CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Somatrogon (Ngenla)

Indication: Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency)

Sponsor: Pfizer Canada ULC

Recommendation: Reimburse with Conditions

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SOMATROGON (NGENLA — PFIZER CANADA ULC)

Therapeutic Area: Growth hormone deficiency

Recommendation

The CADTH Canadian Drug Expert Committee (CDEC) recommends that somatrogon be reimbursed for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency) only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Two phase III, randomized, active-controlled trials (CP-4-006 and CP-4-009) that enrolled pre-pubertal children with growth hormone deficiency and who were at least 3 years of age, demonstrated that for the efficacy outcome of annualized height velocity at 12 months, treatment with somatrogon was non-inferior (CP-4-006) or comparable (CP-4-009) to Genotropin. In study CP-4-006, the least square (LS) mean treatment difference between somatrogon and Genotropin, the annualized height velocity after 12 months of treatment was 0.33 cm/year (95% confidence Interval [CI] −0.24 to 0.89); demonstrating that somatrogon was non-inferior to Genotropin given that the lower bound of the 95% CI was greater than the prespecified noninferiority margin of −1.8 cm/year. In study CP-4-009, the LS mean height treatment difference between somatrogon and Genotropin, in the annualized height velocity after 12 months of treatment was 1.79 cm/year (95% CI, 0.97 to 2.61), indicating that somatrogon was comparable to Genotropin given that the between group difference exceed the estimated margin of −1.8 cm/year. Health-related quality of life (HRQoL) was not assessed in study CP-4-009 and was assessed in study CP-4-006 in select study locations only, and there were substantial amounts of missing data, hence the impact of somatrogon on HRQoL is uncertain.

Using the sponsor submitted price for somatrogon and publicly listed prices for all other drug costs, somatrogon may be more or less costly than various somatropin products. The available clinical evidence suggests that somatrogon is non-inferior to somatropin (Genotropin). As such, there is no evidence to support a price premium for somatrogon.

Table 1. Reimbursement Conditions and Reasons

Reimbursement Condition	Reason
Initiation	
1. Pre-pubertal children who are at least 3 years of age, and who are diagnosed with either isolated growth hormone deficiency, or growth hormone insufficiency as part of multiple pituitary hormone deficiency.	Patients enrolled in study CP-4-006 and study CP-4-009 were pre pubertal children who were at least 3 years of age, with either isolated growth hormone deficiency, or growth hormone insufficiency as part of multiple pituitary hormone deficiency.
Discontinuation	
2. Treatment with somatrogon must be discontinued upon the occurrence of any of the following: 2.1. height velocity is less than 2 cm/year, or 2.2. bone age is more than 16 years in boys and 14 years in girls, or 2.3. height is in the normal adult range (above −2 standard deviation score for an adult of the same sex), or 2.4. closure of the epiphyseal growth plates	Consistent with clinical practice guidelines and aligned with clinical practice in Canada, the clinical expert noted that in children diagnosed with growth hormone deficiency, treatment with recombinant growth hormone is stopped if epiphyseal plates have fused, bone age more than 16 years in boys and 14 years in girls, height velocity less than 2 cm/year, or height in the normal adult range.
Prescribing	
3. The patient must be under the care of a pediatric endocrinologist.	Accurate diagnosis and follow up of patients with growth hormone deficiency is important to ensure that somatrogon is prescribed to the most appropriate patients. In addition, there are several recombinant growth hormone treatment options that may be considered when selecting the most appropriate therapy for patients; these are best determined by a pediatric endocrinologist.
Pricing	
4. Somatrogon should not exceed the drug program cost of treatment with the least costly somatropin reimbursed for the treatment of growth hormone deficiency.	There is no clinical evidence to suggest that somatrogon is superior to Genotropin with regards to gains in height over the period for which there is observed data, nor is there any long-term comparative effectiveness data. As such, there is insufficient evidence to justify a cost premium for somatrogon over somatropin reimbursed for growth hormone deficiency, including Genotropin, the least costly somatropin.
Feasibility of Adoption	
5. The feasibility of adoption of somatrogon must be addressed	At the submitted price, the magnitude of uncertainty in the budget impact must be addressed to ensure the feasibility of adoption, given the difference between the sponsor's estimate and CADTH's estimate(s).

Implementation Guidance

Issues that may impact the drug plan's ability to implement a recommendation as identified by CDEC and the drug plans are summarized in Table 2.

