CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761184Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761184
Priority or Standard	Standard
Submit Date(s)	November 22, 2022
Received Date(s)	November 22, 2022
PDUFA Goal Date	May 22, 2023
Division/Office	Division of General Endocrinology/Office of Cardiology, Hematology, Endocrinology, and Nephrology
Review Completion Date	April 24, 2023
Established/Proper Name	Somatrogon
(Proposed) Trade Name	Ngenla
Pharmacologic Class	Human growth hormone analog
Code name	MOD-4023
Applicant	Pfizer Ireland Pharmaceuticals
Dosage form	20 mg/mL and 50 mg/mL each as 1.2 mL single patient use prefilled pen
Applicant proposed Dosing Regimen	Starting dose of 0.66 mg/kg body weight per week; individualize dosage for each patient based on the growth response
Applicant Proposed Indication(s)/Population(s)	treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Pituitary dwarfism
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Pituitary dwarfism
Recommended Dosing Regimen	Starting dose of 0.66 mg/kg body weight per week; individualize dosage for each patient based on the growth response

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Abbreviations: DGE, Division of General Endocrinology

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Abbreviations: OBP, Office of Biotechnology Products; OPQ; Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology;
DMEPA, Division of Medication Error Prevention and Analysis; DMPP, Division of Medical Policy Programs; DRM, Division of Risk Management; PM, project management; CDRH, Center for Devices and Radiological Health

Glossary

ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AHV	annualized height velocity
BLA	biologics license application
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
COA	clinical outcome assessment
CR	complete response
CRL	Complete Response Letter
CRMO	chronic recurrent multifocal osteomyelitis
CTP	carboxy-terminal peptide
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DCOA	Dyad Clinical Outcome Assessment
FDA	Food and Drug Administration
GHD	growth hormone deficiency
GQ	grouped query
hGH	human growth hormone
IGF-1	insulin-like growth factor 1
IGHD	isolated growth hormone deficiency
MedDRA	Medical Dictionary for Regulatory Activities
OPMA	Office of Pharmaceutical Manufacturing Assessment
OLE	open-label extension
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamics
PEN	prefilled pen device
PK	pharmacokinetics
SDS	standard deviation scores
SOC	system organ class
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant (Pfizer) submitted a complete response for the Biologic License Application (BLA) for somatrogon-ghla, a new biologic product, under Section 351 (a) of the Public Health Act. The Applicant is seeking an approval for somatrogon injection for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone. The original BLA submission received a complete response (CR) letter on January 21, 2021, because of a high rate and persistence of anti-drug antibody (ADA) formation and development of neutralizing antibodies with insufficient evidence that there was no impact on efficacy. In addition, four quality-related deficiencies were communicated in the CR letter.

Somatrogon is a drug-device combination product proposed as a disposable, prefilled pen injector. Somatrogon (also known as MOD-4023) is human growth hormone (hGH) modified by the fusion of one copy of carboxy-terminal peptide (CTP) of human chorionic gonadotropin at the amino terminus of hGH and two CTP copies in tandem at its carboxy terminus. Fusion of the CTP peptides to hGH and a high level of glycosylation extend the half-life of this fusion protein to allow for weekly subcutaneous injection administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant provided substantial evidence of effectiveness of somatrogon for the treatment of pediatric subjects ≥3 years of age with growth failure due to growth hormone deficiency (GHD). This is based on data from one adequate and well-controlled phase 3 study CP-4-006, plus confirmatory evidence consisting of strong mechanistic support. Supportive evidence of efficacy comes from the main period of the phase 2 study, CP-4-004, which provided 12-month controlled data, as well as from the long-term uncontrolled extension period of the phase 3 and phase 2 studies, respectively.

The phase 3 study demonstrated non-inferiority of somatrogon compared to Genotropin in treatment-naïve subjects with pediatric GHD, with respect to annualized height velocity (AHV) at 52 weeks. CP-4-006 was a phase 3, randomized, active-controlled, open label, 52-week study comparing the safety and efficacy of somatrogon to Genotropin in 224 treatment naïve, pre-pubertal pediatric subjects with short stature due to pediatric GHD. Subjects were randomized in a 1:1 ratio to receive somatrogon or Genotropin, respectively. Based on the results of this study, somatrogon was found to be non-inferior to Genotropin in the improvement of AHV. The estimated treatment difference in the mean AHV at week 52 between somatrogon (mean AHV of 10.07 cm/year) and Genotropin (mean AHV of 9.73 cm/year) was 0.34 cm/year [95% confidence interval (CI) -0.23, 0.91]. The lower limit of the 95% CI (-0.23 cm/year) was greater than the prespecified non-inferiority margin of ≥ -1.8 cm/year, thus, the impact of somatrogon on AHV at 52 weeks was non-inferior to that of Genotropin. The results of secondary analyses,

including height standard deviation score (SDS), support the primary efficacy endpoint. Short stature in pediatric patients is defined as height below -2.0 SDS for age, sex, and race. Height SDS is widely used in clinical practice to evaluate the appropriate growth of children at various stages of development. Thus, change in height SDS is traditionally accepted and used as a supportive growth endpoint in studies evaluating the effect of hGH on growth in pediatric patients with GHD. Treatment with both somatrogon and Genotropin resulted in an improved height SDS at week 52 compared to baseline. The height SDS at week 52 was 0.91 in the somatrogon group and 0.86 in the Genotropin group. As expected, treatment with somatrogon and Genotropin led to the normalization of IGF-1 levels, indicating an adequate replacement with missing hormone. At week 52, mean IGF-1 SDS levels were 0.65 in somatrogon group and -0.69 in Genotropin group.

Trials that have supported approval of these drugs have shown that hGH products improve AHV and other growth parameters (e.g., height and height standard deviation scores (SDS)) via IGF-1 mediated action of GH at the growth plate). Long-term studies with the earlier formulations of hGH demonstrated that improvements in AHV observed during the first year of treatment were sustained over the years of treatment and translate into improvement in final height (e.g., Humatrope up to 8 years). Therefore, FDA accepted short term changes in AHV that are non-inferior to an active comparator (approved hGH with known effect on AHV) as a surrogate endpoint to evaluate the efficacy of products with a native GH sequence for the treatment of short stature in pediatric patients with GHD.

A strong mechanistic understanding exists of how GH exerts its effects in subjects with GHD. In pediatric subjects with growth failure due to inadequate secretion of endogenous growth hormone, somatrogon is intended to replace the deficient native GH. Somatrogon is a long-acting recombinant hGH derivative. The active moiety of somatrogon has the same primary amino acid sequence as endogenous growth hormone and is thus expected to have the same action at the target receptor as endogenous human GH. The structure-function relationship of endogenous GH is well understood; the wide variety of GH biological effects are achieved only through a single mechanism of action, i.e., the binding of GH to, and subsequent activation of, growth hormone receptor, with subsequent transcription of genes for a variety of proteins, including insulin-like growth factor 1 (IGF-1). No alternative receptors mediating GH activity have been identified. GH and IGF-1 stimulate epiphyseal growth plates and formation of new bone resulting in linear growth until fusion of the growth plates.

A single adequate and well-controlled trial plus confirmatory evidence is acceptable for this BLA because pediatric GHD is a rare disease. It is therefore challenging to conduct two adequate and well controlled trials, and, historically, the Food and Drug Administration (FDA) has accepted a single adequate and well controlled trial for the approval of hGH products with native GH sequences for the pediatric GHD indication.

Study CP-4-004, the phase 2, open-label, safety, and dose-finding study, which provides supportive evidence of efficacy, compared three doses of somatrogon with Genotropin in pediatric subjects with short stature due to GHD. Changes in AHV and height standard deviation

scores (SDS) at the end of 12 months of treatment were dose-dependent, while the changes observed in the somatrogon 0.66 mg/kg group (the highest dose tested and the one used in the phase 3 study) were similar to changes in growth parameters observed in Study CP-4-006. Additional supportive evidence is derived from the uncontrolled extension period of the phase 3 study, as well as the extension periods of the phase 2 study. Long-term data included in this re-submission demonstrated continued benefit of somatrogon on growth. The high rate of immunogenicity does not appear to impact growth and thus is unlikely to impact final adult height.

1.3. Benefit-Risk Assessment

The Applicant proposes somatrogon, a long-acting recombinant human growth hormone (hGH) modified by the fusion of the carboxy-terminal peptide (CTP), as a weekly injection with the proposed dose of 0.66 mg/kg/week for the treatment of pediatric patients who have growth failure due to inadequate secretion of endogenous growth hormone (GH).

Clinical manifestations of pediatric growth hormone deficiency (GHD) include short stature, decreased height velocity, and delayed bone age (International Classification of Pediatric Endocrine Diagnoses Consortium 2016; Jorge et al. 2020). If untreated, pediatric GHD is associated with poor growth velocity, decreased final adult height, and decreased quality of life. The 2016 Pediatric Endocrine Society Guidelines recommend GH therapy for children with GHD in order to normalize growth and attain normal final adult height (Grimberg et al. 2016). Replacement with hGH leads to improvement in hormone-associated delay in AHV and confers the benefit of increased height in this population.

The clinical development program has shown that treatment with somatrogon provides the benefit of increased height in patients with pediatric GHD. There are multiple hGH therapies approved by FDA for the treatment of pediatric GHD, most are administered daily but two approved products are a once weekly dosing regimen. Therefore, somatrogon will not provide a unique benefit to patients, but will offer an additional option for those patients seeking the reduced burden of injection frequency from once daily to once weekly.

