterogeneity in random effects pairwise and network meta-analyses. Medical Decision Making. 2018;38(4):531-42. Available from: https://doi.org/10.1177/0272989X18759488.

20 Alhussain ZA, Oakley JE. Assurance for clinical trial design with normally distributed outcomes: eliciting uncertainty about variances. Pharmaceutical Statistics. 2020;19(6):827-39. Available from: https://doi.org/https://doi.org/10.1002/pst.2040.

21 Ranke MB, Lindberg A, Tanaka T, Camacho-Hübner C, Dunger DB, Geffner ME. Baseline characteristics and gender differences in prepubertal children treated with growth hormone in Europe, USA, and Japan: 25 years' KIGS® Experience (1987-2012) and review. Hormone Research in Paediatrics. 2016;87(1):30-41. Available from: https://doi.org/10.1159/000452887.

22 Novo Nordisk. Clinical expert interviews to support a cost-comparison STA for NICE for somapactian in paediatric patients with GHD. V1.0. Clarivate Consulting Services; 2023.

23 Maghnie M, Ranke MB, Geffner ME, Vlachopapadopoulou E, Ibáñez L, Carlsson M, et al. Safety and efficacy of pediatric growth hormone therapy: results from the full KIGS cohort. The Journal of Clinical Endocrinology and Metabolism. 2022;107(12):3287-301. Available from: https://doi.org/10.1210/clinem/dgac517.

24 Orso M, Polistena B, Granato S, Novelli G, Di Virgilio R, La Torre D, et al. Pediatric growth hormone treatment in Italy: A systematic review of epidemiology, quality of life, treatment adherence, and economic impact. PLOS ONE. 2022;17(2):e0264403. Available from: https://doi.org/10.1371/journal.pone.0264403.

25 Novo Nordisk. Somapacitan for treating growth hormone deficiency in children [ID6178]. Company budget impact analysis submission. Single technology appraisal (STA): Cost-comparison appraisal. Novo Nordisk; 2023.

26 Sävendahl L, Battelino T, Højby Rasmussen M, Brod M, Röhrich S, Saenger P, et al. Weekly somapacitan in GH deficiency: 4-year efficacy, safety, and treatment/disease burden results from REAL 3. The Journal of Clinical Endocrinology and Metabolism. 2023. Available from: https://doi.org/10.1210/clinem/dgad183.

27 Graham S, Weinman J, Auyeung V. Identifying potentially modifiable factors associated with treatment non-adherence in paediatric growth hormone deficiency: a systematic review. Hormone Research in Paediatrics. 2018;90(4):221-7. Available from: https://doi.org/10.1159/000493211.

28 Graham S, Auyeung V, Weinman J. Exploring potentially modifiable factors that influence treatment non-adherence amongst pediatric growth hormone deficiency: a qualitative study. Patient Preference and Adherence. 2020;14:1889-99. Available from: https://doi.org/10.2147/PPA.S268972.

29 Foo J, Maghnie M, Colao A, Vlachaki I, Colombo G. Cost-consequence analysis for human recombinant growth hormone (r-hGH) treatment administered via different devices in children with growth hormone deficiency in Italy. ClinicoEconomics and Outcomes Research. 2019;11:525-37. Available from: https://doi.org/10.2147/CEOR.S195265.

30 Saz-Parkinson Z, Granados Alonso MdS, Amate JM. Study of adherence to recombinant growth hormone treatment of children with a GH deficiency: contributions to treatment control and economic impact. Public Health Technology Assessment Report. Instituto de Salud Carlos III (ISCIII). Agencia de Evaluación de Tecnologías Sanitarias (AETS); 2013. Available from: http://hdl.handle.net/20.500.12105/5438.

10 Appendices

10.1 Summary of EAG assumptions for heterogeneity prior elicited from clinical expert

Informative heterogeneity priors (between-study SD) were elicited from a single clinical expert (Prof Cheetham) based on methods proposed by Ren and Alhussain.[19,20]

The following assumptions were used to develop the heterogeneity prior:

- median (m) difference on AHV between somatrogon compared with somapacitan = 0.2cm/year
- median difference interval [k1, k2] for AHV = -1 cm/year[k_1] to 1 cm/year[k_2]
- proportion of patients with outcomes between AHV 0.2 cm/year and 1 cm/year (i.e. m, k_2): lower = 0.2, upper = 0.45
- proportion quantiles: 0.05 to 0.95

These elicited assumptions resulted in the following heterogeneity prior (log-normal distribution): between-study SD = 0.74. 95% lower (0.47) and upper (1.49) limits were also estimated and explored in sensitivity analyses (Table 10.1-).