Table 2. Implementation Guidance from CDEC

Condition #	Implementation Considerations and Guidance
1	The clinical expert noted that somatrogon can be initiated in patients with growth hormone deficiency who are treatment naïve or previously received growth hormone replacement therapy. However, CDEC noted that the consequences of switching from other recombinant growth hormone therapies to somatrogon is an evidence gap, as all the patients enrolled in study CP-4-006 and study CP-4-009 were treatment naïve.
2	The clinical expert noted to CDEC that treatment response should be assessed every 3 to 4 months in younger children who are expected to grow more rapidly and then every 6 months in the elementary school-aged child, and then every 4 to 6 months in the pubertal aged children.
3	Somatrogon could be prescribed in a similar manner to other recombinant growth hormone therapies as per the reimbursement criteria for each public drug plan.
3	In order to provide equitable access to somatrogon in communities without a pediatric endocrinologist, virtual appointments could be considered acceptable given that the outcome of height and lab investigations are objective.

Discussion Points

- CDEC discussed that daily injection of recombinant human growth treatments in pediatric patients could have a significant impact on HRQoL, both for the child and the care provider. CDEC noted that weekly injection with somatrogon might improve HRQoL and adherence to treatment, however, outcomes such as HRQoL and other patient reported outcome (PRO) responses were not assessed in study CP-4-009 and were not properly assessed in study CP-4-006, where in study CP-4-006 these outcomes were assessed in select study locations only. There was substantial amounts of missing data, and no minimum important difference (MID) was identified in the literature, hence the effect of somatrogon on HRQoL is unknown.
- Study C0311002 which was designed to evaluate the treatment burden of a weekly injection of somatrogon and a daily injection of Genotropin reported that the proportion of patients indicating preference for somatrogon was greater than the proportion of patients indicating preference for Genotropin. CDEC discussed that study C0311002 was open-label, and that there was no evidence identified in the literature for the validity, responsiveness, or minimal important difference for any of the questionnaires used, and hence there is significant uncertainty related to the benefit of weekly versus daily injection on adherence to treatment and HRQoL.
- CDEC discussed that the injection related adverse events in patients who received somatrogon was higher than the incidence reported in patients who received daily injection with Genotropin, however, this higher incidence of injection related adverse events with somatrogon did not yield higher withdrawal rates due to adverse events.
- CDEC discussed that restriction of prescribing to pediatric endocrinologists is necessary because growth hormone deficiency can be difficult to diagnose and to reduce the possibility of 'off label' use for other conditions in which daily recombinant growth hormone therapies are used, such as patients with chronic renal failure, Turner syndrome, idiopathic short stature, Prader-Willi syndrome, and adult-onset growth hormone deficiency. CDEC also noted that there is no evidence available for somatrogon's effects in patients with diagnoses other than growth hormone deficiency in prepubertal children.
- CDEC discussed that currently available evidence is limited with the small number of patients enrolled in the studies and that there is large variability in height growth, hence evidence from studies with a larger sample size and longer duration would provide more certainty around the efficacy and safety of somatrogon.

Background

Somatrogon has a Health Canada indication for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency). Somatrogon is a modified long-acting analog of human growth hormone and a new molecular entity with receptor binding properties and a mechanism of action analogous to human growth hormone. Somatrogon is available as a single patient use, multi-dose, disposable pre-filled pen for subcutaneous (SC) injection, in two dosages strengths 24 mg in 1.2 mL sterile solution (20 mg/mL) or 60 mg in 1.2 mL sterile solution (50 mg/mL). The Health Canada–approved dose is 0.66 mg/kg body weight administered once weekly by SC injection.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A systematic review that included two RCTs in pre-pubertal children with growth hormone deficiency
- Input from public drug plans that participate in the CADTH review process
- Input from one clinical specialist with expertise in diagnosing and treating patients with growth hormone deficiency
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Input from clinical expert consulted by CADTH

The most important goals that the ideal treatment would address would be optimizing final adult height, restoring metabolic functions associated with growth hormone deficiency, and optimizing quality of life. Some children also have additional, co-existing pituitary hormone deficiencies such as thyroid hormone deficiency, cortisol deficiency, and gonadotropin deficiency, and these hormone deficiencies should also be appropriately replaced to optimize growth. Growth hormone is an important counter-regulatory hormone in the regulation of blood glucose. Growth hormone also helps improve muscular tone and has anabolic effects on bone. While not the primary indications for replacing growth hormone, these additional benefits are appreciated by patients and prescribing physicians.