The risks associated with somatrogon are expected to be those associated with the hGH class in the pediatric population, such as neoplasm, glucose intolerance and diabetes mellitus, intracranial hypertension, severe hypersensitivity, fluid retention, hypothyroidism, adrenal insufficiency, pancreatitis, lipoatrophy, progression of preexisting scoliosis, slipped capital femoral epiphysis, increase in serum levels of phosphorus and alkaline phosphatase. Although some of these risks could be serious, they are uncommon and to date have not been considered to outweigh the benefit of increased final adult height. Common adverse reactions were similar between somatrogon and Genotropin.

High rates of anti-drug antibody formation have not been observed with approved formulations of hGH. However, a high and persistent incidence of antidrug antibodies (ADA) was observed in subjects treated with somatrogon compared to those treated with Genotropin, with some neutralizing antibody formation, leading to a Complete Response in the first review cycle because of insufficient evidence of a lack of impact on efficacy. Review of the data in the resubmission has allowed the conclusion of no impact of immunogenicity on efficacy or safety of the drug in children with GHD exposed to somatrogon for up to 7 years in the clinical program. Although subjects in the development program did not reach final adult height, the clinical relevance of the immunogenicity is considered to be sufficiently low that no postmarketing safety activities are warranted.

In conclusion, the Applicant has provided substantial evidence that somatrogon is an effective treatment of short stature associated with pediatric GHD at the proposed dose in children 3 years of age and older, and the benefits outweigh the risks. Risks can be monitored and mitigated through prescriber and patient labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Growth hormone deficiency (GHD) is a condition characterized by insufficient production of GH by the pituitary gland and subsequent low levels of circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1). • Pediatric GHD manifests primarily as short stature due to decreased height velocity, delayed bone age, delayed puberty and ultimately decreased final adult height. • Guidelines on the treatment of pediatric GHD issued by professional societies (Growth Hormone Research 2000; Grimberg et al. 2016) recommend treating children with proven GHD with GH replacement therapy to normalize height during childhood and attain normal adult height.	• Pediatric GHD is a serious condition that, if left untreated, is associated with delayed growth and ultimately short final adult height. • Treatment with hGH is a replacement therapy intended to improve linear growth and final adult height.
Current Treatment Options	• Multiple human growth hormone (hGH; somatropin) products are Food and Drug Administration (FDA)-approved for the treatment of short stature associated with pediatric GHD and available on the U.S. market. Most approved hGH products require daily or every other day injections via the subcutaneous route. Weekly injections are more recently available. • GH therapy is overall well tolerated. Labeled adverse effects of GH therapy include increased risks of neoplasms, impaired glucose intolerance and diabetes, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, scoliosis progression, lipoatrophy, and pancreatitis.	• Multiple hGH products (short- and long-acting) are available for the treatment of pediatric GHD, including long-acting GH therapy that requires once weekly injections. • Replacement therapy with hGH aims to mimic the action of endogenous GH, leading to an increase in IGF-1 levels that act on growth plates and improve linear growth. • hGH-induced improvement in growth

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		velocity sustained over the years of treatment leads to improvement in final adult height. • Long-acting formulations of hGH have the potential to be less burdensome by requiring less frequent injections.
Benefit	• Somatrogon improves AHV in pediatric GHD as demonstrated in Study CP-4-006, the phase 3, randomized, active-controlled study of 52 weeks duration in 224 pre-pubertal, treatment naïve subjects with GHD, when given at a dose of 0.66 mg/kg/week. The effect of somatrogon on AHV (the primary efficacy endpoint) at the end of 12-month treatment was noninferior to the effect of Genotropin (somatropin daily injection): the mean treatment difference between somatrogon and Genotropin was 0.34 cm/year (95% CI -0.23, 0.91). • The results of the secondary analyses were supportive of the primary analysis: - At month 12, the mean height standard deviation score was 0.91 in somatrogon group and 0.86 in Genotropin group. - Somatrogon therapy also resulted in normalization of IGF-1 levels, indicating an adequate replacement with missing hormone. At month 12, mean IGF-1 SDS was 0.65 in somatrogon group, and -0.69 in the Genotropin group. • Supportive evidence of efficacy consists of data from the 12-month main period of Study CP-4-004 (a phase 2, randomized, active-controlled, dose-finding study), its long-term extension period, as well as the long-term extension period of Study CP-4-006. Changes in AHV and height SDS in somatrogon 0.66 mg/kg group at the end	• FDA has accepted one-year changes in AHV that are noninferior to the active comparator (approved hGH with known effect on AHV) to support the efficacy of products with a native GH sequence for the treatment of short stature in pediatric patients with GHD. The accumulated data with approved hGH formulations indicate that short-term improvement in growth parameters in the absence of attenuation factors translates in the improvement of final adult height. • Somatrogon-induced change in AHV after 12 months was within pre-specified non-inferiority margins compared to Genotropin. The observed improvement in somatrogon-induced is consistent with the effect observed with other hGH products and suggests that the benefit of somatrogon on final adult height may be similar to other available hGH therapies. • The high incidence of ADA formation as

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	of 12-month treatment in the main part of Study CP-4-004 were similar to changes in growth parameters observed in Study CP-4-006: - mean AHV was 11.4 cm/year - mean change in height SDS was 1.35 • A high and persistent incidence of antidrug antibodies (ADA) was observed in subjects treated with somatrogon compared to those treated with Genotropin (see Risk summary below). A total of 8 subjects treated with somatrogon in clinical program developed neutralizing antibodies. However, no impact of immunogenicity on efficacy of the drug was noted in the clinical program: • There was no difference in growth measures between ADA-positive and ADA-negative subjects during the 12-month randomized period of StudyCP-4-006 within each treatment arm and between treatment arms. Also, no difference in growth measures between ADA-positive and ADA-negative subjects was noted during exposure to somatrogon in Study CP-4-006 for up to 4 years and in Study CP-4-004 for up to 8 years. • Similarly, no difference in growth was noted between NAbs positive and NAb negative subjects during clinical program. The significant reduction in AHV following development of NAbs in one subject in Study CP-4-006 was due to a rare genetic condition (isolated GHD type 1A which results in immunological intolerance to GH) and it is not product-dependent.	well as NAbs did not appear to impact growth during the 12-month randomized, controlled periods, or on long-term efficacy of the drug in subjects continuing somatrogon therapy in the uncontrolled non-randomized extension periods.
Risk and Risk Management	• No unexpected safety signals were identified during the 12-month treatment with somatrogon in studies CP-4-006 and CP-4-004. • The most common (≥10%) adverse events (AEs) that occurred in the somatrogon group were local administration reactions (43% somatrogon versus 25% Genotropin), nasopharyngitis (33%	• The safety profile of somatrogon was well characterized in the clinical development program, although the trials were not designed to assess certain long latency or rare safety issues (insufficient size and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	somatrogon versus 29% Genotropin), headache (17% somatrogon versus 22% Genotropin), and pyrexia (17% somatrogon vs 15% Genotropin). Non-serious hypersensitivity reactions[Error! Bookmark not defined.] were observed in 18/109 (16%) of somatrogon-treated subjects compared to 11/115 (10%) in the Genotropin group. All reactions resolved without drug discontinuation. No anaphylactic or Stevens-Johnson syndrome occurred. • Class-related adverse reactions were reported at low incidence (i.e., hypothyroidism, hypoadrenalism, benign skin neoplasia, scoliosis, arthralgia), or not at all (i.e., pancreatitis, intracranial hypertension, slipped capital femoral epiphysis) and no difference between somatrogon and Genotropin-treated subjects was noted. • Chronically elevated IGF-1 levels above normal range (> +2SDS) are associated with potential risk of various AEs including headache, intracranial hypertension, edema, and tumors. In the main period of the phase 3 trial, 24% of somatrogon-treated subjects had IGF-1 SDS > + 2 at least once. All elevated IGF-1 levels were not associated with AEs and normalized either spontaneously or following a dose reduction. • A high and persistent incidence of anti-drug antibodies (ADA) was observed in subjects treated with somatrogon compared to those treated with Genotropin. Of the subjects originally randomized to somatrogon in Study CP-4-006, 77% and 84% developed ADA at Months 12, and 24, respectively. ADA persisted in majority of subjects with continued somatrogon exposure. • Neutralizing antibodies (NAbs) developed in 8 out of 217 subjects after 4 years of exposure in Study CP-4-006. NAbs were detected at one time point only in majority of subjects (6 out of 8), were transient in all subjects, and not dependent on the duration of	duration); these risks will be included in somatrogon labeling based on the known class effects. • The common ARs observed with somatrogon are generally consistent with those of other hGH products. Relationship to somatrogon or Genotropin is unclear as some of these, e.g., nasopharyngitis, pyrexia, are events that occur commonly among the pediatric population. However, relationship to drug cannot be ruled out and these events should be labeled as adverse reactions. • A high incidence and persistence of anti-drug-antibodies was observed in somatrogon clinical development program, with several subjects developing transient neutralizing antibodies. • Immunogenicity did not appear to impact the adverse event profile of the drug. • The risks associated with somatrogon, including class-related adverse reactions, will be mitigated through labeling. The immunogenicity rate will be included in Section 12 of the label for the prescriber's awareness. • There is a potential risk of anti-CTP antibodies interference with hCG-based diagnostic tests and subsequent impact on

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	exposure. • ADAs resolved with somatrogon discontinuation. • There were no differences in frequency or severity of AEs between ADA-positive and ADA-negative subjects treated with somatrogon for 12 months in Study CP-4-006, including injection site reactions and hypersensitivity reactions. • Long-term safety data during the uncontrolled periods of Studies CP-4-006 and CP-4-004 did not reveal any immunogenicity-related safety concerns, such as increase incidence of injection site reactions, hypersensitivity, autoimmune syndromes, or class-related adverse reactions in ADA-positive subjects compared to ADA-negative subjects. • Anti-carboxy terminal peptide (CTP) antibodies were detected in several subjects during somatrogon clinical development program. The potential risks of anti-CTP antibodies are interference with hCG-based diagnostic tests. The applicant's tests for interference in several marketed hCG-based pregnancy tests were negative, therefore the risk is low but cannot be ruled out.	pregnancy diagnosis. In general, the information regarding known interference by a drug with a laboratory test must be included in section 5 Warning and Precautions of labeling. Based upon absence of the interference from somatrogon and five hCG-based pregnancy tests (urine or blood), the threshold for a known interference was not met and inclusion of testing interference in the Warning and Precautions section of labeling is not warranted. However, based upon the limited testing by the applicant, is not possible to exclude the risk of testing interference due to the multitude of commercial pregnancy tests. Therefore, because the risk is still theoretical and was not detected to date in nonclinical or clinical studies, this potential risk should not be included in section 5. However, since the risk cannot be ruled out completely based on the drug mechanism of action and PK of the drug (presence of the drug in blood and urine) it should be mitigated through labeling in Section 8.

