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ORIGINAL RESEARCH

Efficacy and Safety of Somapacitan Relative to Somatrogon and Lonapegsomatropin in Pediatric Growth Hormone Deficiency: Systematic Literature Review and Network Meta-analysis

Lasse de Fries Jensen · Vasileios Antavalis · Jan Odgaard-Jensen · Annachiara Rossi · Alberto Pietropoli · Michael Højby

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ABSTRACT

***Introduction*:** Since direct comparisons of long-acting growth hormones (LAGHs) are lacking, analyses were performed to indirectly compare the efficacy and safety of somapacitan versus somatrogon and lonapegsomatropin in children with growth hormone deficiency (GHD).

***Methods*:** A systematic literature review (SLR) identified studies of once-weekly LAGHs for the treatment of pediatric GHD. Indirect comparisons (ICs) using a Bayesian hierarchical network meta-analysis and a random effects model were performed using daily growth hormone (GH) 0.034 mg/kg/day (base case) or 0.024–0.034 mg/kg/day (alternative analyses) as the common comparator to compare height outcomes to 52 weeks [annualized height velocity, height velocity standard deviation score (SDS), and height SDS]. Identified evidence did not allow IC of safety or longer-term efficacy outcomes so these were qualitatively described.

***Results*:** The SLR identified two somapacitan trials, three somatrogon trials (one included in alternative analyses only), and one lonapegsomatropin trial comparing the LAGH with daily GH in treatment-naïve pre-pubertal children for IC. ICs revealed no differences at 52 weeks between somapacitan versus somatrogon and lonapegsomatropin, as well as daily GH, with respect to all growth outcomes considered in children with GHD. All three LAGHs had sustained efficacy and were generally well tolerated, with comparable efficacy and safety to daily GH, with the exception of observed injection site pain for somatrogon.

***Conclusion*:** No efficacy and safety differences were identified in comparisons of once weekly somapacitan versus somatrogon and lonapegsomatropin, as well as daily GH. All treatments were generally well tolerated, with the exception of observed injection site pain for somatrogon.

PLAIN LANGUAGE SUMMARY

It is valuable to compare similarly acting treatments to determine their relative benefits and

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L. de Fries Jensen (✉) · J. Odgaard-Jensen · A. Rossi · M. Højby
Novo Nordisk, Knud Højgaardsvej 1, 2860 Søborg, Denmark
e-mail: LDFJ@Novonordisk.com

V. Antavalis
Novo Nordisk, Gatwick, UK

A. Pietropoli
Novo Nordisk, Zurich, Switzerland

risks. Direct comparisons of long-acting growth hormones (LAGHs) are lacking, so analyses were performed to indirectly compare the efficacy and safety of the LAGH somapacitan versus the LAGHs somatrogon and lonapegsomatropin in children with growth hormone deficiency. Studies of once-weekly LAGHs for the treatment of pediatric growth hormone deficiency were identified using a systematic literature review, then the data obtained were indirectly compared using standard statistical methods with daily growth hormone 0.034 mg/kg/day (base case) or 0.024–0.034 mg/kg/day (alternative analyses) as the common comparator. Height outcomes to 52 weeks (annualized height velocity, height velocity standard deviation score, and height standard deviation score) were compared between treatments. Sufficient information to allow indirect comparison of safety or longer-term efficacy outcomes were not found so these were qualitatively described. The systematic literature review identified two somapacitan trials, three somatrogon trials (one included in alternative analyses only) and one lonapegsomatropin trial comparing the LAGH with daily growth hormone in previously untreated prepubertal children for inclusion in the indirect comparison. Indirect comparisons identified no differences to 52 weeks between somapacitan versus somatrogon and lonapegsomatropin, as well as daily growth hormone, with respect to all growth outcomes considered in children with growth hormone deficiency. All three LAGHs had sustained efficacy and were generally well tolerated, with comparable efficacy and safety to daily growth hormone, with the possible exception of injection site pain with somatrogon.

Keywords: Indirect comparisons; Somapacitan; Somatrogon; Lonapegsomatropin; Long-acting growth hormone; Growth hormone deficiency; Children

Key Summary Points

Why carry out this study?

Long-acting growth hormone formulations provide similar efficacy and safety to daily growth hormone in children with growth hormone deficiency but do not need to be administered daily and may improve treatment adherence compared to daily growth hormone.

Three once-weekly long-acting growth hormones have United States Food and Drug and European Medicines Agency approval for pediatric use, somapacitan, somatrogon, and lonapegsomatropin; these long-acting growth hormones have not been directly compared.

A systematic literature review and indirect comparisons were performed to allow comparison of somapacitan with somatrogon and lonapegsomatropin for the treatment of pediatric growth hormone deficiency.

What was learned from the study?

Indirect comparison did not identify any differences in growth outcomes when somapacitan was compared with somatrogon and lonapegsomatropin in children with growth hormone deficiency.

The long-acting growth hormones somapacitan, somatrogon, and lonapegsomatropin had sustained efficacy with continued treatment and were generally well tolerated, although somatrogon, but not somapacitan or lonapegsomatropin, may be associated with more injection site pain than daily growth hormone, in children with growth hormone deficiency.

INTRODUCTION

Growth hormone deficiency (GHD) is a rare disorder characterized by inadequate production or secretion of growth hormone (GH) from the anterior pituitary gland; GHD results in reduced longitudinal growth and development during childhood [1, 2]. GH replacement in GHD can often restore normal growth in the child, thereby allowing them to reach the final height that would be expected [within two standard deviation scores (SDS) of the expected mean] taking into account parents' height and other factors; however, it traditionally requires daily injections of GH [3, 4].

Long-acting growth hormone (LAGH) formulations that do not need to be administered daily have been developed to offer minimal disruption and potentially improve treatment adherence compared to daily GH; these have been shown to provide similar efficacy and safety to daily GH in children with GHD [5]. Three once-weekly LAGHs with United States Food and Drug and European Medicines Agency approval for pediatric use, somapacitan (Sogroya®; Novo Nordisk), somatrogon (Ngenla™; Pfizer), and lonapegsomatropin (Skytrofa®; Ascendis Pharma) have been compared with daily GH in clinical trials but have not been directly compared with each other. The three LAGH formulations utilize different mechanisms to achieve their long-acting pharmacokinetics [6]; however, it is not known if these differences affect their efficacy or safety.

To allow comparison of these three LAGHs, a systematic literature review (SLR) and indirect comparisons (ICs) were performed firstly to identify evidence on the efficacy and safety of LAGH for the treatment of pediatric GHD and secondly to provide evidence on the comparative efficacy and safety of somapacitan relative to somatrogon and lonapegsomatropin. The focus is comparisons of height outcomes [annualized height velocity (AHV), height velocity SDS, and height SDS] for children with GHD; additionally, safety is considered.

METHODS

SLR

Electronic searches of Embase (from 1974), MEDLINE (from 1946), and the Cochrane Library databases were conducted via the Ovid platform in October 2021 and supplemented with hand-searches of relevant conference proceedings, previous health technology assessment (HTA) agency websites, clinical trial registries, websites of government/international bodies, other supplementary sources, and reference lists of included studies to identify studies describing the efficacy and safety of LAGHs in children with GHD (and no other growth disorders); updates were conducted in May 2022 and March 2023. Predefined search terms and strings captured literature concerning GHD in children or adolescents receiving a LAGH in a randomized controlled trial (RCT), single-arm trial, or observational study. Study selection criteria were defined in terms of population, interventions, comparisons, outcomes, and study design (PICOS) (Table 1).