Adherence is a major limitation to experiencing the full benefits of recombinant growth hormone therapy. Currently, recombinant growth hormone formulations are given as subcutaneous injections on a daily or near-daily basis (6 days per week). These injections must be given throughout childhood and adolescence. This daily schedule can be inconvenient when patients want to leave their home for any reason (e.g., traveling, visiting, camping) because they have to think about how to transport and store the drug, remember to bring the accompanying supplies (e.g., needles, pen tips, alcohol swabs), and disrupt the activities that they are doing. Furthermore, some patients find the injections painful or anxiety-provoking. These nightly injections cause stress on the families from having to chase after their children and find them and then hold them down for their injections. An ideal recombinant growth hormone treatment would provide benefit on growth and metabolic outcomes while minimizing pain and anxiety. At the moment, the unmet needs with current recombinant growth hormone formulations pertain to suboptimal adherence due to anxiety and pain of injections, frequency of injections, and inconvenience in storing and handling, or simply forgetting.

Somatrogon could be used as first-line treatment for pediatric growth hormone deficiency. Currently there is no evidence available for somatrogon in patients who are younger than 3 years of age, so if growth hormone deficiency was diagnosed in infancy or early childhood, then the child would start with the daily recombinant growth hormone formulations and could be switched to the once weekly formulation after the age of 3 years.

The clinical expert consulted by CADTH indicated that patients who have been using recombinant growth hormone daily are likely to derive similar benefit from somatrogon in terms of impact on growth, in addition, patient's quality of life may significantly improve with a switch from daily injections to once weekly injections.

A positive change in height velocity that results in an increase in height SDS indicates a favorable response to treatment. An inadequate response after initiation of recombinant growth hormone therapy in patients with growth hormone deficiency is often defined by one or more of the following criteria: change in height velocity <2 cm/year, height velocity standard deviation score (SDS) <0 or change in height SDS <0.3/year during the first 6 to 12 months of therapy. With height being the major outcome of interest, treatment response should be monitored every 3 to 4 months in younger children who are expected to grow more rapidly and then every 6 months in the elementary school aged child who grow less rapidly, and then every 4 to 6 months in the pubertal aged child.

Recombinant Growth Hormone is generally very safe and well-tolerated. Prescribers and nurses discuss potential side effects and adverse effects with their patients and their caregivers. In the rare instance where a patient might develop a slipped caput femoral epiphysis or pseudotumor cerebri, growth hormone therapy is paused to allow for treatment or resolution of the adverse event. In cases of glucose intolerance or significantly high IGF-1 levels, the dose of growth hormone may need to be reduced. Reasons to stop treatment before growth is complete would be if the patient and caregiver do not adhere to treatment advice, for example, by neglecting to attend appointments, adjusting doses on their own, or refusing to follow through on recommended laboratory monitoring. Generally, in these cases, the prescriber would first try to determine barriers to care before discontinuing therapy all together.

Somatrogon should be prescribed only by pediatric endocrinologists who have access to the resources to be able to diagnose growth hormone deficiency properly and to endocrine nurses who are knowledgeable in growth hormone deficiency and would be able to support patients who require treatment.

Drug Program Input

Input was obtained from the drug programs that participate in the CADTH reimbursement review process. The following were identified as key factors that could potentially impact the implementation of a CADTH recommendation for somatrogon:

- Relevant comparators
- Considerations for initiation of therapy
- Considerations for continuation or renewal of therapy
- Considerations for discontinuation of therapy
- Considerations for prescribing of therapy
- Generalizability of trial populations to the broader populations in the jurisdictions
- Care provision issues
- System and economic issues

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 3. Responses to Questions from the Drug Programs

Implementation Issues	Response
Relevant Comparators	
The drug plans noted that currently, there are six once-daily human growth hormone products available and that there are currently no other long-acting growth hormone formulations for pediatrics available on the Canadian market. The drug plans also noted that more biosimilar products might become available.	CDEC noted that all currently available preparations human growth hormone products are for once daily injections, and that the use of Genotropin as a comparator in the clinical trials is reasonable. CDEC also noted that the economic analysis is challenging, given that the dose recommended with every comparator may change cost of drug per patient. CDEC also noted that anticipated biosimilar products could decrease cost of these human growth hormone products.