1.4. Patient Experience Data

Patient Experience Data Relevant to This Application (check all that apply)

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	X	Patient preference studies (e.g., submitted studies or scientific publications)		19.3
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data were not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Growth hormone deficiency (GHD), including pediatric GHD, is a condition characterized by insufficient production of growth hormone (GH) by the pituitary gland and subsequent decreased GH and insulin-like growth factor-1 (IGF-1) levels (Growth Hormone Research 2000). The prevalence of pediatric GHD is estimated to be 1:1533 to 1:30,000 worldwide, and 1:3480 in the U.S., with a boy: girl ratio of 2.7:1. Pediatric GHD can be idiopathic or secondary to congenital causes (e.g., pituitary hypoplasia, empty cells, various genetic disorders) or acquired causes (e.g., trauma, infection, tumors) (Dattani and Preece 2004). Genetic causes include mutations in genes that encode GH, growth hormone releasing hormone (GHRH), and transcription factor defects (Alatzoglou and Dattani 2010). Clinical signs and symptoms of GHD in children include hypoglycemia, prolonged jaundice, microphallus or craniofacial midline abnormalities in neonates, and short stature, poor height velocity and delayed bone age (Stanley 2012).

2.2. Analysis of Current Treatment Options

Treatment with hGH (somatropin) therapy is the standard of care for the treatment of short stature due to pediatric GHD. Exogenous hGH treatment aims at mimicking the function of GH secretion (i.e., a replacement therapy), leading to normalization of IGF-1 levels and improvement in linear growth and final adult height. Primary objective of treatment of GHD in children is normalization of height during childhood, and attainment of normal adult height that is consistent with the patient's genetic potential (Richmond and Rogol 2016).

GH replacement therapy was first approved by the FDA in 1985. Since then, multiple short-acting hGH formulations with native GH sequence have been approved for the treatment of pediatric patients with growth failure due to GHD (NIH 2021). Most GH products require daily subcutaneous administration. Long-acting formulations (lonapegsomatropin and somapacitan-beco) that allow for weekly injections were recently approved. Long-acting formulations can potentially reduce discomfort and increase compliance by requiring less frequent injections, which may be a particular advantage in the pediatric population.

These hGH formulations have a native GH sequence and have been approved based on the improvement in AHV and/or change in height SDS, since long-term studies with the earlier formulations of hGH also demonstrated that improvement in AHV translates into the improvement in final adult height (e.g., Humatrope up to 8 years).

The safety profile of hGH products is well-characterized and GH therapy is generally well tolerated. Labeled adverse effects of GH treatment include intracranial hypertension, slipped capital femoral epiphysis, scoliosis progression, pancreatitis, impaired glucose intolerance and

diabetes, prepubertal gynecomastia, arthralgia, and edema. GH treatment can unmask underlying adrenal insufficiency and hypothyroidism. Patients should thus be assessed for adrenal and thyroid axes after initiation of GH therapy. Treatment with GH therapy is contraindicated in patients with active malignancy; because of the mitogenic and antiapoptotic activity of GH and IGF-1, there is a theoretical concern for neoplasia development with GH therapy (Chae et al. 2015). However, at this time, there is no clear evidence that GH therapy leads to tumor development in children with or without a history of prior malignancy (Tuffli et al. 1995; Moshang et al. 1996; Wilton et al. 2010).

The efficacy of hGH therapy in pediatric GHD is monitored in practice by assessing growth. Measurement of IGF-1 levels to evaluate the efficacy is not recommended. Although it is expected that binding of hGH to the human growth hormone receptor will raise IGF-1 levels which is what occurs physiologically, there are no data that establish a clear relationship between IGF-1 levels and growth improvement. Nevertheless, chronically elevated IGF-1 levels above the normal range may be associated with adverse events (AEs) including intracranial hypertension, hyperglycemia, edema, and tumors. Therefore, in pediatric patients with GHD, IGF-1 levels are typically followed to monitor for adherence to therapy and for assessment of safety (Grimberg et al. 2016). Goal IGF-1 levels are typically below +2 or +3 SDS. Precise levels and duration of the exposure to the elevated IGF-1 levels that correlate with potential risk of AEs is unknown. hGH treatment of patients with growth failure due to GHD should not continue at pediatric doses beyond epiphyseal fusion due to concern of causing acromegalic changes. After an interruption in treatment, reevaluation can be done to diagnose adult GHD and assess the need for therapy at lower doses designed for metabolic and body composition benefits. GHD may or may not persist into adult life and the objectives for treatment and dosing in adults with GHD are different.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Somatrogon is a new molecular entity. On October 22, 2020, the Applicant submitted an initial marketing application for somatrogon for treatment of pediatric GHD. On January 21, 2022, FDA issued a Complete Response for Clinical/Immunology and Product Quality deficiencies (refer to the CR Letter in DARRTS and to Section 3.2 below).

3.2. Summary of Presubmission/Submission Regulatory Activity

Refer to Integrated Review In DARRTS, dated January 21, 2021, for a summary of the regulatory history of the drug product prior to initial BLA submission on October 22, 2020.

On October 22, 2020, the Applicant (Pfizer) submitted an initial marketing application for somatrogon (b) (4)

(b) (4) Included in this application was a single phase 3 study (CP-4-006), a supportive phase 2 study (CP-4-004), and data from the open-label extensions for each of these clinical studies.

Because of FDA's communicated concerns related to high immunogenicity of the product, on September 15, 2021, the Applicant submitted additional data that provided an additional 12 months of efficacy, safety, and immunogenicity data from the phase 2 and 3 OLE studies. The submission was accepted as a Major Amendment, and the PDUFA action date was extended by 3 months to January 22, 2022.

On January 21, 2022, the Agency issued a Complete Response Letter (CRL) stating Clinical/Immunology and Product Quality deficiencies. The letter summarized the high rate and persistence of ADAs to somatrogon and its potential implications for loss of efficacy due to development of neutralizing antibodies. There was also a concern with antibodies being cross reactive to other GH products, and if persistent, these could potentially result in non-responsiveness to other hGH replacement (refer to the CRL in DARRTS for additional details). The product quality concerns were related to (b) (4)

To resolve the deficiencies, the Applicant was asked to provide reassurance that the ADA formation caused by somatrogon is not expected to have an impact on long-term growth achieved with somatrogon and does not interfere with other hGH formulations. FDA requested that the Applicant demonstrate, at a minimum, that ADA (including neutralizing antibodies) meaningfully decrease or resolve with somatrogon discontinuation and/or changing patients to other approved hGH formulations. If neutralizing antibodies do not resolve, the Applicant was asked to provide data that long-term growth is not impacted and also to provide mitigation strategies to address the potential impact of neutralizing antibodies.

To resolve product quality deficiencies the Applicant was asked to provide information (b) (4) Lastly, pre-license inspections at the drug substance manufacturing site, Pfizer Ireland Pharmaceuticals (Clondalkin, Ireland; FEI 3004145594), and the drug product manufacturing site, Pfizer Manufacturing Belgium NV (Puurs, Belgium; FEI 1000654629) were required before this application may be approved.

On March 29, 2022, a type A meeting via teleconference was held to discuss the Applicant's proposal to address the clinical deficiencies described in the CRL. The Agency agreed to the Applicant's proposal to submit the following: 1) additional immunogenicity assessments and analyses of the effect of antibody status on safety and efficacy in subjects who continued treatment with somatrogon in the ongoing open-label extension (OLE) periods of studies CP-4-004 and CP-4-006, with a data cut-off of March 31, 2022; 2) an assessment of immunogenicity status in subjects from Study CP-4-006 who discontinued somatrogon and had positive ADA at

the time of study drug discontinuation, including subjects who started other GH therapies; 3) additional information for subject (b) (6) who had a significant growth attenuation corresponding to the time of seroconversion to positive NAb; 4) immunogenicity assessments and analyses of the effect of antibody status on safety and efficacy from Study CP-4-009, a safety and efficacy study of somatrogon in Japanese subjects with pediatric GHD, which was not included with the original BLA submission.

On July 1, 2022, the Agency provided additional written responses to the Applicant regarding the safety data to be included in the BLA resubmission.

On November 22, 2022, the Applicant submitted a complete response to the deficiencies outlined in the CRL.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical sites were selected for inspection to support re-submission of this BLA.