Results from the electronic database searches were downloaded into a bespoke database, and de-duplicated. All identified citations were reviewed based on title/abstract, where available, by two independent reviewers to assess whether they met the PICOS selection criteria. In cases where it was not clear from the title/abstract if a paper was relevant, full publications of studies considered potentially relevant were obtained and examined by two independent reviewers. Full papers were examined by two independent reviewers (second pass), and final inclusion and exclusion of citations were verified by all researchers. Data from the SLR were extracted into a data extraction table, mainly as numerical data, by a single analyst, and quality checked by a second analyst. Disputes were referred to a third party.

Quality assessment of studies, published in full, included in the SLR were conducted by a single statistician. Quality (risk of bias) assessment of

Table 1 PICOS selection criteria for the systematic literature review and indirect comparisons

Criteria	Systematic literature review		Indirect comparison
	Include	**Exclude**	
Population	Pediatric patients with GHD	Adult growth hormone deficiency patients Other growth disorders such as SGA, NS, ISS, TS, Prader–Willi Syndrome Animals / in vitro	Treatment-naïve pre-pubescent boys or girls (≥ 2 and ≤ 12 years) with GHD and impaired height velocity
Intervention/ comparator	LAGH used for treatment for GHD including but not limited to Somapacitan Somatrogon Lonapegsomatropin Eftansomatropin alfa All comparators to LAGHs will be eligible for extraction	Treatments other than LAGH Therapies such as Jintrolong or EutropinPlus which are approved in limited markets only Therapies with development terminated before marketing approval, or withdrawn from market	Somapacitan versus somatrogon Somapacitan versus lonapegsomatropin; At the recommended dose (or intended dose if market authorization pending)
Outcomes	Clinical outcomes including but not limited to Efficacy Growth rate/height velocity/height velocity SDS/AHV Change in height/height SDS score Change in bone age Safety Tolerability: dose reductions and interruptions, discontinuation (any reason, due to AEs) IGF-1 SDS IGFBP-3 Injection site reactions Publications from clinical trials presenting only baseline characteristics or other useful trial related information, were considered for inclusion if trial outcomes were reported in a separate publication	Outcomes not reporting efficacy or safety evidence	Efficacy Height outcomes (AHV, height velocity SDS, height SDS) Safety Overall incidence of any, serious or severe adverse event, injection site reactions, antibody development (neutralizing and non-neutralizing) Short and long term

Table 1 continued

Criteria	Systematic literature review		Indirect comparison
	Include	**Exclude**	
Study design/setting	RCTs Single-arm trials Observational/real-world evidence studies	Phase I clinical trials Systematic reviews and clinical guidelines[a] Studies based on animal models Preclinical and biological studies Narrative reviews, editorials, opinions	
Language of publication	English language publications	Non-English language publications without an English abstract	
Date of publication	No restriction	–	
Countries	No restriction	–	

AE adverse event, *AHV* annualized height velocity, *GHD* growth hormone deficiency, *IGFBP-3* insulin-like growth factor-binding protein 3, *IGF-I* insulin like growth factor I, *ISS* idiopathic short stature, *LAGH* long-acting growth hormone, *NS* Noonan syndrome, *SGA* short for gestational age, *TS* Turner syndrome, *RCT* randomized controlled trial, *SDS* standard deviation score

[a]The reference lists of relevant systematic reviews and clinical guidelines were screened to ensure that no relevant study was missed

included RCTs was conducted using the National Institute for Health and Care Excellence (NICE) checklist [7]. Quality assessment of the single-arm studies (included in the comparison of safety and/or long-term efficacy) was conducted using the Effective Public Health Practice Project quality assessment tool [8].

Indirect Comparisons

The planned ICs were conducted in two parts: Part 1 utilized evidence from RCTs lasting at least 26 weeks; Part 2 utilized evidence from trial extensions. Overall, ICs assessing short-term efficacy outcomes were determined to be feasible. However, evidence from extensions beyond 52 weeks, which could be used to assess long-term outcomes, was limited to single arms, so it was not considered feasible to conduct ICs for long-term efficacy outcomes; therefore, these were qualitatively described and are reported in the Supplementary Material. The current ICs aimed to explore specifically the relative efficacy of approved LAGH preparations, somapacitan versus somatrogon and somapacitan versus lonapegsomatropin, in pediatric GHD.

RCTs identified in the SLR were eligible for the ICs if they satisfied the IC-specific PICOS criteria summarized in Table 1. The main efficacy outcomes of interest for the ICs were height outcomes (AHV, height velocity SDS, height SDS) because they were considered to have the most patient relevance and tend to be primary and key secondary endpoints in GHD clinical trials at 26 and 52 weeks. Bone age was not included as it did not meet these criteria and available data were not assessed by the same central x-ray reader(s), as would be needed to avoid limited and potentially misleading results due to the risk of significant inter-variability in x-ray readings. Availability of data in the included clinical trials is summarized in Table 2.

Base case analyses utilized trials that included daily GH as the comparator at a dose of 0.034 mg/kg/day (the dose of daily GH used in the trials of somapacitan); alternative analyses included all trials with daily GH at any labeling dose for pediatric GHD (0.024–0.034 mg/kg/day).

The safety of the three LAGHs in comparison with daily GH was summarized, in terms of adverse events (AEs), serious AEs, severe AEs, injection site reactions (ISRs), and antibody development, using data from all available studies identified in the SLR.

Statistical Methods

Network Meta-analysis Model The ICs used a Bayesian hierarchical network meta-analysis (NMA) to estimate the differences in efficacy between somapacitan and somatrogon, and somapacitan and lonapegsomatropin, conducted in accordance with guidelines set by the NICE Decision Support Unit [9]. All analyses were of continuous outcomes [mean (standard error; SE) AHV, mean (SE) height velocity SDS, mean (SE) change from baseline in height SDS] and were performed using a normal likelihood, identity link model.

A normal distribution for the mean change from baseline or mean value in arm k in trial i, y_{ik} with change variance V_{ik} was assumed, such that:

$$y_{ik} \sim N(\theta_{ik}, V_{ik}) \quad (1)$$

The parameter of interest was the mean θ_{ik} which was unconstrained on the real line. An identity link was used and therefore the linear predictor was such that:

$$\theta_{ik} = \mu_i + \delta_{ijk} \quad (2)$$

where μ_i was the trial-specific intercept in trial i and δ_{ijk} were the trial-specific treatment effect of treatment in arm k relative to control treatment in arm j.

Study-level effect sizes were considered exchangeable across comparisons, i.e.,:

$$\delta_{ijk} \sim N(d_{jk}, \sigma^2) \quad (3)$$

where d_{jk} is the NMA estimate of the effect size for intervention k relative to intervention j. In the consistency model:

$$d_{jk} = d_{tk} - d_{tj} \quad (4)$$

where t denotes another arbitrary intervention in the model. In the random-effects model, study-level effect sizes were considered

Table 2 Overview of data availability across included trials for indirect comparison of somapacitan versus somatrogon

Outcome	REAL 3 [15]	REAL 4 [16]	NCT01592500 [17]	NCT02968004 [18]	NCT03874013 [11]	heiGHt [20]	No. of studies in network
Phase	2	3	2	3	3	3	
Study 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	Lonapegsomatropin 0.24 mg/kg/week	
Study control	Daily GH 0.034 mg/kg/day	Daily GH 0.034 mg/kg/day	Daily GH 0.034 mg/kg/day	Daily GH 0.034 mg/kg/day	Daily GH 0.025 mg/kg/day	Daily GH 0.034 mg/kg/day	
AHV at 52 weeks[a]	✔	✔[b]	✔	✔[b]	✔[b]	✔[b]	Base case: 5 Alternative analysis: 6
AHV at 26 weeks[a]	✔	✔	✔	✔	✔	✔	Base case: 5 Alternative analysis: 6
Height velocity SDS at 52 weeks	✔	✔	✔[c]			✔	Base case: 4 Alternative analysis: 4
Height velocity SDS at 26 weeks	✔[b]	✔					NA
Height SDS at 52 weeks	✔	✔	✔	✔	✔	✔	Base case: 5 Alternative analysis: 6
Height SDS at 26 weeks	✔	✔	✔	✔	✔[d]	✔	Base case: 5 Alternative analysis: 6