Implementation Issues	Response
Considerations for Initiation of Therapy	
The drug plans noted that there is some variability between jurisdictions in the clinical criteria of the currently listed options.	CDEC noted that all currently available preparations of human growth hormone products are for once-daily injections and that the use of Genotropin as a comparator in the clinical trials is reasonable.
Considerations for continuation or renewal of therapy	
The drug plans noted that most drug plans would likely approve with no renewal criteria required, but reimbursement would only be until adulthood.	CDEC noted that once treatment with growth hormone product is initiated, treatment can be renewed as long as the patient does not meet any of the discontinuation criteria.
Considerations for discontinuation of therapy	
At what age should somatrogon be stopped?	CDEC agreed with the clinical expert that age to stop therapy varies significantly, and that continuation of treatment is endocrinologist dependent. It was also noted that once treatment is initiated, treatment would continue until growth is considered complete, which could be based on either fusion of epiphyseal plates, bone age more than 16 years in boys and 14 years in girls, height velocity less than 2 cm/year, or height is in the normal adult range.
What criteria should be taken into consideration when assessing whether treatment should be stopped? Would such criteria be depended on growth velocity or fusion of growth plate?	CDEC agreed with the clinical expert that in children diagnosed with growth hormone deficiency, treatment with recombinant growth hormone should be stopped if epiphyseal plates have fused, bone age more than 16 years in boys and 14 years in girls, height velocity less than 2 cm/year, or height is in the normal adult range
Considerations for prescribing of therapy	
The drug plans noted that somatrogon is supplied in a prefilled, multidose pen to be administered weekly.	CDEC noted that somatrogon would be the only weekly recombinant growth hormone available on the Canadian market, and that that multidose pen method would allow administration at home.
Generalizability	
There could be indication creep. Is it anticipated that somatrogon will be prescribed off label in patients with chronic renal failure, Turner syndrome, idiopathic short stature, Prader-Willi syndrome, or adult growth hormone deficiency?	CDEC agreed with the clinical expert that to enable less frequent injections, somatrogon might be prescribed off label for patients with chronic renal failure, Turner syndrome, idiopathic short stature, Prader-Willi syndrome, or adult growth hormone deficiency, or patients with inconclusive growth hormone deficiency tests, and that indication creep could also happen in children under 3 years of age. CDEC also noted that the only available evidence is in pubertal children who are at least 3 years of age and who have growth hormone deficiency.
Care provision issues	
The drug plans noted that although somatrogon injections are weekly, injection site reactions were the most common side effect, which is significant in a pediatric population. Most side effects did not result in discontinuation of treatment.	CDEC noted that the increase in injection site events with the weekly administration somatrogon in comparison with the daily administration of Genotropin. CDEC also noted that children rarely need to stop growth hormone injections due to injection site reactions, and that usually after an initial period of adjustment, the daily shots could become second nature, with patients seeking a goal of higher adult height.
System and economic issues	
The drug plans noted that wastage could be an issue with human growth hormone products including somatrogon.	CDEC noted that wastage is not unique to somatrogon and that consideration should be given to wastage of the drug.

Clinical Evidence

Pivotal Studies and Protocol Selected Studies

Description of studies

Two phase III studies (CP-4-006 and CP-4-009) were included in the systematic review.

CP-4-006 (N = 224) was an open label, multi-center, randomized, active controlled, parallel group study evaluating the efficacy and safety of weekly somatrogon to daily growth hormone, genotropin. Patients enrolled in CP-4-006 study were pre pubertal children with growth hormone deficiency and who were at least 3 years of age and younger than 11 years for girls and 12 years for boys. CP-4-009 was a 12 month, open-label, multicenter, randomized, active-controlled, parallel group study conducted in Japan, which compared the efficacy and safety of the weekly somatrogon to daily genotropin in Japanese pre-pubertal children with growth hormone deficiency and who were at least 3 years of age, and younger than 11 years for girls and 12 years for boys. In both studies, patients were randomized in a 1:1 method to receive weekly SC doses of somatrogon or daily SC of genotropin for 12 months. Following the completion of the 12-month treatment period, in both studies, eligible patients were enrolled in a single-arm open label extension treatment phase with somatrogon. The open label extension treatment phase of study CP-4-009 (CP-4-009-Japan-OLE) is summarized under other relevant evidence section, and the open label extension treatment phase of study CP-4-006 was not available at the time of writing this report.

The primary efficacy outcome of CP-4-006 and CP-4-009 trials was annualized height velocity after twelve months of treatment. The secondary efficacy outcomes of both studies were annualized height velocity at six months, change in height SDS at 6 and 12 months, change in bone maturation at 12 months.