The inspection for the original submission of BLA consisted of two domestic clinical sites and the co-sponsor (OPKO Health, Inc.) of Study CP-4-006. Based on the inspections of the two clinical sites and the co-sponsor, the inspectional findings supported validity of data as reported by the Sponsor under this BLA. Refer to the Integrated Review in DARRTS from January 21, 2022.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ)/ Office of Biotechnology recommends approval of BLA 761184 for Ngenla manufactured by Pfizer Pharmaceuticals Ireland. OPQ concluded that the data submitted in this application is adequate to support the conclusion that the manufacture of Ngenla is well controlled and leads to a product that is pure and potent (refer to the review from June 25, 2023).

The reviewer concluded that the product quality deficiencies that were identified during the first assessment cycle were adequately addressed in this resubmission (refer to CR Letter in DARRTS from January 21, 2022, and to the latest OPQ review from April 10, 2023). The manufacturing process is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process were adequately validated, and the product was consistently manufactured from multiple production runs.

Lastly, the Applicant did not provide the real time shipping study results and protocol but agreed to perform real-time shipping studies as part of Postmarketing Commitment (refer to the Applicant's response to the Agency's Information Request from March 23, 2023, and to Section 13). OPQ found the Applicant's approach to be acceptable.

4.3. Clinical Microbiology

The Office of Pharmaceutical Manufacturing Assessment (OPMA) reviewed the data included in the original BLA submission and recommended approval from a sterility assurance perspective (refer to OPMA review from July 27, 2021). No new data were included in this resubmission.

4.4. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) recommends approval of BLA 761184.

During the first cycle, CDRH reviewed the proposed device, which is a disposable pre-filled pen injector, and recommended approval of the device constituent parts of the combination product (pen-injector) (refer to the Integrated review in DARRTS from January 21, 2022).

CDRH reviewed the data included in this resubmission of BLA including the updated batch analyses, stability data of the proposed device pen-injector, pen-injector performance and device performance and found no deficiencies. CDRH also confirmed that labeling adequately covers the device requirements for labeling.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical review of the original application recommended approval.

All of the nonclinical information provided from the development of somatrogon have been reviewed and were summarized in the integrated assessment for BLA 761184 during the first cycle. Reference is made to the nonclinical review in the first cycle since no new data have been submitted in the resubmission. Minor edits have been made to the proposed language in Sections 8.1 and 13.1 of the label for somatrogon-ghla based on the original nonclinical review and consistent with other listed growth hormone products.

Based on the prior review, the nonclinical review team continues to recommend approval of BLA 761184 for somatrogon manufactured by Pfizer Pharmaceuticals.

6 Clinical Pharmacology

6.1. Executive Summary

The original BLA was acceptable from a clinical pharmacology perspective. The Clinical Pharmacology team reviewed the BLA resubmission and recommends approval.

A detailed clinical pharmacology review on the original BLA and major amendment submission can be found in the integrated review for BLA 761184.

The original BLA was submitted on October 22, 2020, with the data cut-off date of November 1, 2019. During the review cycle, a major amendment with the data cut-off date of December 21, 2020, was submitted on September 15, 2021.

In this resubmission, the Applicant included additional long-term data on safety, efficacy, and immunogenicity data for both the ongoing phase 3 (CP-4-006) as well as the phase 2 (CP-4-004) with a data cut-off date of March 31, 2022, together with other supportive safety data.

Samples for determining serum somatrogon concentrations (i.e., every 6 months) and IGF-1 were collected from patients in the ongoing Study 004 and 006 after December 21, 2020, and submitted in this resubmission. The clinical pharmacology review team evaluated the impact of anti-drug antibody on pharmacokinetics (PK) and PD based on the additional data. The findings from the additional data are consistent with the conclusion during the first review cycle: although ADA-positive (ADA+) subjects had slightly higher concentrations of the drug compared to ADA-negative (ADA-) subjects, the difference does not appear to impact efficacy based on growth velocity and IGF-1 SDS. In addition, there was no apparent impact of ADA on safety

profile of the drug; no new safety signals and/or immunogenicity-related safety signals such as increase incidence of injection site reactions, hypersensitivity, autoimmune syndromes, or class-related adverse reactions in ADA-positive subjects were identified.

6.2. Summary of Clinical Pharmacology Assessment

In this resubmission, the Applicant submitted additional data for both the ongoing phase 3 (CP-4-006) as well as the phase 2 (CP-4-004) with a data cut-off date of March 31, 2022. This review focused on the impact of ADA on PK and PD for each study.

6.2.1. Impact of ADA on PK

Study CP-4-004

A summary of PK data by ADA status is shown in Table 1 for Study CP-4-004. Mean somatrogon concentrations were higher in ADA+ subjects, compared to those in ADA- subjects at different visits between Month 6 prefilled pen device (PEN) period Year 2 visit and Month 6 PEN period Year 3 visit. Between the Month 12 PEN period Year 3 visit and Month 6 PEN Period Year 4, the difference in mean somatrogon concentrations in ADA-positive and ADA-negative subjects diminished. Across all visits, the difference was not statistically significant due to large variability in somatrogon concentrations.

Table 1. Mean and 95% CI of Somatrogon Concertation (ng/mL), Study CP-4-004 (From Month 6 PEN Period Year 2* to the Data Cut-off Date of 31 Mar 2022)

	ADA-			ADA+		
0.66 mg/kg	**Mean**	**N**	**95% CI**	**Mean**	**N**	**95% CI**
Month 6 PEN period year 2	67.7	16	(43.9, 91.6)	167.6	15	(28.9, 306.4)
Month 12 PEN period year 2	152.2	14	(15.5, 288.9)	164.5	13	(10.5, 318.4)
Month 6 PEN period year 3	93.1	13	(58.0, 128.3	110.3	14	(-7.5, 228.0)
Month 12 PEN period year 3	97.4	11	(11.2, 183.6)	53.9	13	(23.6, 84.2)
Month 6 PEN period year 4	79.4	11	(31.7, 127.0)	72.0	11	(23.4, 120.5)

Source: FDA analysis. ADA status were determined based on SN0049 and SN0077. PK data were from SN0077.
*last visit reviewed for the major amendment was Month 12 PEN Period Year 1.
Note: The terms in the first column refers to the treatment duration of subjects who received vial presentation first and later switched to the single-patient-use, prefilled disposable pen device [hereafter referred to as pen], at the same dose in Study CP-4-004. For example, Month 6 PEN period Year 2 refers to a duration of 18 months on somatrogon pen and Month 6 PEN period Year 3 for a duration of 30 months on somatrogon pen, etc.
Abbreviations: ADA, anti-drug antibody; CI, confidence interval; PEN, prefilled pen device

The overall trend is consistent with what was observed in the data submitted in the original BLA review cycle (including the major amendment).

Study CP-4-006

A summary of PK data by ADA status is shown in Table 2 for Study CP-4-006. From OLE Month 18 visit, mean somatrogon concentrations were higher in ADA+ subjects, compared to those in ADA- subjects at different visits. Except for OLE Month 18 visit ($p = 0.036$), the differences were not statistically significant due to large variability in somatrogon concentrations.

Table 2. Mean and 95% CI of Somatrogon Concentration (ng/mL), Study CP-4-006 (From Month 6 PEN Period Year 2* to the Data Cut-off Date of 31 Mar 2022)

	ADA-			ADA+		
0.66 mg/kg	**Mean**	**N**	**95% CI**	**Mean**	**N**	**95% CI**
OLE month 18 (month 30 since 1st dose)	82.6	40	(58.5, 106.7)	140.5	116	(92.5, 188.5)
OLE month 24 (month 36 since 1st dose)	107.5	46	(61.4, 153.6)	139.7	121	(83.5, 195.9)
OLE month 30 (month 42 since 1st dose)	81.8	42	(56.3, 107.3)	105.3	115	(67.9, 142.7)
OLE month 36 (month 48 since 1st dose)	102.2	13	(46.9, 157.5)	112.7	4	(23.4, 202.0)

Source: FDA analysis based on data submitted in SN 0077.
*last visit reviewed for the major amendment was OLE Month 12 (month 24 since 1st dose).
Abbreviations: ADA, anti-drug antibodies; CI, confidence interval; OLE, open-label extension; PEN, prefilled pen device

The overall trend is consistent with what was observed in the data submitted in the original BLA review cycle (including the major amendment).