Tick indicates estimate and assessment of uncertainty, unless otherwise stated. Trials not included in the base case evidence network are in light gray

AHV annualized height velocity, *BMI* body mass index, *GH* growth hormone, *SDS* standard deviation score

[a]Primary measure of interest for indirect comparisons

[b]Primary efficacy endpoint of study (no primary efficacy endpoint was specified for NCT01592500)

[c]Results presented only in plots

[d]No assessment of uncertainty

exchangeable across comparisons, and the trial-specific treatment effects come from a common distribution (as per Eq. 3). The fixed-effect model was a special case of the model described in Eq. (3), with $\sigma^2 = 0$, where σ was the between-trial standard deviation (SD). This assumed homogeneity of the underlying true treatment effects.

The programming language R (version 4.3.1) was used for implementation. Analyses were conducted utilizing function nma in version 0.5.0 of the publicly available package multinma [10]. Four chains of 10,000 iterations were run: 5000 for burn-in and 5000 for sampling. Default package values were used for thinning and initial values. For convergence, target average proposal acceptance was set to 0.99.

The base case model consisted of all relevant RCTs identified following application of the PICOS statement (Table 1) to studies identified in the SLR except for the somatrogon trial in Japanese children (NCT03874013) [11], which was included only in an alternative analysis, as it evaluated daily GH at a different dose from that used in the somapacitan studies (0.025 mg/kg/day, rather than 0.034 mg/kg/day). In trials with multiple doses of the same LAGH treatment, only the recommended or intended dose range was used for analysis. All formulations of daily GH used in the studies were considered to have equivalent efficacy as per NICE guidance [12], and in the base case network, all arms where the daily GH dose was 0.034 mg/kg/day were pooled. In the alternative network, the somatrogon trial in Japanese children (NCT03874013) [11] was connected through the somatrogon node. The approximately 30% reduction in daily GH dose (from 0.034 to 0.025 mg/kg/day) was evaluated to be too great for the treatments to be considered similar so both the relative treatment difference versus the daily GH 0.034 mg/kg/day dose and the 0.025 mg/kg/day dose were presented. The base case and alternative evidence networks are summarized in Fig. 1.

All trials reported mean change from baseline for height SDS, so no additional data transformation was needed. For height velocity SDS, post hoc analyses on somapacitan trials were conducted to align with reported outcomes in other trials. Since different measures of uncertainty were reported across the trials, SDs and confidence intervals were transformed to standard errors (SEs), respecting the normal distribution of all the variables.

Fixed effect and random effect models with different priors (informative, non-informative) for heterogeneity were performed for each outcome. Choice of model was evaluated on the model fit as measured by the deviance information criteria [13], the assessment of residual deviance, and the convergence of the models. The random effects model was found to have the better fit (data not shown), so it was used for the reported analyses. Results were presented as median treatment differences with an associated 95% credible interval (CrI). Additionally, for each endpoint in the base case network, a plot of relative treatment estimates with the associated 95% CrI were created.

Assessment of Model Assumptions Homogeneity was assessed by an assessment of differences in trial designs, with a review of all included trial design characteristics, specifically inclusion and exclusion criteria, treatment and comparator dosing, blinding, and randomization. In addition, the three outcomes of interest reported across the trials, as well as the method of analyses utilized, were assessed. Finally, baseline characteristics, including prognostic factors, were compared graphically across trials. Transitivity (similarity of patients included are sufficiently similar in the two sets of common comparator-controlled trials) was assessed to allow the assumption that relative treatment effects were exchangeable between different treatment comparisons of a network. No formal assessment of consistency was performed since the network contained no loops.

Prior Distributions The prior represents the prior probability distribution; a vague prior contains no information about the parameters of interest. Vague priors were used for the study-specific treatment effect μ_I and treatment effect sizes relative to reference d_{1k} in the form of a normal distribution with a mean of 0 and a variance of 10,000, as recommended by NICE [13].

Due to the size of the network and limited trial replication, vague priors were not used

for between-trial heterogeneity in the random effects model. Instead, information that all the daily GH products 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 random effects, for each endpoint. The estimated between-trial variability (τ) was then used as a prior for between-trial SD (σ) in the treatment-level random-effect models for the endpoint.

Sensitivity Analysis AHV analyses for the base case network were conducted using informative priors based on a random effects class model. A sensitivity analysis was performed using expert elicited priors. One expert provided data for these priors. Both analyses are consistent with the approaches used in the NICE evaluation assessment group report.

Ethical Considerations This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. Ethical approval was not needed to reuse this information.

RESULTS

SLR

A total of 279 titles were identified; after deduplication, 221 citations were screened for inclusion and a total of 28 publications describing 10 unique studies were included in the SLR (Fig. 2). In total, the SLR included five publications reporting findings from one Phase III and one Phase II trial investigating the efficacy and safety of once-weekly somapacitan compared with daily GH in treatment-naïve pre-pubertal children; 12 publications describing two unique Phase III trials (one was not included in the base case analyses, but was included in the alternative analyses) and one Phase II trial reporting the safety and efficacy of somatrogon compared with daily GH in treatment naïve pre-pubertal children with GHD; and nine publications reported findings from three Phase III trials and one Phase II trial investigating safety and efficacy of lonapegsomatropin compared with daily GH in either treatment-naïve (two studies) or -experienced (one study) children with GHD. The third lonapegsomatropin Phase III trial was a long-term uncontrolled extension study with treatment-naïve and previously GH-treated children with GHD from the other two Phase III trials.

Supplementary Table 1 summarizes the included studies evaluating somapacitan, somatrogon, and lonapegsomatropin compared with daily GH. Quality assessment of the RCTs showed that all studies reported baseline characteristics, and cohorts within each study presented with similar key prognostic factors; there were no unexpected imbalances between the cohorts of each study. Overall, there was no evidence of a selection bias as participants were representative of the target population. Additionally, some of the studies employed interactive Web response technology systems to randomize participants, thus lowering the risk of allocation bias. Similarly, the two single-arm studies included in the safety and long-term efficacy analyses included populations that seemed

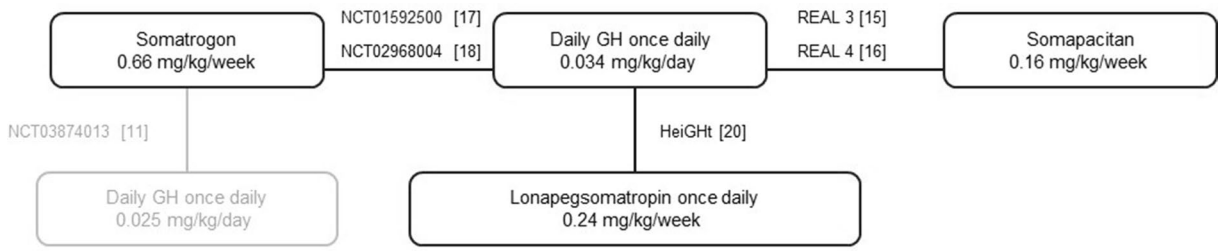

Fig. 1 Base case and alternative evidence network for the indirect comparisons of somapacitan versus somatrogon and lonapegsomatropin. Nodes shown in light gray are included only in the alternative evidence network. *GH* growth hormone

representative of the target population and there were no differences in key demographic characteristics at baseline; both were considered to be of good quality. A summary of the quality assessment is illustrated in Supplementary Fig. 1.