10.2 Sensitivity analyses excluding the Horikawa trial[7]

Use of expert-elicited and random-effects estimated priors led to similar 95% CrIs. These CrIs were wider than the company ITC analyses. Table 10.1 shows ITC estimates for models excluding the Horikawa trial.[7] Similar results were found when including this trial in analyses.

Table 10.1 Sensitivity analyses for AHV excluding the Horikawa trial and including expert elicited or random-effects estimated heterogeneity priors[7]

	Somatrogon 26 weeks: MD (95% CrI)	**Somatrogon 52 weeks: MD (95% CrI)**	**Somatropin 26 weeks: MD (95% CrI)**	**Somatropin 52 weeks: MD (95% CrI)**
Heterogeneity Prior from EAG base-case (expert elicited)	-0.21 (-3.69 to 2.62) Total residual deviance = 8.3,* DIC = 15.6	-0.48 (-3.73 to 2.56) Total residual deviance = 8.2,* DIC = 15.9	-0.25 (-2.49 to 1.77) Total residual deviance = 8.3,* DIC = 15.6	-0.50 (-2.72 to 1.62) Total residual deviance = 8.2,* DIC = 15.9
Random-effects estimated heterogeneity prior	-0.11 (-3.37 to 2.44) Total residual deviance = 8.8,* DIC = 16.1	-0.49 (-3.78 to 2.49) Total residual deviance = 8.3,* DIC = 16.1	-0.21 (-2.34 to 1.53) Total residual deviance = 8.8,* DIC = 16.1	-0.52 (-2.88 to 1.60) Total residual deviance = 8.3,* DIC = 16.1

Source: Data and R code provided in the company response to points for clarification, EAG clinical expert opinion[16,18]
*From 8 data points
Abbreviations: AHV = annualised height velocity; CrI = credible intervals; DIC = deviance information criterion; MD = mean difference

Cost Comparison Appraisal

Somapacitan for treating growth hormone deficiency in children [ID6178]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Monday 21 August 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the chair and vice chair and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Wording of the conclusions regarding the ITC do not represent accurately the results of the EAG base-case and do not acknowledge the full extent of the uncertainty	1. <u>Current wording (pages 6, 20, 33):</u> 'When the EAG used expert elicited priors or modified empirical priors, somapacitan no longer met the criteria for non-inferiority with somatrogon, although remained non-inferior to somatropin.' <u>Proposed amendment:</u> 'When the EAG used expert elicited priors or modified empirical priors,	- Novo Nordisk agree with the EAG, that the main comparator in this decision problem is somatropin given it is still the standard of care as shown by its dominance in the market. Nevertheless, some of the conclusions from EAG's ITC of somapacitan compared with somatrogon only partially capture the context of the results. - Current EAG conclusions on the comparison between somatrogon and somapacitan (*"When the EAG used expert elicited priors or modified empirical priors, somapacitan no longer met the criteria for non-inferiority with somatrogon[…]."* while not incorrect, could be misinterpreted (potentially suggesting to readers the posterior probabilities in the new scenario more fully support conclusive inference such as	The EAG consider this interpretation rather than a factual inaccuracy. Consequently, no changes are made to the report.

	somapacitan no longer met the criteria for non-inferiority with somatrogon, although remained non-inferior to somatropin. *The results of the analyses using the EAG expert elicited priors also highlight somatrogon did not meet the criteria for non-inferiority with somapacitan, either, with the same non-inferiority margin of 1.8 cm/y. Therefore, the EAG conducted results also suggest that there is no evidence of*	inferiority of somapacitan, and perhaps drawing stronger conclusion than the data warrants). The conclusions as written do not acknowledge the full context of the results, and the uncertainty (due to the width of the 95% credible intervals it is also true that somatrogon would not meet the criteria for non-inferiority to somapacitan in this scenario). NB: The criteria: probability that the difference in AHV between somapacitan and somatrogon is greater than the non-inferiority margin of 1.8 cm/y>0.025). - There is a similar probability, when assessing AHV at 52 weeks that the difference between somapacitan and somatrogon is greater than 1.8 cm/y and that the difference between somatrogon and somapacitan is greater than 1.8cm/y. - In a replication of the EAG base case (with small differences on	