6.2.2. Impact of ADA on PD

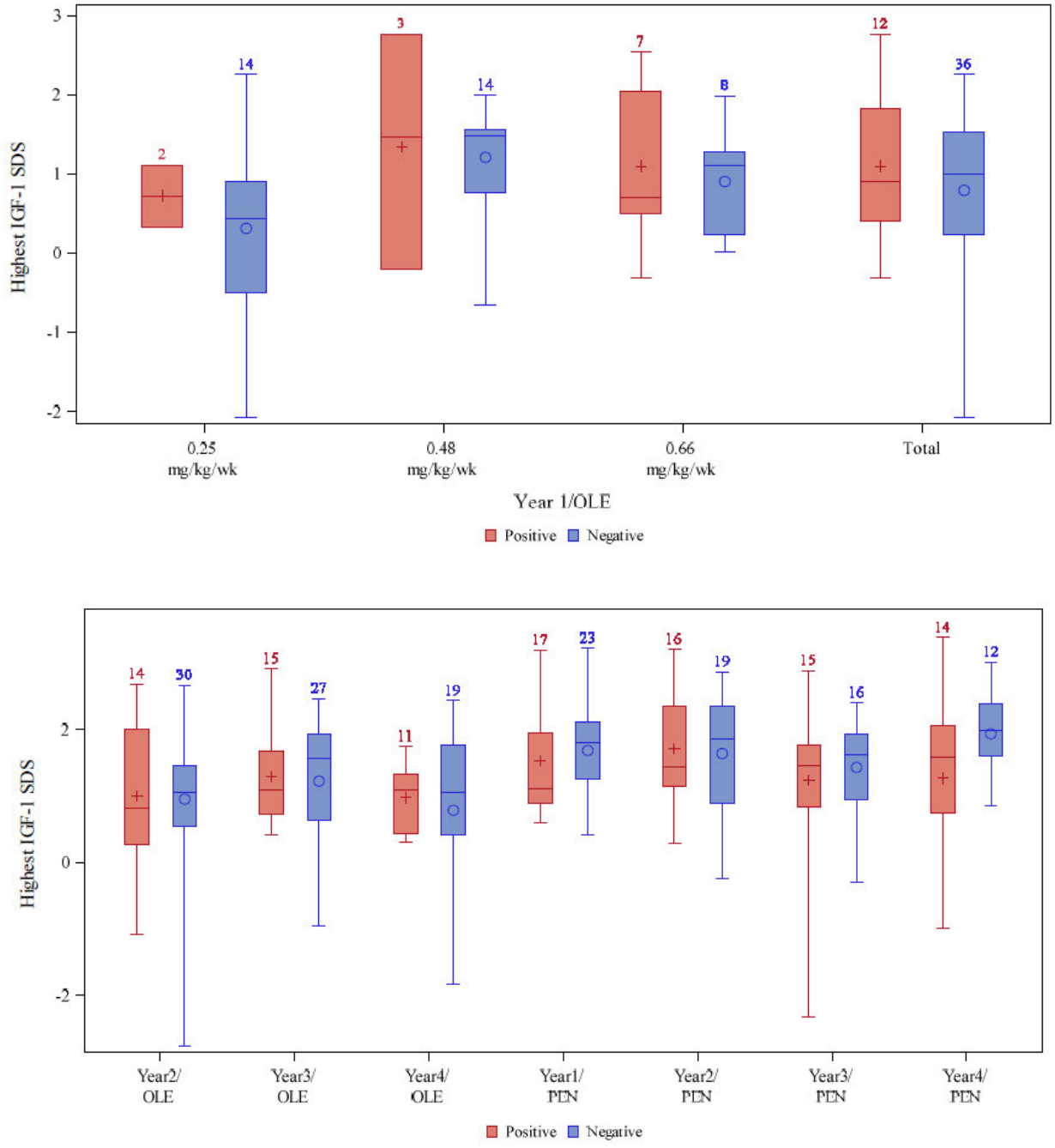
To evaluate whether there is an effect of ADA on PD, IGF-1 SDS over time in subjects randomized to somatrogon dosing cohorts were plotted by ADA status.

Note that the tables and figures in this section include additional immunogenicity data beyond what was previously provided during the first BLA review cycle. Because in these analyses a participant is considered ADA+ throughout the study if they tested ADA+ at any time during the study (including throughout the OLE period), there may be small differences in total counts of ADA+ participants from previously reported results. However, majority of subjects who developed ADA had persistent ADA positivity throughout the entire study period (refer to Section 8.1.1.2, Table 10, for details).

Study CP-4-004

The peak IGF-1 SDS values across the time period in ADA+ and ADA- participants are shown in Figure 1 and Table 3. Participants who tested ADA+ for somatrogon during the OLE, including Pen Year 3 and 4, had values for IGF-1 SDS comparable to ADA- participants. This is consistent with what was observed in the data submitted in the original BLA review cycle (including the major amendment).

Figure 1. Peak IGF-1 SDS by Year by ADA Status in Study CP-4-004 (Data Cut-Off Date of March 31, 2022)



Notes: The circle and plus in the box are mean; line in the box is median.
A subject is counted in the Positive row beginning in the year that he/she has a Positive status, and in every year thereafter.
Source: Adapted from Figure 3 of isi.pdf
Abbreviations: ADA, anti-drug antibodies; IGF-1, insulin-like growth factor-1; SDS, standard deviation scores; OLE, open-label extension; PEN, prefilled pen device

Table 3. Peak IGF-1 SDS in Study CP-4-004 by ADA Status (With Date Cut-off Date of March 31, 2022)

	Year 1							
	0.25 mg/kg/wk		0.48 mg/kg/wk		0.66 mg/kg/wk		Total	
IGF-1 SDS	N=16		N=17		N=16		N=48	
(Z)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	2	14	3	14	7	8	12	36
Mean (SD)	0.72 (0.55)	0.31 (1.17)	1.34 (1.48)	1.21 (0.71)	1.09 (1.00)	0.90 (0.68)	1.09 (1.01)	0.79 (0.97)
Median	0.72	0.44	1.46	1.48	0.69	1.11	0.90	0.99
Min, max	0.33, 1.11	-2.08, 2.25	-0.20, 2.76	-0.66, 1.99	-0.32, 2.54	0.01, 1.98	-0.32, 2.76	-2.08, 2.25

	Year 2		Year 3		Year 4	
IGF-1 SDS	N=44		N=43		N=38	
(Z)	Positive	Negative	Positive	Negative	Positive	Negative
N	14	30	15	27	11	19
Mean (SD)	1.00 (1.14)	0.96 (0.99)	1.29 (0.73)	1.23 (0.84)	0.98 (0.48)	0.79 (1.15)
Median	0.82	1.07	1.10	1.56	1.10	1.06
Min, max	-1.08, 2.69	-2.76, 2.67	0.42, 2.92	-0.96, 2.47	0.31, 1.75	-1.84, 2.44

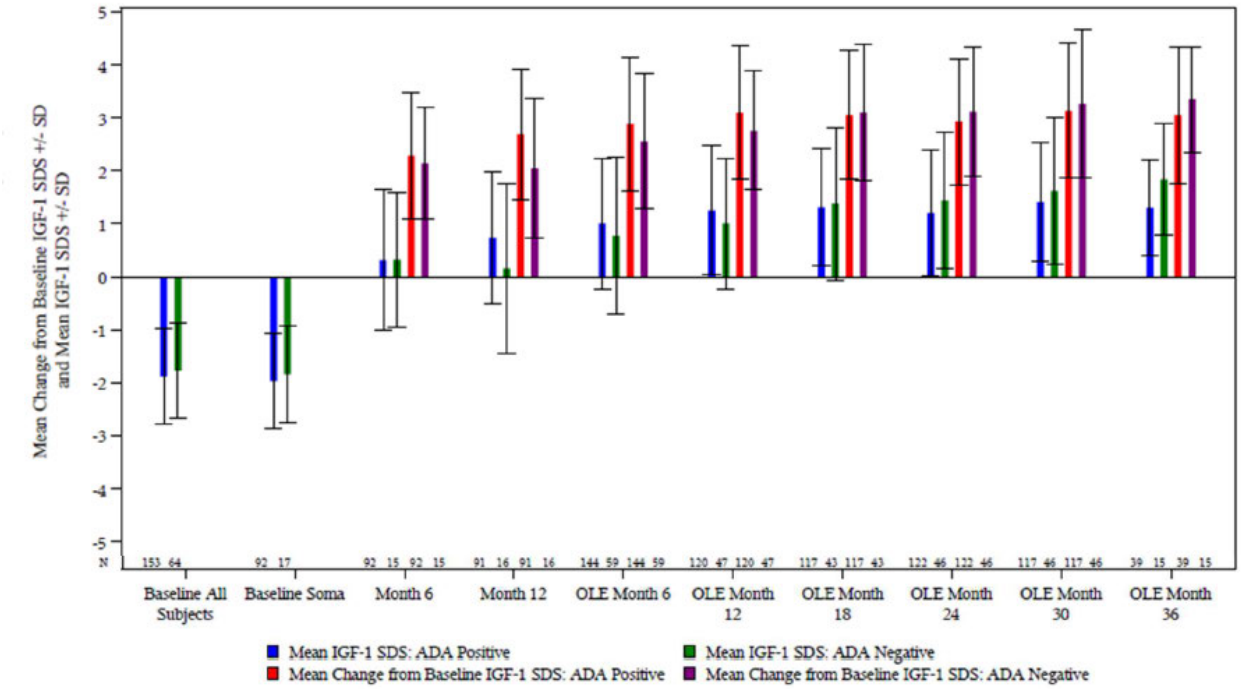
	PEN Year 1		PEN Year 2		PEN Year 3		PEN Year 4	
IGF-1 SDS	N=40		N=35		N=31		N=26	
(Z)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	17	23	16	19	15	16	14	12
Mean (SD)	1.53 (0.83)	1.69 (0.69)	1.71 (0.91)	1.64 (0.92)	1.24 (1.20)	1.43 (0.73)	1.27 (1.15)	1.94 (0.63)
Median	1.12	1.80	1.44	1.87	1.45	1.62	1.59	1.99
Min, max	0.60, 3.20	0.41, 3.23	0.29, 3.21	-0.24, 2.87	-2.32, 2.89	-0.29, 2.41	-1.00, 3.39	0.85, 3.02

Notes: A subject is counted in the Positive row beginning in the year that he/she has a Positive status, and in every year thereafter.
Source: Adapted from Table 4 of isi.pdf
Abbreviations: ADA, anti-drug antibodies; IGF-1, insulin-like growth factor-1; SDS, standard deviation scores; PEN, prefilled pen device

Study CP-4-006

IGF-1 SDS and change from baseline in IGF-1 SDS through OLE Month 36 between ADA+ and ADA- participants for all participants are shown in Figure 2, Table 4, and Table 5. Overall, there was considerable overlap between ADA+ and ADA- subjects in terms of IGF-1 SDS values and change from baseline in IGF-SDS. This is consistent with what was observed in the data submitted in the original BLA review cycle (including the major amendment).