Indirect Comparisons of Efficacy

Studies included in the two ICs are summarized in Table 2. Overall, where data were reported, baseline characteristics identified as potential prognostic factors (age, gender, race, height parameters, and peak GH level) were generally balanced across treatment arms in the various trials. However, some differences were observed (Table 3). In addition, dose reduction based on insulin-like growth factor-I (IGF-I) was handled differently across various trials, with the extent of reduction varying, along with the thresholds and ways of confirming the original value, and differing sampling times (peak, trough, or mean) for IGF-I levels between trials. Nevertheless, study design characteristics were comparable in terms of inclusion criteria, blinding, and randomization, so it was presumed that the assumption of transitivity was met. The outcomes of interest (AHV, height velocity SDS, and height SDS) are standard outcomes in the disease area, and there were no key differences in outcome definitions across the different trials. In addition, when reported, the analysis of continuous endpoints was generally similar across trials, with most trials considering treatment, age, sex, peak GH level, region, and height as covariates in their analyses.

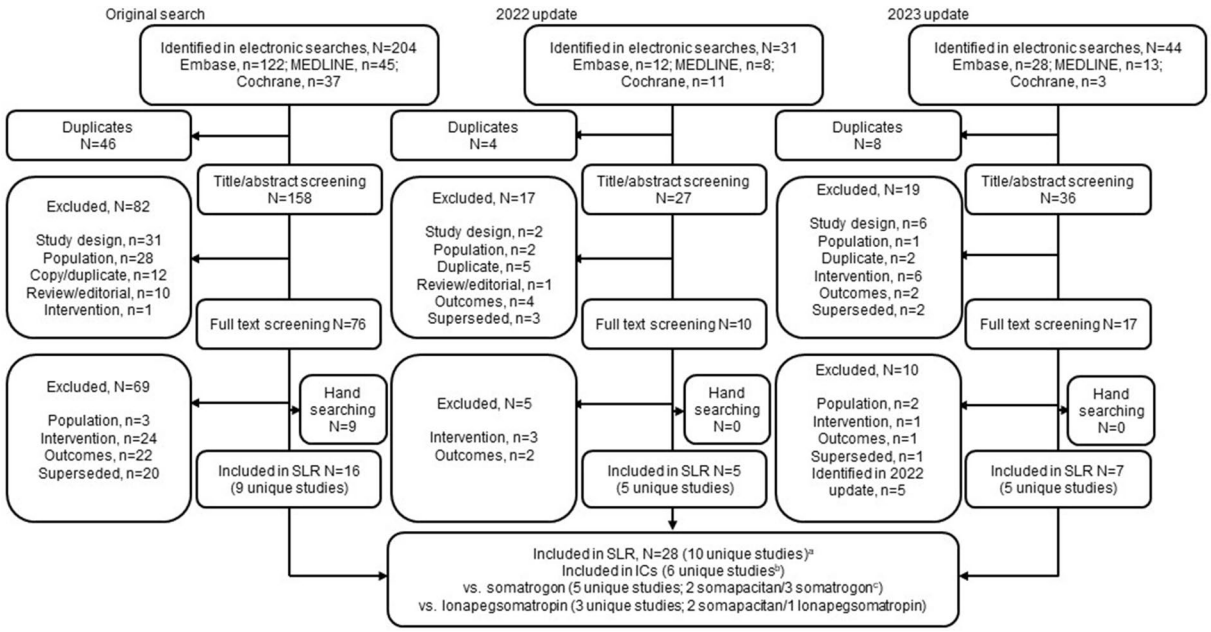

Fig. 2 PRISMA flow diagram for SLR and studies included in ICs of somapacitan versus somatrogon and lonapegsomatropin. [a]Some of the unique studies identified in the updates had been identified in the original review and thus may not count as unique trials when combining numbers from all three reviews. The total number of unique studies included one study of eftansomatropin, which was not included in the ICs. [b]The fliGHt lonapegsomatropin study [22] was excluded from the IC because it was a single arm study in treatment-experienced patients but was included in the safety analyses; enliGHten (lonapegsomatropin) was included in the long-term assessment of efficacy and safety only [34, 35]; NCT01947907 was excluded from the IC because it did not evaluate the recommended dose of lonapegsomatropin but was included in the safety analyses [21]. [c]One somatrogon study [11, 14] was included only in the alternative analyses, not the base case analyses. *IC* indirect comparison, *SLR* systematic literature review

Annualized Height Velocity

Data on AHV were available from all six trials at weeks 26 and 52 (Table 4). There were generally no observed differences in improvements in AHV with somapacitan, somatrogon, and lonapegsomatropin at weeks 26 and 52 compared to daily GH. The results of the base case IC did not reveal any differences in AHV when somapacitan was compared with daily GH, somatrogon, or lonapegsomatropin at weeks 26 and 52 (Fig. 3a).

In the alternative analysis, the point estimate for the difference in AHV improvement favoring somapacitan was larger versus low-dose daily GH (0.025 mg/kg/day) than versus standard dose of daily GH, both at weeks 26 and 52. The comparisons between somapacitan and the other comparators showed similar findings to those observed in the base case analysis (Fig. 3b).

Height Velocity SDS

Data on height velocity SDS were available from two and four trials at weeks 26 and 52, respectively; a network model for week 26 data was not feasible (Table 5). Overall, there were generally no observed differences in improvements in height velocity SDS with somapacitan, somatrogon, and lonapegsomatropin at weeks 26 and 52 compared to daily GH. The results of the base case IC did not reveal any differences in height velocity SDS when somapacitan was compared with daily GH, somatrogon, or lonapegsomatropin at week 52 (Fig. 3a).

The Japanese study [11, 14] did not provide height velocity SDS data, so alternative analyses were not performed.

Height SDS

Data on height SDS were available from all six trials at weeks 26 and 52 (Table 6). Overall, there was generally no observed difference in improvements in change from baseline in height SDS with somapacitan, somatrogon, and lonapegsomatropin at weeks 26 and 52 compared to daily GH. The results of the base case IC did not reveal any differences in change from baseline in height SDS when somapacitan was compared with daily GH, somatrogon, or lonapegsomatropin at weeks 26 and 52 (Fig. 3a).

In the alternative analysis, the point estimate for the change from baseline in height SDS favoring somapacitan was larger versus low-dose daily GH (0.025 mg/kg/day) than versus standard dose daily GH, at week 52. The comparisons between somapacitan and the other comparators showed similar findings to those observed in the base case analysis (Fig. 3b).

Long-Term Efficacy

Long-term efficacy findings are summarized in the Supplementary Material. Overall, results from all study extension phases showed somapacitan, somatrogon, and lonapegsomatropin had sustained efficacy after continued treatment (Supplementary Table 2).

Sensitivity Analysis

Sensitivity analysis results using alternative priors showed similar findings for AHV to the base case analyses at both weeks 26 and 52 (Supplementary Fig. 2).

Safety

Adverse Events to 1 Year

AE data were available to 1 year for somapacitan [15, 16], somatrogon [17–19], and lonapegsomatropin [20], and to 6 months for lonapegsomatropin in two studies excluded from the efficacy ICs [21, 22]. Across all trials, the three LAGHs were generally well tolerated and demonstrated comparable safety to daily GH. Most AEs were mild to moderate in severity. The proportion of patients experiencing at least one AE in 26 and 52 weeks of treatment varied across trials from 46 to 100% (Table 7).