	a clinically meaningful difference between somapacitan and somatrogon.' 2. <u>Current wording (page 33):</u> 'Overall, and as summarised below, the EAG identified no critical issues that would deter NICE from proceeding with the cost-comparison approach for the comparison of somapacitan and somatropin *(though potentially not with the far less commonly used somatrogon)*.'	the second decimal in the estimates), the probabilities were: **AHV 52 weeks** P((somatrogon-somapacitan)>1.8cm/y)=0.09215 P((somapacitan-somatrogon)>1.8cm/y)=0.07065 **AHV 26 weeks** P((somatrogon-somapacitan)>1.8cm/y)=0.13465 P((somapacitan-somatrogon)>1.8cm/y)=0.0511 - The EAG conclusion regarding the somatrogon comparison might be overly strong because it does not take into account the clinical plausibility or that most of the posterior mass precludes a conclusion that any treatment is meaningfully different.	

	Proposed amendment: 'Overall, and as summarised below, the EAG identified no critical issues that would deter NICE from proceeding with the cost-comparison approach for the comparison of somapacitan and somatropin.' 3. Current wording (page 22): 'However, given the differences estimated in the EAG analyses (see Section 4.4), the EAG suggests that a more sophisticated analysis would be required		

	balancing cumulative costs and effects.' <u>Proposed amendment:</u> Novo Nordisk proposes removing this sentence.		

Issue 2

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**EAG response**
Approach to wastage calculations and potential errors in the results (Pages 7, 9, 22, 24, 27-31, 34)	The EAG provided three cost comparison analyses which assume disposal of cartridges/pens once there is less than a full (daily or weekly) dose left (tables 6.2, 6.4, 6.5). Novo Nordisk proposes aligning with the EAG report of TA863 on this issue.	- Novo Nordisk believes that including wastage in the analyses is incorrect and inconsistent with the EAG report for TA863, which concludes that any wastage is expected to have a very minor impact on cost differences between the GH products. - Furthermore, the EAG wastage scenarios do not reflect the full treatment duration to accurately capture the effect of wastage on the treatment costs. When wastage is calculated, the weight (kg) used has an impact on the relative treatment	The EAG believe that this is opinion and not a factual inaccuracy. Whilst TA863 assumes that differences in wastage are not large enough to significantly impact the results, this is not explored in their analysis. The EAG considers the impact on wastage based on clinical advice received. This clinical advice suggested that this a relevant issue, moreover, the EAG reproduced approaches to calculate wastage from published economic evaluations on GH products (see Section 6.2.2.1). No changes are

costs. This is evident in the following scenario which considers the whole treatment duration and uses the mean start age and finishing age from the calculation of the average weight in the analyses presented in the company submission (CS) and EAG report (9 years and 16 years, respectively). The results show that the cost of somapacitan [redacted].

	Cartridge waste scenario (overall treatment duration)	Cost difference (versus somapacitan)
Somapacitan	[redacted]	-
Somatrogon	£96,437.12	[redacted]
Norditropin FlexPro	£83,736.12	[redacted]
Norditropin Nordiflex	£91,255.44	[redacted]
Saizen	£89,963.84	[redacted]
Omnitrope	£58,066.49	[redacted]
NutropinAQ	£81,518.44	[redacted]
Genotropin	£71,059.94	[redacted]
Zomacton*	£64,830.36	[redacted]
Humatrope	£70,860.93	[redacted]

made to the text of the report with respect to the inclusion of wastage.

The EAG acknowledges that wastage costs will vary according to the complete dose required and also the size of the vials/cartridges used to deliver GH. The EAG analysis presented in the report is an attempt to accommodate these variables when framing the decision problem made in the company's base-case.

The EAG recognises that an analysis looking at wastage costs over the full duration of treatment can be informative; however, the wastage scenario provided by the company as part of the factual accuracy check is a new analysis and not a factual accuracy point. Nevertheless, the EAG note two things about this analysis:

1) The dose of somatropin is based upon 0.034mg/kg/day and not the EAG preferred analysis of 0.025mg/kg/day
2) The change in weighted average of somatropin suggested by the company (which is also new analysis and not a factual inaccuracy) slightly favours the

- Novo Nordisk attempted to replicate the EAG's wastage calculations. Most results seem to be accurate; however, below are some results where discrepancies were found. To note, the EAG report provided limited information on the methods used which could be the reason for differences in the results. An Excel spreadsheet with all the presented wastage results is provided along this form.