Figure 2. Mean IGF-1 SDS and Change From Baseline IGF-1 SDS vs Time Point by ADA Status for All Subjects in Study CP-4-006 (Data Cut-off Date of March 31, 2022)



Notes: Baseline is the main period baseline for the study.
ADA positive defined as those who tested positive after receiving drug at any time during the study.
Source: Adapted from Figure 9 of isi.pdf.
Abbreviations: ADA, anti-drug antibodies; IGF-1, insulin-like growth factor-1; SDS, standard deviation scores; OLE, open-label extension; SD, standard deviation

Table 4. Summary of IGF-1 SDS by ADA Status, Study CP-4-006, Main Period (With Data Cut-Off Date of March 31, 2022)

		Originally Randomized to Somatrogon			
		ADA+		ADA-	
Visit	Variable	Observed	Change From Baseline	Observed	Change From Baseline
Baseline	N	92	N/A	17	N/A
	Mean (SD)	-1.97 (0.89)		-1.84 (0.91)	
	Median	-1.89		-1.74	
	(Min, max)	-4.39, -0.62		-3.26, -0.21	
Month 3	N	92	92	17	17
	Mean (SD)	0.08 (1.45)	2.05 (1.21)	0.32 (1.40)	2.16 (1.26)
	Median	-0.05	2.05	0.24	2.15
	(Min, max)	-3.32, 3.69	-0.5, 5.13	-2.09, 3.41	0.20, 5.28
Month 6	N	92	92	15	15
	Mean (SD)	0.32 (1.32)	2.29 (1.20)	0.32 (1.26)	2.14 (1.06)
	Median	0.48	2.24	0.11	2.06
	(Min, max)	-3.54, 2.99	-0.44, 5.57	-1.67, 3.10	0.46, 4.97
Month 9	N	92	92	16	16
	Mean (SD)	0.60 (1.29)	2.57 (1.36)	0.47 (1.45)	2.36 (1.24)
	Median	0.76	2.63	0.82	2.25
	(Min, max)	-3.86, 2.99	-0.39, 5.20	-2.76, 2.46	-0.51, 4.33
Month 12	N	91	91	16	16
	Mean (SD)	0.74 (1.25)	2.69 (1.23)	0.16 (1.60)	2.05 (1.30)
	Median	0.82	2.72	0.57	2.12
	(Min, max)	-3.64, 3.22	0.02, 6.11	-3.2, 2.77	-0.27, 3.90

Note: Main study visits are only presented for "somatrogon/somatrogon" group since subjects in "Genotropin/somatrogon" group are not tested for Somatrogon ADA in main study.
Source: Adapted from Table 16 of isi.pdf.
Abbreviations: ADA, anti-drug antibodies; IGF-1, insulin-like growth factor-1; SDS, standard deviation scores; SD, standard deviation

Table 5. Summary of IGF-1 SDS by ADA Status, Study CP-4-006, OLE Period (With Data Cut-Off Date of March 31, 2022)

		All subjects (N = 224)			
		ADA+		ADA-	
Visit	Variable	Observed	Change From Baseline	Observed	Change From Baseline
Baseline	N	153	N/A	64	N/A
	Mean (SD)	-1.88 (0.91)		-1.76 (0.90)	
	Median	-1.78		-1.68	
	(Min, max)	-4.39, -0.51		-3.91, -0.20	
OLE month 3	N	148	148	60	60
	Mean (SD)	0.80 (1.38)	2.68 (1.30)	0.77 (1.46)	2.57 (1.34)
	Median	0.97	2.66	0.77	2.60
	(Min, max)	-3.64, 3.06	-0.30, 5.79	-2.04, 3.50	-0.15, 4.99
OLE month 6	N	144	144	59	59
	Mean (SD)	1.01 (1.23)	2.89 (1.26)	0.77 (1.48)	2.56 (1.26)
	Median	1.11	2.87	0.84	2.61
	(Min, max)	-3.24, 3.72	-0.17, 5.49	-2.75, 3.37	0.61, 5.24
OLE month 9	N	130	130	53	53
	Mean (SD)	1.10 (1.24)	2.92 (1.28)	1.14 (1.49)	2.88 (1.32)
	Median	1.36	3.05	1.27	2.88
	(Min, max)	-3.07, 4.00	-0.18, 5.59	-2.84, 3.57	0.20, 5.70
OLE month 12	N	120	120	47	47
	Mean (SD)	1.26 (1.23)	3.10 (1.26)	1.01 (1.23)	2.76 (1.12)
	Median	1.46	3.04	0.91	2.66
	(Min, max)	-4.20, 3.90	-0.54, 7.12	-1.55, 3.68	-0.34, 4.93
OLE month 18	N	117	117	43	43
	Mean (SD)	1.32 (1.12)	3.06 (1.21)	1.38 (1.44)	3.10 (1.30)
	Median	1.42	3.05	1.58	3.30
	(Min, max)	-2.86, 3.51	0.44, 5.94	-2.06, 3.91	0.17, 5.34
OLE month 24	N	122	122	46	46
	Mean (SD)	1.20 (1.19)	2.93 (1.19)	1.45 (1.28)	3.12 (1.22)
	Median	1.24	3.10	1.69	3.28
	(Min, max)	-3.53, 3.05	-0.22, 5.40	-2.26, 3.58	-0.56, 5.23
OLE month 30	N	117	117	46	46
	Mean (SD)	1.42 (1.11)	3.14 (1.28)	1.63 (1.37)	3.27 (1.39)
	Median	1.52	2.97	1.81	3.60
	(Min, max)	-2.87, 4.55	-1.68, 6.67	-1.81, 3.96	0.00, 5.97
OLE month 36	N	39	39	15	15
	Mean (SD)	1.31 (0.90)	3.06 (1.29)	1.84 (1.05)	3.35 (1.00)
	Median	1.36	2.97	1.68	3.46
	(Min, max)	-4.2, 3.36	-0.54, 5.78	-1.55, 2.58	0.54, 4.66
OLE month 42	N	1	1	1	1
	Mean (SD)	1.96	3.72	1.49	2.78
	Median	1.96	3.72	1.49	2.78
	(Min, max)	1.96, 1.96	3.72, 3.72	1.49, 1.49	2.78, 2.78

Note: Data from all subjects are summarized.
Source: Adapted from Table 17 of isi.pdf.
Abbreviations: ADA, anti-drug antibodies; IGF-1, insulin-like growth factor-1; OLE, open label extension; SDS, standard deviation scores; SD, standard deviation

6.2.3. Bioanalytical Methods for Determining Serum Somatrogon Concentrations

Per the Applicant's response to an IR submitted on March 2, 2023 (SN 0086), the somatrogon PK ECL method format has not changed since the original BLA submission.

Per the November 1, 2019, data cut-off for the original BLA, PK samples from Study CP-4-004 (Main Study, Main OLE Years 1, 2, 3, and 4 and PEN) were analyzed using the PK ECL method at (b) (4) Since the original BLA submission and due to (b) (4) site closure, the PK ECL assay was transferred and validated at (b) (4) and supported CP-4- 004 PEN OLE Years 2, 3, and 4.

Per the November 1, 2019, data cut-off for the original BLA, PK samples from Study CP-4-006 (Main Study and initial OLE) were analyzed using the ECL method at (b) (4) (b) (4) Since the original BLA submission and due to (b) (4) site closure, the PK ECL assay was transferred, partially validated and cross-validated at (b) (4) and supported CP-4-006 (OLE).

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Refer to the original BLA review for details. The proposed dosing has not changed.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The following table summarizes the trials in the clinical development program for somatrogon for the indication of growth failure in pediatric subjects with inadequate secretion of GH. Trials that provided additional data included in this submission are marked with asterisks.

Table 6. Clinical Trials Relevant to This BLA-Resubmission

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-006 (main)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: active concurrent noninferiority Randomization: stratified randomization Blinding: open-label	Somatrogon 0.66 mg/kg/wk Number treated:109 SC Injection Q1W × 12 months Genotropin 0.034 mg/kg/day Number treated: 115 SC injection QD × 12 months	Primary: AHV in cm/year after 12 months of treatment Secondary: AHV after 6 months of treatment Change in height SDS at 6 and 12 months compared to baseline	Planned: 220 Actual: 228	Centers: 157 Countries: 24
CP-4-006 (OLE)	Prepubertal, children with GHD who have completed main period of Study CP-4-006	Control type: no treatment concurrent (single arm) Randomization: none (single-arm) Blinding: open-label	Somatrogon 0.66 mg/kg/wk Number treated: 212 SC Injection Q1W (ongoing)	Primary: AHV in cm/year after 12 months of Treatment Secondary: AHV after 6 months of treatment	Actual: 212	Centers: 157 Countries: 24

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-004 (main)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: active concurrent noninferiority Randomization: stratified randomization Blinding: Open-label	Somatrogon 0.25 mg/kg/wk Number treated: 13 SC Injection Q1W × 12 months Somatrogon 0.48 mg/kg/wk Number treated: 15 SC injection Q1W × 12 Months Somatrogon 0.66 mg/kg/wk Number treated: 14 SC injection Q1W × 12 Months Genotropin 0.034 mg/kg/day Number treated:11 SC injection QD × 12 months	Primary: AHV in cm/year after 12 months of treatment Secondary: AHV after 6 months, change in HT SDS at 6 months, change in HT SDS at 12 months	Actual: 53	Centers: 14 Countries: 7