When ISRs were considered, variability was observed across clinical trials, perhaps as a result of slight differences in the methods used for determining the frequency of injection site pain, although these variations are unlikely to explain the differences observed (Table 7). The rates of

Table 3 Summary of baseline characteristics of participants in studies included in the indirect comparisons

Trial	Treatment arm	Age, years Mean (SD)	*n* (%) of males	Race, *n* (%)[a]	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 [15]	Somapacitan 0.16 mg/kg/week (*n* = 14)	6.1 (2.3)	8 (57.1)	White: 6 (42.9) Asian: 8 (57.1)	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)
	Daily GH 0.034 mg/kg/day (*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 [16]	Somapacitan 0.16 mg/kg/week (*n* = 132)	6.4 (2.2)	99 (75.0)	White: 78 (59.1) Asian: 46 (34.8) 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)
	Daily GH 0.034 mg/kg/day (*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)	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)

Table 3 continued

Trial	Treatment arm	Age, years Mean (SD)	*n* (%) of males	Race, *n* (%)[a]	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)
Somatrogon											
NCT01592500 [17]	Somatrogon 0.66 mg/kg/week ($n = 14$)	6.1 (2.2)	9 (64.3)	White: 14 (100.0%)	NR	NR	NR	− 3.01 (1.42)	− 4.21 (1.45)	− 1.97 (0.83) ng/mL	NR
	Daily GH 0.034 mg/kg/day ($n = 11$)	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
NCT02968004 [18]	Somatrogon 0.66 mg/kg/week ($n = 109$)	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) Other: 3 (2.8)	NR	NR	− 0.28 (1.04)	NR	− 2.94 (1.29)	NR	− 1.95
	Daily GH 0.034 mg/kg/day ($n = 115$)	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) 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
NCT03874013 [11, 14][b]	Somatrogon 0.66 mg/kg/week ($n = 22$)	5.28 (1.84)	9 (40.9)	NR	14.49 (3.33)	15.27 (1.3)	NR	NR	− 2.61 (0.44)	72.9 (33.5) µg/L	− 1.39 (0.90)
	Daily GH 0.025 mg/kg/day ($n = 22$)	6.78 (2.34)	12 (54.5)	NR	17.87 (4.85)	15.89 (1.09)	NR	NR	− 2.53 (0.40)	80.5 (30.7) µg/L	− 1.62 (0.84)

Table 3 continued

Trial	Treatment arm	Age, years Mean (SD)	*n* (%) of males	Race, *n* (%)[a]	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)
Lonapegsomatropin											
heiGHt [20]	Lonapegsomatropin 0.24 mg/kg/week (*n* = 105)	8.51 (2.7)	86 (81.9)	White: 100 (95.2)	21.0 (6.5)	16.1 (1.8)	− 0.32 (0.95)	− 2.20 (2.22)	− 2.89 (0.85)	78.4 (43.9)	− 2.08 (0.88)
	Daily GH 0.034 mg/kg/day (*n* = 56)	8.50 (2.8)	46 (82.1)	White: 52 (92.9)	21.2 (6.7)	16.5 (2.2)	− 0.14 (1.07)	− 2.14 (2.02)	− 3.00 (0.90)	88.1 (56.8)	− 1.96 (0.98)

BMI body mass index, *GH* growth hormone, *HV* height velocity, *IGF-1* insulin-like growth factor, *NR* not reported, *SD* standard deviation, *SDS* standard deviation score

[a]Other included races other than White, Black or Africa American or Asian

[b]Included in the alternative analyses only

injection site AEs and pain were low in all somapacitan trials, with a similar incidence reported in the somapacitan and daily GH arms. Similarly, in lonapegsomatropin trials, there was no difference in incidence of injection site AEs or pain between the lonapegsomatropin and daily GH arms. However, the incidence of injection site pain was higher with somatrogon compared with daily GH across trials of somatrogon.

The incidences of non-neutralizing antidrug antibodies and neutralizing antibodies were reported across trials, with neutralizing antibodies reported infrequently and only with somatrogon. Where reported, analyses from trials showed the presence of antidrug antibodies did not have any effect on efficacy or safety.

No neutralizing anti-human GH (hGH) antibodies were detected in any of the somapacitan trials. One patient (7.1%) treated with daily GH had persistent non-neutralizing anti-hGH antibodies of low titer, and two patients (14.2%) treated with somapacitan 0.16 mg/kg/week had a single transient measurement of low-titer, non-neutralizing antibodies in the Phase II REAL 3 trial [15]. In the Phase III REAL 4 trial [16], two patients (1.5%) treated with somapacitan and one patient (1.5%) treated with daily GH had ≥ 2 consecutive positive non-neutralizing antidrug antibodies samples.

In trials of somatrogon, two patients (14.3%) treated with somatrogon 0.66 mg/kg/week and one (9.1%) patient treated with daily GH had non-neutralizing antidrug antibodies in NCT01592500 [17], whereas 84 patients (77.1%) treated with somatrogon 0.66 mg/kg/week and 18 (15.6%) treated with daily GH tested positive for non-neutralizing antidrug antibodies in NCT02968004 [18]. In the Japanese trial of somatrogon, 18 patients (81.8%) treated with somatrogon 0.66 mg/kg/week, and four (18.2%) treated with daily GH tested positive for non-neutralizing antidrug antibodies; two patients (9.1%) treated with somatrogon tested positive for neutralizing antibodies at one visit [11].

No neutralizing anti-hGH antibodies were detected in any of the lonapegsomatropin trials (6- or 12-months' duration). A low incidence of non-neutralizing antibodies (0–8.3%) was reported across all doses of lonapegsomatropin at 26 and 52 weeks with minimal variability between trials. In the Phase III heiGHt trial, a low titer of anti-hGH binding antibodies were detected in seven (6.7%) patients treated with 0.24 mg/kg/week lonapegsomatropin and two (3.6%) patients treated with 0.24 mg/kg/week daily GH; detected antibodies did not appear to affect safety or efficacy [20]. In NCT01947907, across the three lonapegsomatropin doses (0.14, 0.21, and 0.3 mg/kg/week) over 26 weeks, only one patient (8.3%) in the 0.14 mg/kg/week group had very low-titer non-neutralizing anti-GH antibodies and no neutralizing antibodies [21]. There were no neutralizing or non-neutralizing antibodies detected in the 13 patients treated with daily GH 0.21 mg/kg/week for 26 weeks.

Long-Term Adverse Events

Safety data were not consistently reported in publications of the extension periods/studies. Overall, continued treatment with somapacitan and somatrogon was well tolerated, with no new safety signals identified in the extension trials. No long-term safety data for lonapegsomatropin were identified, although it was stated that the drug had an acceptable safety profile in the longer-term. The proportion of patients experiencing at least one AE with somapacitan and somatrogon ranged from approximately 40% to 80% (**Supplementary Table 3**). Most reported AEs were mild to moderate in severity, and severe AEs were reported infrequently.

Although varying proportions of patients receiving daily GH or lonapegsomatropin tested positive for non-neutralizing antibodies (< 25%), no neutralizing antibodies were detected in either of the long-term somapacitan or lonapegsomatropin studies. In contrast, 17 patients (35.4%) had low titers of anti-somatrogon antibodies, none of whom had neutralizing antibodies, and 84 (77%) had antidrug antibodies, of whom two tested positive for neutralizing antibodies, in the extension period of NCT01592500 [23] and NCT02968004 [24]. Where reported, analyses indicated that the presence of antibodies did not have any impact with respect to efficacy outcomes.