i. Table 6.2: Novo Nordisk's calculations showed that the Genotropin cost including cartridge waste is £9,493.38 instead of £8,860.28. By default, the '% difference from baseline', the 'Cost difference (versus somapacitan)' and 'Somatropin (weighted average)' were also found to be different.

ii. Table 6.4: Novo Nordisk's calculations showed that the Humatrope cost for the 'EAG final base-case' is £6,552 instead of £6,329.05. By default, the '% difference from baseline', the 'Cost difference (versus somapacitan)' and 'Somatropin (weighted average)' were also found to be different.

use of more costly versions of somatropin.

3) It is unclear to the EAG whether the analysis include alternative vials/cartridge sizes that can help minimise wastage costs.

Taken together these three features drive the company findings. Adopting the EAG assumptions of dose and market share is shown in the Table below

	EAG base-case	Cost difference versus somapacitan
Somapacitan	[redacted]	
Somatrogon	£96,437.12	[redacted]
Somatropin	[redacted]	[redacted]
Norditropin FlexPro	£60,926.68	[redacted]
Norditropin Nordiflex	£66,397.76	[redacted]
Saizen	£65,904.99	[redacted]
Omnitrope	£42,249.52	[redacted]
NutropinAQ	£58,877.18	[redacted]
Genotropin	£50,394.01	[redacted]
Zomacton*	£51,364.77	[redacted]
Humatrope	£50,385.39	[redacted]

		iii. Table 6.5: Novo Nordisk's calculations showed that the somapacitan cost for the 'Patient weight 16.5kg' scenario is [redacted] instead of [redacted]. By default, the '% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different. iv. Table 6.5: Novo Nordisk's calculations showed that the Saizen cost for the 'Patient weight 16.5kg' scenario is £3,552.64 instead of £3,616.08. By default, the '% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different. v. Table 6.5: Novo Nordisk's calculations showed that the Humatrope cost for the 'Patient weight 16.5kg' scenario is £2,711.17 instead of £2712.45. By default, the '% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different. vi. Table 6.5: Novo Nordisk's calculations showed that the Genotropin cost for the 'Patient weight 16.5kg' scenario is £2,713.39 instead of £2,712.45. By default, the	With respect to the discrepancies in cost calculations with the EAG model: i) The company's Genotropin annual cost is for dose of 0.034 mg/kg/day for a 40 kg patient using 12 mg cartridges. The EAG uses annual cost for a 1.4 mg powder and solvent for injection, reducing vial wastage costs (see EAG Model; sheet EAG treatment costs; cells P66 and P61). ii) The company's Humatrope annual cost is based on the NHS indicative price of £216.00 for a 12 mg powder and solvent for injection. The EAG uses the lower Drug tariff price of £208.65 for the same 12 mg powder to calculate annual costs.(see EAG Model; sheet EAG treatment costs; cell D52). iii) This change was amended in the EAG report iv) The EAG was not able to find the source of the discrepancy in the cost of Saizen, an EAG base-case model will be submitted with a clearer breakdown of cost and wastage calculations.

		'% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different. vii. Table 6.5: Novo Nordisk's calculations showed that the Genotropin cost for the 'Patient weight 50kg' scenario is £8,385.82 instead of £8,385.65. By default, the '% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different. viii. Table 6.5: Novo Nordisk's calculations showed that the Humatrope cost for the 'EAG base-case (40kg)' is £6,552 instead of £6,329.05. By default, the '% change from baseline', the 'Cost difference versus somapacitan' and 'Somatropin (weighted average)' were also found to be different.	v) The EAG was not able to find the source of the discrepancy in the cost of Humatrope, an EAG base-case model will be submitted with a clearer breakdown of cost and wastage calculations. vi) The EAG was not able to find the source of the discrepancy in the cost of Genotropin, an EAG base-case model will be submitted with a clearer breakdown of cost and wastage calculations. vii) The EAG was not able to find the source of the discrepancy in the cost of Genotropin, an EAG base-case model will be submitted with a clearer breakdown of cost and wastage calculations. viii) See clarification #2)