CP-4-004 (OLE)	Prepubertal, children with GHD who have completed main period of Study CP-4-004	Control type: No-treatment concurrent Randomization: Genotropin population randomized to 0.25, 0.48, or 0.66 mg/kg/wk somatrogon. subjects already on somatrogon continued dose from main study Blinding: open-label	Period III X 12 months Somatrogon 0.25 mg/kg/wk Q1W Number treated: 16 Somatrogon 0.48 mg/kg/wk Q1W Number treated: 17 Somatrogon 0.66 mg/kg/wk Q1W Number treated: 15 Period IV× 12 Months Somatrogon 0.66 mg/kg/wk Q1W Number treated: 44 Period V PEN Year 1 Somatrogon 0.66 mg/kg/wk Q1W Number treated: 40 PEN Year 2 Somatrogon 0.66 mg/kg/wk Q1W Number treated: 35 PEN Year 3 Somatrogon 0.66 mg/kg/wk Q1W Number treated: 31 PEN Year 4(ongoing) Somatrogon 0.66 mg/kg/wk Q1W Number treated: 26	Primary: AHV in cm/year after 12 months of treatment Secondary: AHV after 6 months, change in height SDS at 6 months, change in height SDS at 12 months	Period III Actual: 48 Period IV Actual: 44 Period V Actual: 40	Centers: 13 Countries: 7

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-009 and OLE	Japanese pre-pubertal children with growth hormone deficiency	Control type: active concurrent noninferiority Randomization: stratified randomization Blinding: open-label	Main: × 12 months Somatrogon: 0.66 mg/kg/week Q1W (dose titrated in 3 stepwise escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week), each for 2 weeks, sequentially). Number treated: 22 Genotropin: 0.025 mg/kg daily Number treated: 22 OLE: Originally randomized to Somatrogon Somatrogon: 0.66 mg/kg/week Number treated: 22 Originally randomized to Genotropin Somatrogon: 0.66 mg/kg/week Number treated: 20	Main: Primary: AHV in cm/year after 12 months of treatment Secondary: AHV after 6 months of treatment Change in height SDS at 6 and 12 Months compared to baseline OLE: Primary: AHV in cm/year after 12 months of treatment Secondary: AHV after 6 months of treatment	Main: Actual: 44 OLE: Actual: 42	Centers: 24 Countries: 1

Source: Data excerpted from the Clinical Study Reports, CP-4-004, CP-4-004(OLE), CP-4-006, CP-4-006 (OLE), CP-4-009 and adsl.xpt
Abbreviations: AHV, annualized height velocity; BLA, biologics license application; GHD, growth hormone deficiency; HT SDS, height standard deviation score; HV, height velocity; LTE, long-term extension study; N, number of subjects; OLE, open-label extension; PEN, prefilled pen device; Q1W, once weekly; QD, once daily; SC, subcutaneous

7.2. Review Strategy

The review team evaluated the data (with a cutoff date of December 21, 2020) from Study CP-4-006 [main phase (1 year) and OLE Year 1], and Study CP-4-004 [main phase (1 year), OLE Years 1-3, and OLE PEN Years 1 and 2] during the first review cycle (refer to Integrated Review in DARRTS, dated January 21, 2021, for further details) and therefore these data will not be discussed here. Briefly, data from the original BLA submission demonstrated that somatrogon increased AHV at the end of a 12-month treatment period and was shown to be non-inferior to Genotropin.

FDA has accepted short-term changes in AHV that are noninferior to the active comparator (approved hGH with a known effect on AHV) as a surrogate to evaluate the efficacy of products with a native GH sequence for the treatment of short stature in pediatric patients with GHD. It is expected that hGH-induced changes in AHV ultimately translate into increased final adult height. This evidence is supported by a clear mechanistic rationale (replacement therapy in subjects with GHD, as described above) and clinical data from the earlier trials of short acting hGH formulations (e.g., Humatrope up to 8 years) where some subjects had been treated to final adult height and demonstrated that improvement in AHV was associated with improvement in final adult height. However, reliance on one-year data presupposes the absence of factors, such as immunogenicity (all approved hGH formulations had low immunogenicity rate), that may offset growth and affect final adult height.

In the somatrogon clinical program, there was a markedly high incidence of antidrug antibodies to the GH sequence which raised uncertainties about the potential impact on long-term efficacy, leading to the CR (refer to Section 3, Regulatory background, for details).

With this resubmission, the Sponsor provided additional data to support the favorable benefit - risk assessment of somatrogon in the context of the high rate of immunogenicity (Table 6).

This review focuses on the newly submitted long-term data from the ongoing open-label extension (OLE) studies, CP-4-006 and CP-4-004, as well as data from a new Study CP-4-009. Study CP-4-009 is a phase 3, randomized, active-controlled study of 12-month duration, followed by an uncontrolled OLE period of 12-month duration, which was conducted exclusively in Japan (Table 7). The new data for studies CP-4-006 and CP-4-004 cover the period December 22, 2020, through March 31, 2022 (i.e., CP-4-006 OLE Year 2 and OLE Year 3, and CP-4-004 OLE Year 6 [PEN Year 3] and OLE Year 7 [PEN Year 4]). Comparison to the data previously reviewed by the Agency was only performed as appropriate.

The review included Applicant's analyses as well as analyses generated by the FDA review team.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The original submission included clinical data from Study CP-4-006 and Study CP-4-004. The main period of Study CP-4-006 together with mechanistic evidence provided substantial evidence of effectiveness. Additional supportive evidence of effectiveness was provided from phase 2 Study CP-4-004, main period of 12-month duration. Refer to Integrated Review in DARRTS, dated January 21, 2021, for details. Briefly:

- Study CP-4-006 was a phase 3, randomized, active-controlled, open-label, 52-week study assessing efficacy and safety of somatrogon 0.66 mg/kg/wk versus Genotropin 0.034 mg/kg/week in 224 subjects ≥ 3 years old with growth failure due to GHD. The trial demonstrated non-inferiority of somatrogon compared to Genotropin in treatment-naïve subjects with pediatric GHD after 12 months of treatment. The mean treatment difference in AHV between somatrogon and Genotropin was 0.34 cm/year (95% CI -0.23, 0.91). Somatrogon was not superior to Genotropin (lower limit of 95% CI was less than zero. The results of secondary analyses were supportive and demonstrated comparable improvement in all growth parameters as well as normalization of IGF-1 SDS in both treatment groups.
- Supportive evidence was provided from Study CP-4-004. Study CP-04-004 was a phase 2 open-label safety and dose-finding study of four somatrogon dose levels compared to daily Genotropin administered for 12 months to 53 prepubertal subjects > 3 years old with GHD. Changes in AHV and height SDS at the end of 12-month treatment in somatrogon 0.66 mg/kg group were similar to changes in growth parameters observed in Study CP-4-006: mean AHV was 11.4 cm/year and mean change in height SDS was 1.35. The trial also provided additional efficacy and safety data for up to 6 years of somatrogon use when all subjects were switched to somatrogon dose of 0.66 mg/kg/wk.

This section will discuss the results from the ongoing open label extension (OLE) studies, CP-4-006 and CP-4-004 and from a new Study CP-4-009. The design of OLE of studies CP-4-006 and CP-4-004 are discussed in detail in Integrated Review in DARRTS, dated January 21, 2021.

CP-4-006 OLE

This was a single arm, open label extension trial. Subjects who completed 12 months of treatment in the main period of Study CP-4-006 were switched to somatrogon and continued on somatrogon 0.66 /kg/week. Data from OLE Year 2 and OLE Year 3 are included in this submission and discussed below.

CP-4-004 OLE

Year 6 [PEN Year 3] and OLE Year 7 [PEN Year 4]) This was an open label, single arm period.

Somatrogon was administered using vial/syringe from the main period (Periods I to II) through the Periods III and IV in OLE study. All subjects had an option to switch from somatrogon administration using vial/syringe to the administration using a pen injector in PEN Period V during or after completing Year 2, Year 3, or Year 4 of Period IV. Subjects who completed PEN Period Year 1 could proceed to PEN Period Year 2. The Applicant included additional data from PEN Year 3 and Year 4 in this submission.

Study CP-4-009

During the pre-BLA resubmission meeting, the Agency asked the Applicant to submit all available data evaluating the immunogenicity effect on safety and effectiveness of somatrogon.

As such, the Applicant provided data from Study CP-4-009, a phase 3, open-label, multicenter, randomized, active-controlled study of 12-month duration, followed by an open-label single arm extension period, evaluating the safety and efficacy of somatrogon compared to Genotropin in 44 Japanese pre-pubertal children with GHD.

Eligible subjects were randomized 1:1 to receive somatrogon or daily Genotropin. During the first 6 weeks, somatrogon was administered in 3 stepwise escalating doses (0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week), each for 2 weeks sequentially, then subjects continued to receive somatrogon at a dose of 0.66 mg/kg/week for the remaining 46 weeks. The dose of Genotropin was 0.025 mg/kg/day. The study was followed by an uncontrolled OLE period of 12-month duration in which all subjects were treated with somatrogon 0.66 mg/kg/week.

The study included prepubertal children (3 to < 11 years for boys and 3 to < 10 years for girls) with a confirmed diagnosis of GHD by two GH provocative tests, who were naïve to treatment with hGH, and had impaired growth defined as AHV below the 25th percentile for chronological age (HV < -0.7 standard deviation score) and sex, and with a baseline IGF-1 level of at least 1 SD below the mean.

The primary efficacy endpoint was AHV after 12 months of treatment. The Applicant's prespecified analysis of the primary efficacy endpoint was performed using an analysis of covariance model. The model included treatment and gender as factors, and peak GH levels at screening and height SDS as covariates. Non-inferiority was to be establish if the lower limit of the two-sided 95% CI for mean difference "somatrogon-Genotropin" in the primary analysis was ≥-1.8 cm/year. Secondary endpoints included growth parameters (AHV after 6-months of treatment, change in height SDS at 6 and 12-months from baseline, change in bone maturation at 12 months compared to screening bone age), biochemical marker measurements (absolute

IGF-1 levels and IGF-1 SDS across study visits, IGFBP-3 levels, and IGFBP-3 SDS across study visits).