Table 4 Annualized height velocity trial results used for the indirect comparisons

Trial	Arm	AHV			
		Mean	Difference	Mean	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3 [15]	Somapacitan 0.16 mg/kg/week (n = 14)	12.9[a] (SE: 0.67)	1.7 (– 0.2, 3.6)	11.7[a] (SE: 0.46)	1.8 (0.5, 3.1)
	Daily GH 0.034 mg/kg/day (n = 14)	11.4[a] (SE: 0.66)		9.9[a] (SE: 0.46)	
REAL 4 [16]	Somapacitan 0.16 mg/kg/week (n = 132)	12.25[a] (SE: 0.27)	– 0.51 (– 1.41, 0.39)	11.2[a] (SE: 0.19)	– 0.5 (– 1.1, 0.2)
	Daily GH 0.034 mg/kg/day (n = 68)	12.75[a] (SE: 0.37)		11.7[a] (SE: 0.27)	
Somatrogon					
NCT01592500 [17]	Somatrogon 0.66 mg/kg/week (n = 13 at 26 weeks; n = 14 at 52 weeks)	13.5 (SD: 5)	NR	11.93 (SD: 3.5)	NR
	Daily GH 0.034 mg/kg/day (n = 11)	15 (SD: 2.9)		12.5 (SD: 2.1)	
NCT02968004 [18]	Somatrogon 0.66 mg/kg/week (n = 109)	10.59[a] (9.96, 11.22)	0.55 (– 0.13, 1.23)	10.1[a] (9.58, 10.63)	0.33 (– 0.24, 0.89)
	Daily GH 0.034 mg/kg/day (n = 115)	10.04[a] (9.47, 10.62)		9.78[a] (9.29, 10.26)	
NCT03874013 [11, 14][b]	Somatrogon 0.66 mg/kg/week (n = 22)	10.35[a]	1.88 (0.74, 3.03)	9.65[a]	1.79 (0.91, 2.61)
	Daily GH 0.025 mg/kg/day (n = 22)	8.47[a]		7.87[a]	

Table 4 continued

Trial	Arm	AHV			
		Mean	Difference	Mean	Difference
		Week 26		Week 52	
Lonapegsomatropin heiGHt [20]	Lonapegsomatropin 0.24 mg/kg/week (n = 105)	12.7[a] (SE: 0.41)	1.4 (0.5, 2.3)	11.2[a] (SE: 0.2)	0.9 (0.2, 1.5)
	Daily GH 0.034 mg/kg/day (n = 56)	11.2[a] (SE: 0.34)		10.3[a] (SE: 0.3)	

Data are mean (95% CI) unless otherwise indicated

AHV annualized height velocity, *CI* confidence interval, *GH* growth hormone, *LSM* least square mean, *SD* standard deviation, *SE* standard error

[a]LSM

[b]Included only in the alternative analysis

DISCUSSION

Direct comparisons of LAGH for the treatment of pediatric GHD are lacking. The short-term (≤ 52 weeks) comparative efficacy of somapacitan versus somatrogon and lonapegsomatropin were therefore summarized and assessed via IC for this indication. The analyses did not identify any differences in the improvements in AHV, height velocity SDS, and height SDS compared with age- and sex-matched children seen in clinical trials of somapacitan, somatrogon, and lonapegsomatropin, as well as daily GH. These results are in general agreement with another IC of LAGHs conducted by Schaible and colleagues [25], which found similar AHV and changes in height SDS with somatrogon versus lonapegsomatropin and daily GH using Phase III data only. The restriction to Phase III data in that IC was to try to reduce heterogeneity, but GHD is a rare disease and few studies—predominantly with small sample sizes—are available, so heterogeneity remained high. A fixed effects model was used in the base case of the IC of Schaible and colleagues [25]. In contrast, a random effects model was used in the current ICs to account for heterogeneity potentially introduced by the additional studies, an approach supported by the NICE evaluation assessment group.

Additionally, the LAGHs were found to have sustained efficacy after continued long-term treatment in the current review: mean AHV results generally reflected a sustained growth rate, while changes in height SDS values reflected height normalization over time. Where reported, results were similar among patients who switched from daily GH to somapacitan, somatrogon, or lonapegsomatropin versus continued treatment with the respective LAGH. Although IC was not considered feasible, descriptive analyses supported that the three LAGHs generally demonstrated similar long-term efficacy.

The safety outcomes considered included AEs, ISRs, and anti-hGH antibodies/antidrug antibodies. Across trials, somapacitan, somatrogon, and lonapegsomatropin were generally well tolerated and demonstrated comparable overall safety to daily GH. Most AEs were mild to moderate in severity in the short and longer term. However, in the somapacitan and lonapegsomatropin trials to 52 weeks, injection site pain reported with similar frequency with the LAGH and daily GH, but, in the somatrogon trials to 52 weeks, injection site pain was more