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Dose of somatropin formulation in the EAG cost comparison base-case. (Section 5.3.1, page 23, section 6.1.1, page 26)	Novo Nordisk believes that a dose of 0.034mg/kg/day is the correct dose to be used in the EAG analyses.	- Novo Nordisk used the 0.034mg/kg/day as the dose for the somatropin preparations because it was the average dose in the REAL 4 clinical trial, and it is consistent with the recommended BNF dosage interval for the treatment of GHD in the submitted population. - This dose was used in REAL 4 and REAL 3 – the dose finding trial – which demonstrated that somapacitan has similar efficacy with somatropin. - Importantly, as included in the Points for Clarification stage, there is a dose response relationship with somatropin therefore reducing its dose by 26.5% while still assuming identical treatment benefits lacks validity.	The EAG acknowledges that currently there is no evidence to compare the clinical efficacy of somapacitan with other somatropin doses besides 0.034mg/kg/day. However, the EAG presents reasons why the doses of 0.034mg/kg/day are not representative of UK practice in sections 5.3.1 and 6.1.1 of its report. Additionally, the currently accepted position of NICE is that all somatropin formulations in doses ranging from 0.023mg/kg/day to 0.039mg/kg/day have equivalent efficacy and safety profiles. Therefore, the EAG maintains its position and has not made any changes to the report.

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Weighted average acquisition cost of somatropin per year in the cost comparison base case analysis. (section 5.3.3, page 24 ; section 6, pages 26–30)	Novo Nordisk suggest removing the somatropin (weighted average) annual treatment costs from the base case analysis made by EAG.	- Novo Nordisk provided the annual acquisitions costs estimates for each somatropin formulation reflecting current prices. The cost comparison analysis was performed independently of the market position of the different somatropin formulations. - Market shares were only added to give context to the cost comparison analysis. The somatropin weighted average results presented in the EAG report use market shares sourced from a legacy functionality in the budget impact model (BIM) that was not intended to be used in the CS. This functionality is not relevant for the cost comparison since it calculates the market shares of the GH treatments as the average of the estimated market shares for years 1-5 in the BIM. Even though these estimates are based on the market shares presented in the	This is opinion and not a factual inaccuracy. Therefore, the EAG has maintained this analysis which it believes is informative.

		CS they are not reflective of the current uptake of the treatments.	

Issue 5

Description of problem	**Description of proposed amendment**	**EAG response**
Factual and typographical errors:	Respective amendments:	
1) "…and REAL 3, a phase II dose-finding study of **28** participants." *(section 1.1, page 6)*	1) "…and REAL 3, a phase II dose-finding study of **57** participants."	1) The EAG has made this amendment.
2) "…cohort III of the extension focuses on nine **paricipants** with ages ranging between 10.2 and 16.1 years. Two of these **paricipants** received somapacitan as (…)" (*section 3.1, page 9)*	2) "…cohort III of the extension focuses on nine **participants** with ages ranging between 10.2 and 16.1 years. Two of these **participants** received somapacitan as (…)"	2) The EAG has made this amendment.
3) "The company carried out **multiple** systematic literature reviews (SLRs) to identify clinical evidence (…)" *(section 4.1., page 11)*	3) "The company carried out **a systematic literature review (SLR) that was later updated twice** to identify clinical evidence (…)"	3) The EAG has made this amendment.

4) Both trials were open-label and compared weekly somapacitan and daily somatropin. *(section 4.1.3, page 12)*	**4)** Both trials were open-label and compared weekly somapacitan and daily somatropin. **REAL 3 was double-blinded with regard to different dose levels of once-weekly somapacitan.**	4) The EAG does not consider this omission to be a factual error, therefore this change was not implemented in the report.
5) "…criteria related to height or **boby** mass index or deviations (…)" *(section 4.1.3, page 12)*	5) "…criteria related to height or **body** mass index or deviations (…)"	5) The EAG has made this amendment.
6) "… due to children having one or two GH stimulation tests performed more than the maximum of 12 months prior to randomisation." *(section 4.1.3, page 12)*	6) "… due to children having one or two GH stimulation tests performed more than the maximum of 12 months prior to randomisation. **Per protocol analyses were included in the CS that excluded these 14 children and results were almost identical to the main results and with the same non-inferiority conclusion.**"	6) The EAG report has been amended to acknowledge the per protocol analyses in the CS.
7) "…height velocity standard deviation score (SDS; adjusted for age and sex); height SDS (Yes) bone age; and **IGF**." *(section 4.1.3, page 12)*	7) "…height velocity standard deviation score (SDS; adjusted for age and sex); height SDS (Yes) bone age; and **IGF-I SDS and IGFBP-3 SDS**."	7) The EAG has made this amendment.
8) "…with a similar safety profile to once-daily somatropin in the REAL 4 **(up to 52 weeks)** (…)" *(section 4.1.4.2, page 13)*	8) "…with a similar safety profile to once-daily somatropin in the REAL 4 (**up to 104 weeks**) (…)"	8) The EAG has made this amendment.