Efficacy Results

In study CP-4-006, the primary objective was to demonstrate that annual (12 month) height velocity from weekly somatrogon administration is noninferior to daily genotropin administration in children with GHD, and the primary objective in study CP-4-009 was to demonstrate that annual (12 month) height velocity from weekly somatrogon administration is comparable to daily genotropin administration in children with GHD. Non-inferiority in study CP-4-006 was concluded if the lower bound of the two-sided 95% CI for the mean treatment difference between somatrogon and genotropin, in the annualized height velocity after twelve months of treatment was ≥-1.8 cm/year. Comparability in study CP-4-009 was concluded if the mean treatment difference "somatrogon – genotropin" in the annualized height velocity after twelve months of treatment was ≥ -1.8 cm/year. In study CP-4-006, the least square (LS) mean treatment difference for the mean height velocity after twelve months of treatment was 0.33 cm/year (95% confidence Interval [CI], -0.24 to 0.89); the lower bound of the two-sided 95% CI for mean height velocity was greater than the prespecified noninferiority margin of -1.8 cm/year, indicating that weekly somatrogon administration is noninferior to daily genotropin administration. [redacted] In study CP-4-009, the treatment difference (somatrogon - Genotropin) in LS mean height velocity (cm/year) was 1.79 cm/year with a 2-sided 95% CI (0.97 to 2.61). Since the point estimate of 1.79 cm/year was greater than the preestablished margin of -1.8 cm/year, weekly somatrogon was concluded to be comparable to daily Genotropin.

The LS mean treatment difference for annualized HV at 6 months was [redacted] cm/year (95% CI, [redacted]) in CP-4-006 and [redacted] cm/year (95% CI, [redacted]) in study CP-4-009. The LS mean treatment difference for change in height SDS from baseline to 6 months was [redacted] (95% CI, [redacted]) in CP-4-006 and [redacted] (95% CI, [redacted]) in study CP-4-009. The LS mean treatment difference for change in height SDS from baseline to 12 months was 0.05 (95% CI, -0.06, 0.16) in CP-4-006 and [redacted] (95% CI, [redacted]) in study CP-4-009. The statistical significance of these results cannot be interpreted due to lack of reporting of p values.

In both studies, advancement in bone age [redacted] advancement in chronological age; mean bone maturation (defined as the ratio of bone age to chronologic age) at 12 months was [redacted] in both treatment groups, however, [redacted] was reported.

Health related quality of life (HRQoL) was assessed in CP-4-006 using Quality of Life in Short Stature Youth (QoLISSY) questionnaire, which assesses the impact of short stature on children from the perspectives of both the patients and their parents. In addition, the number of successful injection attempts by patients using the somatrogon multidose prefilled pen was evaluated based on the Observer Assessment Tool (OAT) and Participant Assessment Tool (PAT) were also assessed in CP-4-006, where the OAT was used to record the observer's assessment of an administration with the device after the patient or caregiver injected somatrogon. The PAT was used to record all of the patients' or caregiver's injections of somatrogon and was completed by the actual user of the pen or parent/legal guardian. However, the analyses for QoLISSY was performed in select locations only, and the analyses for other PRO responses were reported for the somatrogon treatment arm only, analyses were conducted in observed case patients, there were substantial amounts of missing data which would introduce significant biases, and no minimum important difference (MID) was identified in the literature for QoLISSY, OAT, and PAT. Hence the effect of these assessments in support of somatrogon are highly uncertain.

Harms Results

In CP-4-006, 87.2% and 84.3% of the patients in the somatrogon and genotropin group, and in CP-4-009, [redacted] and [redacted] of the patients in the somatrogon and genotropin group, respectively, reported at least one adverse event. In both studies the most commonly occurring adverse events were injection site pain, nasopharyngitis, pyrexia, and headache. There was no death reported in either of the studies. In CP-4-006, the most notable harm reported was an injection related event which was reported in [redacted] and [redacted] of patients in somatrogon and Genotropin treatment groups, respectively. In CP-4-009, of the common notable harm reported was injection related event which was reported in 72.7% patients in somatrogon treatment. The clinical expert did express concern that the injection site reaction in somatrogon was higher compared to genotropin. As somatrogon is a once weekly injection and genotropin is a once daily injection these analyses may warrant further explanation. The long-term safety concerns from the CP-4-006 study remains unknown.

Critical Appraisal

Internal validity

The clinical expert noted that the commonly used treatment for growth hormone deficiency in Canada is humatrope. Both CP-4-006 and CP-4-009 studies had only genotropin as the active comparator despite other approved comparators being available for treatment in Canada, hence the comparative efficacy and safety of somatrogon against other somatropin regimens is unknown.