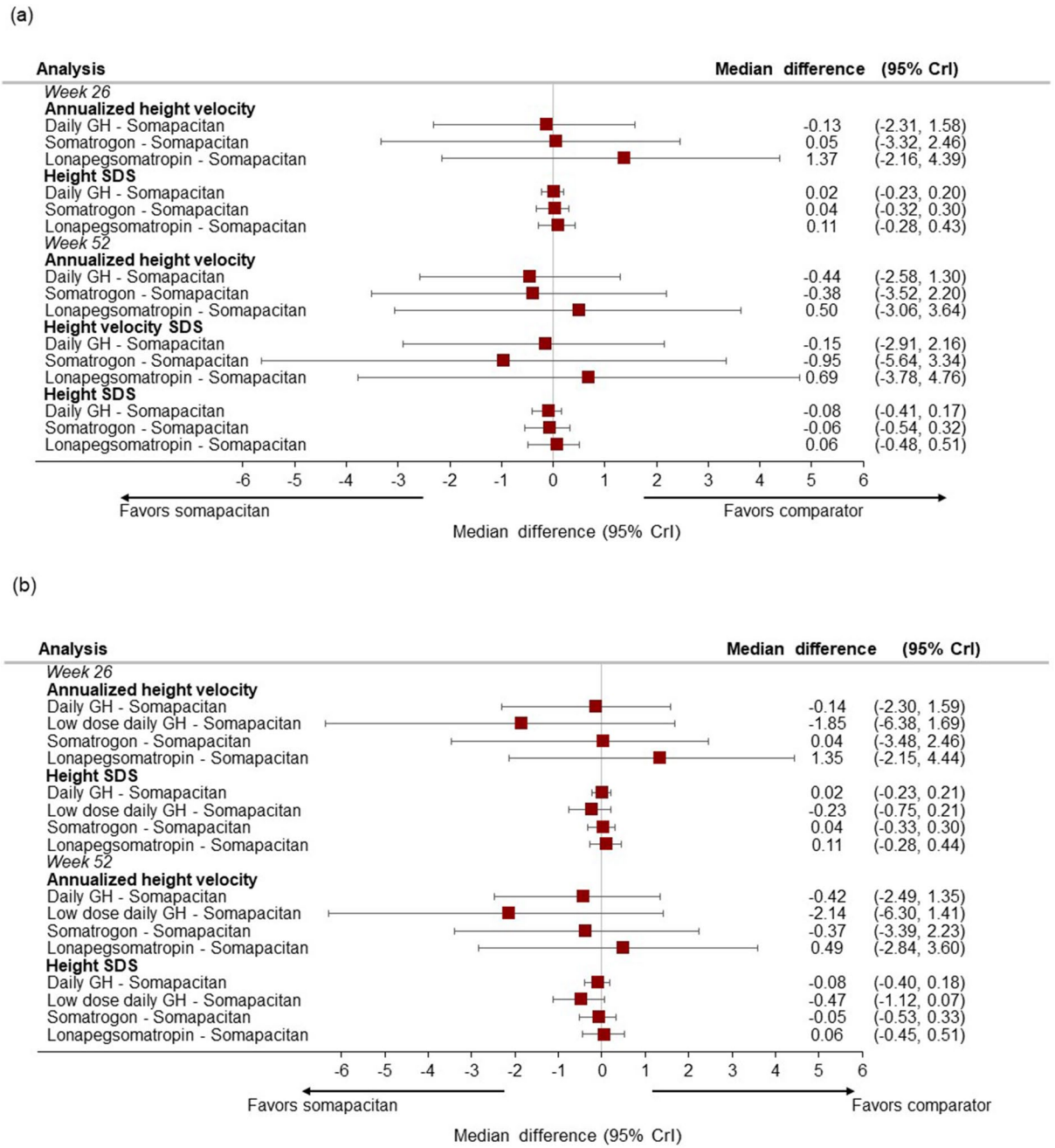

Fig. 3 Forest plots of results of **a** base-case and **b** alternative evidence analyses for the indirect comparisons of somapacitan versus somatrogon and lonapegsomatropin. *Crl* credible interval, *GH* growth hormone, *SDS* standard deviation score

commonly reported with the LAGH than with daily GH, possibly because of reporting practices [26]. For example, in somatrogon trials [11, 18], injection site pain was recorded weekly, capturing each once-weekly somatrogon injection, but for daily GH was recorded as the most severe pain for the week rather than after each daily GH injection, so, even if there were multiple occurrences of severe pain, only one occurrence would be recorded per week. The same difficulty in comparing rates across arms within this trial should also be extended to comparing rates

Table 5 Height velocity SDS trial results used for the indirect comparisons

Trial	Arm	Height velocity SDS			
		Mean	Difference	Mean	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3 [15]	Somapacitan 0.16 mg/kg/week (n = 14)	7.19[a] (SE: 0.9)	1.61 (– 0.97, 4.19)	5.72[a] (SE: 0.58)	1.64 (– 0.02, 3.31)
	Daily GH 0.034 mg/kg/day (n = 14)	5.58[a] (SE: 0.92)		4.07[a] (SE: 0.59)	
REAL 4 [16]	Somapacitan 0.16 mg/kg/week (n = 132)	6.62[a] (SE: 0.33)	– 0.62 (– 1.74, 0.49)	5.62[a] (SE: 0.25)	– 0.82 (– 1.68, 0.04)
	Daily GH 0.034 mg/kg/day (n = 68)	7.24[a] (SE: 0.46)		6.44[a] (SE: 0.35)	
Somatrogon					
NCT01592500 [17]	Somatrogon 0.66 mg/kg/week (n = 14)	NR	NR	6.57 (SE: 0.6)	NR
	Daily GH 0.034 mg/kg/day (n = 11)	NR		7.38 (SE: 0.44)	
Lonapegsomatropin heiGHt [20]	Lonapegsomatropin 0.24 mg/kg/week (n = 105)	NR	NR	5.88[a] (SE: 0.31)	0.82 (– 0.04, 1.67)
	Daily GH 0.034 mg/kg/day (n = 56)	NR		5.06[a] (SE: 0.39)	

Data are mean (95% CI) unless otherwise indicated

CI confidence interval, *GH* growth hormone, *LSM* least square mean, *NR* not reported, *SDS* standard deviation score, *SE* standard error

[a]LSM

across trials. Nonetheless, injection site pain was reported infrequently in trials of somapacitan, variably in lonapegsomatropin trials, and at a high frequency in somatrogon trials. These differences could have resulted from the volume of each injection, preservatives in buffer solution, needle size, or other needle features; however, they are an important consideration

Table 6 Change from baseline in height SDS trial results used for the indirect comparisons

Trial	Arm	Height SDS			
		Change from baseline	Difference	Change from baseline	Difference
		Week 26		Week 52	
Somapacitan					
REAL 3 [15]	Somapacitan 0.16 mg/kg/week (n = 14)	0.87[a] (SE: 0.08)	0.16 (− 0.06, 0.38)	1.42[a] (SE: 0.1)	0.35 (0.05, 0.65)
	Daily GH 0.034 mg/kg/day (n = 14)	0.71[a] (SE: 0.08)		1.07[a] (SE: 0.1)	
REAL 4 [16]	Somapacitan 0.16 mg/kg/week (n = 132)	0.73[a] (SE: 0.03)	− 0.09 (− 0.20, 0.02)	1.25[a] (SE: 0.04)	− 0.05 (− 0.18, 0.08)
	Daily GH 0.034 mg/kg/day (n = 68)	0.82[a] (SE: 0.04)		1.30[a] (SE: 0.05)	
Somatrogon					
NCT01592500 [17]	Somatrogon 0.66 mg/kg/week (n = 13)	0.90 (SD: 0.39)	NR	1.45 (SD: 0.61)	NR
	Daily GH 0.034 mg/kg/day (n = 11)	1.00 (SD: 0.35)		1.51 (SD: 0.47)	
NCT02968004 [18]	Somatrogon 0.66 mg/kg/week (n = 109)	0.54 (0.48, 0.61)	0.06 (− 0.01, 0.13)	0.92 (0.82, 1.02)	0.05 (− 0.06, 0.16)
	Daily GH 0.034 mg/kg/day (n = 115)	0.48 (0.42, 0.54)		0.87 (0.78, 0.96)	
NCT03874013 [11, 14][b]	Somatrogon 0.66 mg/kg/week (n = 22)	0.58[a]	0.26 (0.12, 0.41)	0.94[a]	0.42 (0.23, 0.61)
	Daily GH 0.025 mg/kg/day (n = 22)	0.31[a]		0.52[a]	

Table 6 continued

Trial	Arm	Height SDS			
		Change from baseline	Difference	Change from baseline	Difference
		Week 26		Week 52	
Lonapegsomatropin heiGHt [20, 33]	Lonapegsomatropin 0.24 mg/kg/week (n = 105)	0.63[a] (SE: 0.02)		1.1[a] (0.04)	0.14 (0.03, 0.26)
	Daily GH 0.034 mg/kg/day (n = 56)	0.54[a] (SE: 0.04)		0.96[a] (0.05)	

Data are mean (95% CI) unless otherwise indicated

CI confidence interval, *GH* growth hormone, *LSM* least square mean, *NR* not reported, *SDS* standard deviation score, *SE* standard error

[a]LSM

[b]Included only in the alternative analysis

when using GH for pediatric use since injection site pain is one of the major factors influencing compliance [27].

IGF-I levels were measured in all three pivotal LAGH trials and the same assay was used to measure IGF-I and to quantify IGF-I SDS [16, 18, 20]. However, only the heiGHt trial [20] found a statistically significant difference in the IGF-I level between the LAGH (lonapegsomatropin) and the daily GH comparator. In the context of the known dose–response relationship between GH and IGF-I SDS, achievement of similar IGF-I SDS and clinical outcomes in a non-inferiority setting confirms the comparable titration of treatment groups and the clinical relevance of findings when interpreting data.

The rates of detected anti-hGH antibodies or antidrug antibodies varied across the trials, with rates being considerably higher in the somatrogon trials than in trials of the other two LAGHs; additionally, neutralizing antibodies were observed with somatrogon but not with somapacitan, lonapegsomatropin, or daily GH. Where reported in the studies included in the current analyses, subjects who were positive for antibodies did not experience reduced efficacy or safety issues compared with those without antibodies. Similarly, additional analyses of a Phase III trial of somatrogon also found the presence of antidrug antibodies to have no effect on the incidence of AEs, and no association between the incidence of AEs and antidrug antibody titer [19].