9) "Adherence rates were high for somatropin (ranging from 87.2% to 88.3%) and **somatrogon** (ranging from 92.2% to 95.8%)." *(section 4.1.4.3, page 13)*	9) "Adherence rates were high for somatropin (ranging from 87.2% to 88.3%) and **somapacitan** (ranging from 92.2% to 95.8%)."	9) The EAG has made this amendment.
10) "…based on data from the REAL 4 trial (up to **52 weeks**) and the REAL 3 trial (up to 156 weeks)." *(section 4.1.4.2, page 13)*	10) "based on data from the REAL 4 trial (up to **104 weeks**) and the REAL 3 trial (up to 156 weeks)."	10) The EAG has made this amendment.
11) "**Five trials were included** in the company's indirect comparison analyses see section B.3.9 of the CS." *(section 4.2, page 13)*	11) "**The company's SLR identified five trials that met the PICOS criteria,** see section B.3.9 of the CS."	11) This is not a factual inaccuracy, therefore the amendment was not made in the EAG report. The additional information requested is available in the CS which is cross-referenced.
12) Table 4.1 Summary characteristics of studies included in ITC analyses *(section 4.2, page 14)* • Race: White **43%** (REAL 3 Population cell) • Race: White **92%** (OPKO II Population cell)	12) Table 4.1 Summary characteristics of studies included in ITC analyses • Race: White **46%** • Race: White **96%**	12) The EAG has made this amendment.
13) "Since the trial dose for somatropin (**0.023** mg/kg/day) was within the BNF recommended range, in common with TA863 (…)" *(section 4.2, page 14)*	13) "Since the trial dose for somatropin (**0.025** mg/kg/day) was within the BNF recommended range, in common with TA863 (…)"	13) The EAG has made this amendment.

14) "Single node for somatropin (the company used a separate node for **0.023** mg/kg/day in the alternative network ITC analyses)." *(section 4.3, page 17)*	14) "Single node for somatropin (the company used a separate node for **0.025** mg/kg/day in the alternative network ITC analyses)."	14) The EAG has made this amendment.
15) "(…) both 26 and 52 weeks when using an expert elicited prior (see **Table 4.3**) (…)" *(section 4.3, page 18)*	15) "(…) both 26 and 52 weeks when using an expert elicited prior (see **Table 4.4**) (…)"	15) The EAG has made this amendment.
16) "The company carried out **multiple SLRs** to identify cost and resource data." *(section 5.1, page 21)*	16) "The company carried out **a SLR that was later updated** to identify cost and resource data."	16) The EAG has made this amendment.
17) [redacted]	17) [redacted]	17) The EAG rejects this amendment, the values used in the CS base-case model refer to 5 year projections by the company and therefore do not correspond exactly to the values the company is quoting here, or the values in the CS document.
18) "The cost of weekly somatrogon was estimated annually at **£9499.76**. The cost of weekly somapacitan was estimated annually at **£9499.76**, (…)" *(section 6.1 page 26)*	18) "The cost of weekly somatrogon was estimated annually at **£9499.78**. The cost of weekly somapacitan was estimated annually at **£9499.78**, (…)"	18) The EAG has made this amendment.
19) "**Further sensitivity analyses conducted by the EAG show that wastage costs may increase as patients**	19) Please remove this sentence. Wastage will be dependent on the dose as a proportion of vial size. For example, if the dose is 50% of the vial size, then there will be no wastage. But there would also be	19) The text has been amended to: "Further sensitivity analyses conducted by the EAG show that wastage

receive larger treatment doses" (*section 6.3, page 31)* 20) "… a phase II dose-finding study of **28** participants. Outcomes were consistent with the NICE scope" *(section 8.1, page 33)*	no wastage if the dose was twice the vial size. 20) "… a phase II dose-finding study of **57** participants. Outcomes were consistent with the NICE scope"	costs are dependent on the number of complete doses as a proportion of vial size and therefore may vary depending on the dose required, the size of the vial used, and any further brand-specific delivery instructions**."** 20) The EAG has made this amendment.