No justification for the comparability criteria was provided in study CP-4-009. While study CP-4-009 met the pre-specified criteria for comparability, this should not be confused with unequivocal demonstration of equivalence, non-inferiority or superiority.

The clinical expert consulted by CADTH that the imbalance in age and sex in study CP-4-009 could influence the efficacy results in favor of somatrogon, however the difference in age would not impact outcomes observed within the first year, but it would impact the final adult height.

The primary outcome of CP-4-006 and CP-4-009 look to establish non inferiority and comparability of somatrogon with genotropin respectively. Once non inferiority was established, analyses of the secondary efficacy outcomes was conducted however, these secondary endpoints were not part of a hierarchical statistical testing plan and were not controlled for multiplicity and statistically significant p values have not been reported. [redacted]

CP-4-006 reported HRQoL and other PRO responses however, the administration of these tools was only in selective locations with very small sample size and as the study was open-label, this could bias the results of the efficacy outcomes. Moreover, only a complete case analysis was completed for this data with different subsets of patients at each time point which would be subjected to an increased risk of bias due to the complete case analysis approach. No MID was identified from literature for the QoLISSY questionnaire or the OAT and PAT instruments.

External validity

The clinical expert noted that based on baseline demographic and disease characteristics, the study population was fairly generalizable to Canadian patients, however the clinical expert was of the opinion that the age for inclusion within both studies i.e., ≥ 3 years was not reflective of Canadian practice, and patients with growth hormone deficiency would be identified in infancy. It was also noted that in CP-4-006, 20% of the cohort was Asian, which is higher than what is seen in Canada. The clinical expert also commented on how First Nations people who are treated in Canada are underestimated in both studies. The clinical expert also noted that the proportion of patients with peak growth hormone level of > 7ng/dL was higher than what is observed in Canadian clinical practice.

Growth hormone therapies are long term therapies, and even though the primary endpoint of the study was met, in the absence of long-term comparative efficacy and safety results, interpreting the long-term clinical meaningfulness of somatrogon is limited.

Other Relevant Evidence

Description of C0311002 (Study 002)

C0311002 (N = 87) was a randomized, open-label, multi-center, 2-period crossover study that enrolled children with growth hormone deficiency who are younger than 18 but at least 3 years of age. Patients were randomized in a 1:1 ratio to one of two sequences (sequence 1, sequence 2). Patients randomized to sequence 1 received treatment with daily somatropin for 12 weeks followed by 12 weeks of treatment with once weekly somatrogon. Patients randomized to sequence 2 received treatment with once weekly somatrogon for 12 weeks followed by 12 weeks of treatment with daily somatropin.

The primary objective of C0311002 was to evaluate the treatment burden of a weekly injection of somatrogon and a daily injection of somatropin (Genotropin). Secondary objectives included an evaluation of patient and caregiver self-assessments of treatment experience, and an evaluation of the psychometric properties of the Dyad Clinical Outcome Assessment (DCOA) questionnaires.

Efficacy Results

In C0311002, all of the domains of the DCOA1 Questionnaire were associated with numerically greater overall scores during treatment with genotropin than during treatment with somatrogon, with two exceptions: injection signs and symptoms domain (from the patient aged 8 years and above) and assessment of signs domain (from the Caregiver for children < 8 years old). The reported overall score for these two domains did not suggest a preference for either treatment based on the reported overall scores. The primary endpoint of C0311002 demonstrated that the treatment burden, as evaluated by the Patient Life Interference questionnaire, of the once weekly somatrogon injection schedule was lower than that of the once daily genotropin injection schedule. The least squares mean for the total score of the Overall Life Interference, was lower for the once weekly somatrogon injection schedule than for the once daily Genotropin injection schedule. The mean treatment difference (95% CI; p-value) between somatrogon and genotropin was -15.49 (95% CI: -19.71, -11.27; p<0.0001).

The results of the DCOA2 Questionnaire showed that the overall proportion of patients that responded to the questionnaire indicating preference for somatrogon was greater than the proportion of patients indicating preference for genotropin. The proportion of patients that preferred somatrogon and genotropin in terms of the item regarding “injecting the medicine” was [redacted] and [redacted], respectively.

Harms Results

Thirty-eight patients (44.2%) and 47 patients (54.0%) reported at least one adverse event during treatment with genotropin and somatrogon, respectively. The most frequently reported adverse event was injection site pain. One patient stopped treatment due to adverse events, which occurred during treatment with somatrogon as a result of injection site pain. With regards to notable harms for this review, injection related events were reported by [redacted] and [redacted] of patients during treatment with genotropin and somatrogon, respectively.