The current analyses did not reveal any differences with respect to efficacy between the different technologies used to prolong the action of GH: somapacitan is a GH with reversible non-covalent albumin-binding properties, somatrogon is a GH-fusion protein moiety, and lonapegsomatropin utilizes covalent or transient pegylation [6]. Additionally, no differences in efficacy and safety between the three LAGHs (somapacitan, somatrogon, and lonapegsomatropin) and daily GH were found, with the possible exception of injection site pain with somatrogon. Therefore, LAGHs which are administered once weekly are expected to reduce the burden and distress associated with daily injections, decrease interference with daily life, and thereby potentially improve treatment adherence and, consequently, clinical outcomes in children with GHD. These assumptions are supported by several analyses of preference and treatment burden conducted in children treated with once-weekly LAGH after switching from daily GH and/or their parents/caregivers.

Table 7 Safety data for somapacitan, somatrogon and lonapegsomatropin from clinical trials identified in the systematic literature review

Trial	Arm (no. of participants)	Adverse events			Injection site reactions		
		Any AE, *n* (%)	Serious AE, *n* (%)	Severe AE, *n* (%)	AE, *n* (%)	Pain, *n* (%)	Severe pain, *n* (%)
To week 52							
REAL 3 [15]	Somapacitan 0.16 mg/kg/week (*n* = 14)	13 (92.9)	1 (7.1)	0	0	0	0
	Daily GH 0.034 mg/kg/day (*n* = 14)	14 (100)	1 (7.1)	0	0	0	0
REAL 4 [16]	Somapacitan 0.16 mg/kg/week (*n* = 132)	94 (71.2)	6 (4.5)	4 (3.0)	7 (5.3)	2 (1.5)	0
	Daily GH 0.034 mg/kg/day (*n* = 68)	41 (60.3)	2 (2.9)	1 (1.5)	4 (5.9)	1 (1.5)	0
NCT01592500 [17]	Somatrogon 0.66 mg/kg/week (*n* = 13)	10 (71.4)	0	0	NR	NR	1 (7.1)
	Daily GH 0.034 mg/kg/day (*n* = 11)	8 (72.7)	0	0	NR	NR	0
NCT02968004 [18]	Somatrogon 0.66 mg/kg/week (*n* = 109)	95 (87.2)	3 (2.8)	9 (8.3)	NR	43 (39.4)	5 (4.6)
	Daily GH 0.034 mg/kg/day (*n* = 115)	97 (84.3)	2 (1.7)	6 (5.2)	NR	29 (25.2)	3 (2.6)
NCT03874013 [11, 14]	Somatrogon 0.66 mg/kg/week (*n* = 22)	22 (100)	2 (9.1)	2 (9.1)	NR	16 (72.7)	0
	Daily GH 0.025 mg/kg/day (*n* = 22)	19 (86.4)	2 (9.1)	2 (9.1)	NR	3 (13.6)	0

Table 7 continued

Trial	Arm (no. of participants)	Adverse events			Injection site reactions		
		Any AE, *n* (%)	Serious AE, *n* (%)	Severe AE, *n* (%)	AE, *n* (%)	Pain, *n* (%)	Severe pain, *n* (%)
heiGHt [20]	Lonapegsomatropin 0.24 mg/kg/week (*n* = 105)	81 (77.1)	1 (0.95)	0	2 (1.9)	NR	NR
	Daily GH 0.24 mg/kg/week (*n* = 56)	39 (69.6)	1 (2.56)	0	1 (1.8)	NR	NR
To week 26							
NCT01947907 [21]	Lonapegsomatropin 0.14 mg/kg/week (*n* = 12)	5–7 (46–58)[a]	NR	NR	NR	5 (41.7)	0
	Lonapegsomatropin 0.21 mg/kg/week (*n* = 14)	6–8 (46–58)[a]	NR	NR	NR	6 (42.9)	0
	Lonapegsomatropin 0.3 mg/kg/week (*n* = 14)	6–8 (46–58)[a]	NR	NR	NR	6 (42.9)	0
	Daily GH 0.21 mg/kg/week (*n* = 13)	8 (61.5)	NR	NR	NR	6 (46.2)	0
fliGHt [22]	Lonapegsomatropin 0.24 mg/kg/week (*n* = 146)	83 (56.8)	1 (0.7)	0	NR	4 (2.7)	NR

AE adverse event, *GH* growth hormone, *NR* not reported

[a]The incidence of any AE was reported as a range across the three lonapegsomatropin arms combined

In REAL-4, 90% of parents/caregivers preferred once-weekly somapacitan over daily GH, usually because of the reduced injection frequency [28]. Additional results of this study suggested lower treatment burden with somapacitan [16].

In the fliGHt trial, > 80% of children and their parents/caregivers preferred lonapegsomatropin, again mainly because of the reduced injection frequency, and, overall, children and their

parents/caregivers had a reduced treatment burden following the switch from daily GH [29].

Another important factor to consider when selecting a GH treatment is the administrative device and dosing options. For example, somapacitan and somatrogon have pen devices with options to fine tune the dose, whereas the lonapegsomatropin pen device has pre-loaded cartridges which limit the flexibility of dosing.

Limitations

The SLR captured only studies written in English, so potentially relevant studies written in other languages may have been missed, and it has the limitations associated with all SLRs. That is, possible publication bias (study findings may influence investigators' decision to publish trial findings), time-lag bias (studies with less positive findings take longer to publish), language bias (non-English language articles reporting significant results are more likely to be rewritten in English), and selective outcome reporting (non-significant outcomes are excluded from publication).

The main limitation of the IC was the small number of relevant trials, with a number not fully published, and the lack of trial replication, which limited the information on heterogeneity in the network. In the random effects 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 the same data were used to both calculate the prior and to update it, and the former was not taken from an alternative external source. However, hierarchal class effects models have been used for HTA submissions to explore treatment effects as a class [30]. In addition, the identified studies predominantly included small numbers of patients, as expected for analyses of rare diseases. Imbalance in prognostic factors (such as age, race, and gender) between arms in the trials was limited and adjusted, since they were used as covariates in the statistical analyses. However, although there were differences between the trials for these prognostic factors, no effect modification was expected, and this was not considered a severe limitation. Furthermore, height SDS and height velocity SDS are standardized for age and gender. The differences in handling of dose reduction (e.g., daily GH vs. once-weekly treatment, based on IGF-I levels across trials) also had potential to impact outcomes, suggesting caution is needed when interpreting results.

For the alternative network, a different dose of daily GH in one of the trials was not adjusted for through dose–response modeling but was connected as a separate treatment. Although a dose–response relationship for daily GH in GHD has been identified [31, 32], the small size of the network meant that a meta-regression was deemed unfeasible.

CONCLUSION

ICs, feasible only for short-term efficacy outcomes (≤ 52 weeks), identified no differences between somapacitan versus somatrogon and lonapegsomatropin with respect to AHV, height velocity SDS, and change in height SDS in children with GHD. One LAGH (lonapegsomatropin) was associated with an elevated IGF-I level compared to daily GH. All three LAGHs had sustained efficacy and were generally well tolerated, with the exception of differences in the observed injection site pain for somatrogon. In general, they seemed to have comparable efficacy and safety to daily GH, in both the short and long term, and may have advantages to daily GH in terms of acceptability and adherence to GH replacement therapy.

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Data Availability. The data are available upon reasonable request.

Declarations

Conflict of Interest. Lasse de Fries Jensen, Vasileios Antavalis, Jan Odgaard-Jensen, Annachiara Rossi, Alberto Pietropoli and Michael Højby are full-time employees of Novo Nordisk.

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