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Somapacitan for treating growth hormone deficiency in children [ID6178]

Questionnaire for Clinical Experts

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

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. To help provide insights, please use the questionnaire below.

Name	Joanne Blair
1. What is the mean dose of somatropin used in NHS clinical practice?	The dose of growth hormone should be personalised based, with in the licenced range, on the following characteristics: The diagnosis being treated, the child's growth response to treatment, IGF1 measurements and height and age at the start of treatment. This starting doses are dependent on the licensed doses quoted in the BNFC.

2. What are the range of doses of somatropin used in NHS clinical practice?	Growth hormone dose is a dependent on diagnosis: Growth hormone deficiency 23-30 9 micrograms/kilogram/day Turner syndrome: 45 to 50 micrograms/kilogram/day Prader-Willi syndrome: 35 micrograms/kilogram/day Chronic renal disease: 45 to 50 micrograms/kilogram/day SHOX deficiency: 45 to 50 micrograms/kilogram/day Doses can also be calculated according to body surface area where children her significantly overweight
3. Would you dispose of a cartridge/injection pen once there is less than a full (daily or weekly) dose left so that patients receive no more than one injection per dose?	This would depend on the dose, the age of the child, whether there any any issues regarding needle phobia and how much wastage there is likely to be.
4. When (if ever) would you dispose of a	This would depend on the same factors noted above

cartridge/injection pen that was not empty?	
5. Would you expect any differences in drug wastage between weekly dosing (e.g. somatrogon and somapacitan) and daily dosing (e.g. somatropin)?	Again, this will depend on the dose of growth hormone prescribed, the degree of needle phobia child exhibit and the likely volume of wastage. It might be anticipated that the children most anxious about injections will be prescribed a weekly growth hormone formulation, so it is possible that wastage will be higher in this population of chills
6. Would you expect any differences in adherence between weekly dosing (e.g. somatrogon and somapacitan) and daily dosing (e.g. somatropin)?	We anticipate that children given growth hormone on a weekly basis will show better do not treatment in children given growth hormone on a daily basis. This is what the clinical trial show, but it will need to be evidenced in clinical practice. I think the flexibility that there is in giving the weekly growth hormone, whereby there is a window of 3 days for the dose to be given, is likely to be key in it dear insult.

Thank you for your time.

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Name	Ross Burrows
1. What is the mean dose of somatropin used in NHS clinical practice?	In my practice the mean dose is 0.9mg daily. I would expect this to be similar across other trusts.

2. What are the range of doses of somatropin used in NHS clinical practice?	In my practice I see doses from 0.2mg to 2mg daily of somatropin. The lowest dose of somatropin would be 0.2mg, and we would not normally exceed 2mg daily for a maximum dose. This is dependent on the IGF-1 levels, some patients will never reach 2mg daily due to supraphysiological IGF-1 levels.
3. Would you dispose of a cartridge/injection pen once there is less than a full (daily or weekly) dose left so that patients receive no more than one injection per dose?	We advise families not to waste a dose unnecessarily, and to give two injections if needed. However, there are a proportion of patients that would not tolerate this and parents would dispose of the cartridge/pen early, to reduce the distress to their child. We would accept this as we would not want the child overly distressed and impact their overall compliance.
4. When (if ever) would you dispose of a cartridge/injection pen that was not empty?	• As above if the child is very distressed and it would not be appropriate to expose them to more than one injection per dose. • If the cartridge or pen had exceeded temperature requirements and not safe to use. • A patient has experienced a severe adverse effect and needed to stop treatment immediately.
5. Would you expect any differences in drug wastage between weekly dosing (e.g. somatrogon and	Overall I would expect that giving two injections for one dose once a week would be better tolerated and accepted by families than with a daily dose, therefore resulting in less wastage than the daily. However, there are still some families, where the child will be very distressed and giving them two injections may be too upsetting, resulting in some wastage.

somapacitan) and daily dosing (e.g. somatropin)?	
6. Would you expect any differences in adherence between weekly dosing (e.g. somatrogon and somapacitan) and daily dosing (e.g. somatropin)?	Not necessarily. There may be some improvement in adherence for some patients, but my experience is that if a patient is non-adherent with daily somatropin, they will also struggle to adhere to a once weekly preparation. The important difference is that poor adherence with the once weekly form will have a greater impact on its efficacy and make it more challenging to monitor the patient biochemically.

Thank you for your time.

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