Critical Appraisal

The primary objective of C0311002 evaluated using subjective, patient-reported outcomes within an open-label study design, which has potential for significant bias in the results. Evidence of reliability was demonstrated; however, there was no evidence of validity or

responsiveness, and an MID was not identified from the literature. Additionally, results for the DCOA1 questionnaire included P values, but the statistical tests were not controlled for multiplicity and consequently at risk of type I error. The other secondary outcomes were reported descriptively. Both of these factors and the lack of an established MID make it difficult to determine the clinical meaningfulness of the results.

C0311002 had concerns of generalizability to the Canadian patient population, lack of appropriate assessment period.

Description of CP-4-009-Japan-OLE

The CP-4-009 LT-OLE (N =42) evaluated the long-term efficacy and safety of somatrogon in a single-arm trial in Japanese pre-pubertal children. Patients who were treated with Genotropin and completed 12-months of treatment during the CP-4-009 main study were switched to a somatrogon dose of 0.66 mg/kg/week and somatrogon-treated patients who completed 12-months treatment during the main study continued to receive somatrogon with the same mg/kg/week dose in the open label extension (OLE) treatment phase. The OLE phase would continue until the somatrogon marketing registration in Japan.

Efficacy Results

The efficacy outcomes reported were annualized height velocity at 24 months and bone maturation at 24 months. These efficacy outcomes were not part of a pre-specified statistical testing plan. The mean (SD) change from baseline of the open label phase at month 24, for annualized height velocity in the somatrogon group (N =) was [redacted] and in the genotropin group (N =) was [redacted]. The mean (SD) change from baseline at month 24, for height SDS in the somatrogon group (N =) was [redacted] and in the genotropin group (N =) was [redacted]. The mean (SD) change from baseline of the open label phase at month 24, for bone maturation in the somatrogon group (N =) was [redacted] and in the genotropin group (N =) was [redacted].

Other endpoints identified in the CADTH review protocol were not undertaken in the long-term open label phase of the CP-4-009 study.

Harms Results

The most commonly reported adverse event was [redacted] ([redacted] in somatrogon and [redacted] in the genotropin-followed-by-somatrogon treatment group). [redacted] patient reported [redacted] as a serious treatment related adverse event, in the genotropin-followed-by-somatrogon treatment group. There were no deaths reported and no patient who stopped treatment due to adverse events.

Critical Appraisal

CP-4-009-OLE was conducted to evaluate the long-term efficacy and safety of once weekly somatrogon. The efficacy results of the open-label extension phase are selectively reported. The analyses are not part of a statistical testing plan and hence the effect of somatrogon, at the data cut-off date of March 13, 2020, is considered uncertain. There are no efficacy analyses for HRQoL or other PRO measures that have been conducted hence, the long-term effect of somatrogon on HRQOL is unknown. CP-4-009-OLE was conducted exclusively in Japanese pre-pubertal children and did not include any Canadian patients, this is not reflective of Canadian clinical practice. Hence CP-4-009-OLE has noted generalizability issues. The CP-4-009-OLE study, excluded patients less than 3 years of age, also leads to a Canadian generalizability issue as the clinical expert consulted by CADTH stated that in clinical practice patients with GHD are seen as early as in their infancy.

Economic Evidence

Cost and Cost-Effectiveness

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population(s)	Pre-pubertal children (3 to 11 years for girls and 3 to 12 years for boys) with either isolated growth hormone deficiency (GHD) or GH insufficiency associated with multiple pituitary hormone deficiencies and who are treatment naïve.
Treatment	Somatrogon (Once weekly injection)
Submitted Price	Somatrogon, 24 mg/1.2 mL pre-filled pen : $345.84 Somatrogon, 60 mg/1.2 mL pre-filled pen: $864.60
Treatment Cost	At the recommended dose of 0.66 mg/kg administered once weekly, the annual cost of somatrogon is approximately $9,684, assuming a patient weight of 19.30 kg and considering wastage of unused product.
Comparator	Somatropin (Once daily injection, average cost of all branded somatropin products weighted by market share)
Perspective	Canadian publicly funded health care payer
Outcome	QALYs
Time horizon	Maximum of 15 years (i.e., until the age of 18, total length of time horizon depends on age of treatment initiation)
Key data source	CP-4-006, a Phase 3, 24-week, multi-center, randomized crossover trial.
Key limitations	• The sponsor's base case included yearly height velocities for patients treated with somatrogon that were greater than those predicted for patients treated with somatropin. This assumption does not align with the available clinical evidence, which demonstrated somatrogon was non-inferior [redacted] to, somatropin (Genotropin). • The magnitude of the quality-of-life benefit associated with weekly somatrogon injections in comparison with daily somatropin injections over the time horizon is uncertain. • The administered dose for all somatropin treatments was likely overestimated and did not reflect the typical dose administered in Canadian clinical practice, which overestimated total drug acquisition costs of somatropin. The clinical expert consulted by CADTH indicated the efficacy and safety of somatropin in comparison with somatrogon is expected to be similar with this lower dose as with the sponsor's assumed dose. • Market share distributions used to derive treatment cost with somatropin may not reflect the distribution of these treatments in isolated GHD or GH insufficiency as various brands of somatropin are indicated for other conditions. • The applicability of the patient utility values by height standard deviation score identified in the literature, which were further modified by the sponsor, to pediatric patients with GHD or GH insufficiency, is associated with uncertainty. • There is no data to support the sponsor's assumption of improved adherence with somatrogon. As a result, the sponsor's assumption is uncertain.
CADTH reanalysis results	• CADTH conducted reanalyses which included assuming equal height velocities and corresponding standard errors for both somatrogon and somatropin, and revising the dose for all somatropin products to align with the dose commonly used in Canadian clinical practice. • Based on the CADTH reanalyses, the ICER for somatrogon versus somatropin was $107,714 per QALY gained. A 11% price reduction was required for somatrogon to be considered cost-effective at a $50,000 per QALY threshold. • CADTH tested the impact of removing the utility benefit from weekly vs. daily injections and of a comparison of somatrogon to Genotropin exclusively, the least costly somatropin, among several scenario analyses. When the utility benefit from weekly vs. daily injections was removed, the ICER rose to $368,381 per QALY; when somatrogon was compared to Genotropin exclusively, the ICER rose to $186,120 per QALY

GH = growth hormone; GHD = growth hormone deficiency; ICER = incremental cost-effectiveness ratio; LY = life-year; QALY= quality-adjusted life-year.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: the daily dose for somatropin products was likely overestimated and not aligned with the dose commonly prescribed in Canadian clinical practice; the sponsor adjusted drug costs by patient compliance rate which is inappropriate as it does not account for potential drug wastage; the generalizability of the market share distributions of various somatropin brands used in the reference scenario to the indication of interest is uncertain, and the sponsor inappropriately included a hypothetical long-acting growth hormone (LAGH) comparator that is not yet on the market; and limitations were identified with several inputs used to estimate the population size eligible for treatment with somatropin or somatrogon, leading to an underestimation of the population size.

CADTH estimated a revised base case which included the following changes: updating the daily dose for all somatropin products to align with the dose commonly received in practice; removing the adjustment of drug costs by the treatment compliance rate; removal of the LAGH comparator; revising the proportion of the indicated population between ages 3 and 16 years, and the proportion of the indicated population aged 17, likely to be prescribed growth hormone treatment; and changing the proportion of patients covered by publicly funded drug plans.

Based on the CADTH reanalyses, the estimated budget impact from the reimbursement of somatrogon would be $317,914 in Year 1, $577,612 in Year 2 and $1,069,685 in Year 3, for a total incremental budget impact of $1,965,211 over the three-year time horizon. This estimate was substantially different from that of the sponsors. CADTH was unable to address the limitations related to the uncertainty in the market share estimates of the various brands of somatropin products. Significant changes in the market shares of somatropin and anticipated uptake of somatrogon would be associated with changes in the budget impact. Additionally, the estimated budget impact is sensitive to changes in the dosing of somatropin, as well as the anticipated population size.

Canadian Drug Expert Committee (CDEC) Information

Members of the Committee:

Dr. James Silvius (Chair), Dr. Sally Bean, Mr. Dan Dunsky, Dr. Alun Edwards, Mr. Bob Gagne, Dr. Ran Goldman, Dr. Allan Grill, Dr. Christine Leong, Dr. Kerry Mansell, Dr. Alicia McCallum, Dr. Srinivas Murthy, Ms. Heather Neville, Dr. Danyaal Raza, Dr. Emily Reynen, and Dr. Peter Zed.

Meeting Date: October 28, 2021

Regrets

Two expert committee members did not attend

Conflicts of Interest

None