Safety endpoints included immunogenicity assessment.

Of note, the study protocol including statistical analysis plan were not reviewed by the Agency prior to the study initiation.

The study met its primary efficacy endpoint. The estimated treatment difference in the mean AHV at week 52 between somatrogon (mean AHV of 10.07 cm/year) and Genotropin (mean AHV of 9.73 cm/year) was 0.34 cm/year [95% confidence interval (CI) -0.23, 0.91]. The lower limit of the 95% CI (-0.23 cm/year) was greater than the prespecified non-inferiority margin of ≥ -1.8 cm/year, thus, the impact of somatrogon on AHV at 52 weeks was non-inferior to that of Genotropin. The results of secondary analyses were supportive and demonstrated comparable improvement in all growth parameters as well as normalization of IGF-1 SDS in both treatment groups.

8.1.1. Assessment of Efficacy and Immunogenicity Across Trials

8.1.1.1. Patient Disposition

Study CP-4-006, OLE

Table 7 shows the disposition of subjects. All subjects who completed the main phase entered the OLE period (212 subjects). Of the 212 subjects who entered the OLE, 166 subjects were ongoing by the time of data cutoff for the current submission. Of 46 who discontinued treatment during the OLE period, 24 subjects did so as they completed the study after 1 year in OLE according to protocol requirements in India. Of 22 subjects who discontinued OLE period prematurely, 9 subjects discontinued the study due to the AEs. The subjects who discontinued study drug due to AEs are reviewed in Section 8.2.3. Of the 22 who discontinued study preliminary, 14 (64%) were ADA positive during OLE period of Study CP-4-006.

Of 212 subjects enrolled in OLE, 61 subjects (29%) completed OLE Year 3.

Table 7. Subjects Disposition, Study CP-4-006, OLE

Number (%) of Subjects	Total (N = 212)
Discontinued	22 (10.4)
Adverse event	9 (4.2)
Withdrawal by caregiver/subject	11 (5.2)
Other	2 (0.9)
Completed Study [a]	24 (11.3)
Ongoing	166 (78.3)
Completed OLE year 1	204 (96.2)
Completed OLE year 2	172 (81.1)
Completed OLE year 3	61 (28.8)
Achieved final adult height	0

Source: Data excerpted from Table 7, Integrated Summary of Immunogenicity BLA Resubmission
[a] All subjects in Indian stopped treatment and completed study at the end of OLE Year 1, according to the protocol
Abbreviations: OLE, open-label extension

Study CP-4-004

Table 8 shows the disposition of subjects during the OLE periods. Of the 48 subjects who entered the OLE period of Study CP-4-004, 26 (54%) subjects finished OLE Pen Year 3, and 23 (48%) subjects were ongoing at the data cutoff for the current submission. Of the 31 subjects entering in Pen Year 3, 5 subjects discontinued the study during Pen Year 3 (one subject due to AE) and 3 subjects discontinued the study during Pen Year 4 (no subject discontinued due to AE). Four (8.3%) subjects had achieved final adult height during Study CP-4-004.

Table 8. Disposition, Study CP-4-004, OLE

Number (%) of Subjects	Total (N = 48)
Discontinued	23 (48)
Adverse event	3 (6.2)
Withdrawal by caregiver/subject	14 (29.1)
Other*	6 (12.5)
Ongoing	23 (48)
Completed OLE year 1	43 (89.5)
Completed OLE year 2	41 (85.4)
Completed OLE year 3	37 (77)
Completed PEN year 1	35 (73)
Completed PEN year 2	31 (64.6)
Completed PEN year 3	26 (54.1)
Completed PEN year 4	2 (4.2)
Achieved final adult height [b]	4 (8.3)

Source: Data excerpted from Table 1, Integrated Summary of Immunogenicity BLA Resubmission
* Lost to follow up, protocol violation.
Abbreviations: OLE, open label extension; PEN, prefilled pen device

Study CP-4-009

Out of 44 subjects who were randomized during the main study period (22 to somatrogon and 22 to Genotropin), 1 subject discontinued due to an AE in the Genotropin treatment arm. Out of 43 who completed the 12-month main study, 42 subjects entered the OLE period. One subject discontinued the OLE period due to withdrawal by the parent/guardian.

8.1.1.2. Immunogenicity Results

Study CP-4-006, OLE

A high incidence of ADA in somatrogon-treated subjects was noted in the clinical development program during the review of the initial submission (refer to Integrated Review, Section 6.3.1, for details), with 77% of the subjects becoming ADA positive during the main 12-month of main period (Table 9).

The incidence of ADA remained elevated during the OLE period but did not increase during the subsequent years of treatment; in subjects originally randomized to somatrogon, the incidence of ADA positivity during 3 years of exposure to somatrogon in the OLE was similar to the incidence of ADA during the main treatment period (Table 9). For subjects switched from Genotropin to somatrogon, the incidence of ADA increased during the first 12 months of OLE but remained lower during the subsequent years of treatment compared to subjects who were originally randomized to somatrogon (Table 9).

ADAs most often showed specificity to hGH, while very few subjects (2 in OLE Year 2 and one in OLE Year 3) with ADA had antibodies that showed specificity to CTP.

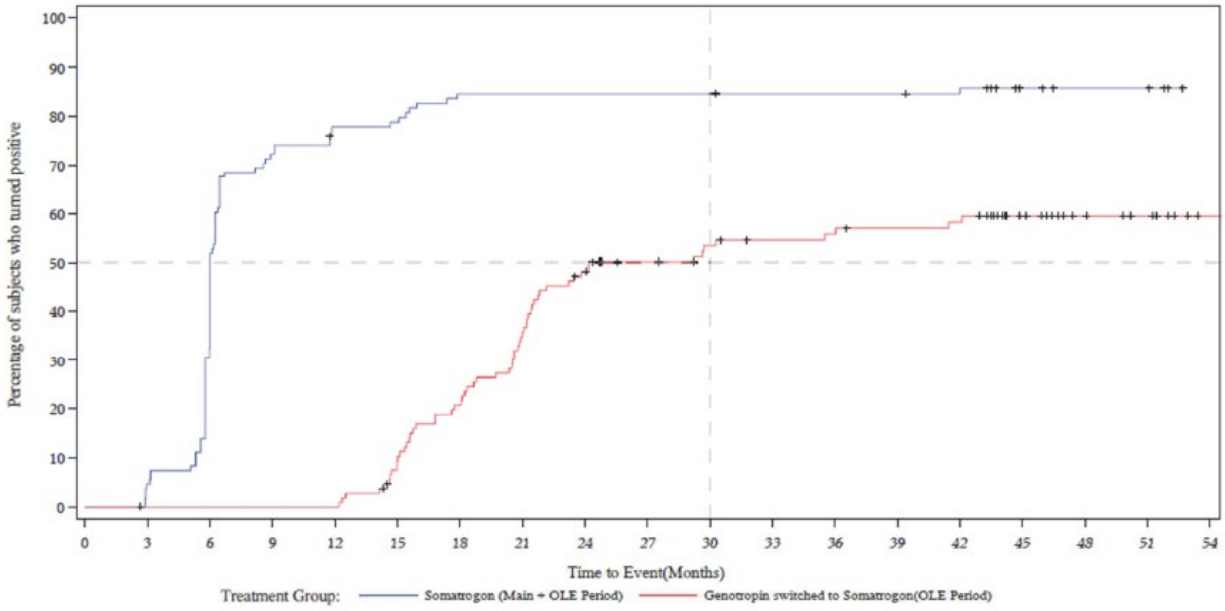
Table 9. Incidence of ADA by Year in Study CP-4-006

	N	ADA+	Nab
Main period			
Somatrogon	109	84 (77%)	2 (2%)
Genotropin	115	18 (16%)	
OLE month 12			
Somatrogon/somatrogon	104	78 (75%)	3 (3%)[1]
Genotropin/somatrogon	108	36 (33%)	
OLE month 24			
Somatrogon/somatrogon	87	60 (69%)	4 (5%)[2]
Genotropin/somatrogon	84	31 (37%)	
OLE month 36			
Somatrogon/somatrogon	27	21 (78%)	
Genotropin/somatrogon	28	13 (46%)	

Source: Data excerpted from Table 9, Integrated Summary of Immunogenicity BLA Resubmission
Gray text indicates data provided with previous submission
[1] Of these 3 subjects, one (# (b) (6)) was not reported with previous submission
[2] Of these 4 subjects, two (# (b) (6) # (b) (6)) were new, one subject (# (b) (6)) had Nabs during main period, and one subject had Nabs during OLE Year 1
Abbreviations: ADA, antidrug antibodies; Nab, neutralizing antibody; OLE, open-label extension

Figure 3 shows the cumulative time to ADA seroconversion during Study CP-4-006. The figure illustrates that majority of the subjects originally randomized to somatrogon during main period of Study CP-4-006 seroconverted during the first 6 to 12 months of exposure to study drug (70% ADA+ at Month 6, 77% at Month 12), with 84% developing antibodies by Month 24. Subjects originally randomized to Genotropin during the main period of Study CP-4-006 had a lower rate of seroconversion, with 50% and 55% of the subjects developing antibodies after 12 and 24 months, respectively, of exposure to somatrogon. Overall, 70.5% (153 out of 217) of all subjects exposed to somatrogon during Study CP-4-006 developed ADA.

Figure 3. Cumulative Time to First Positive ADA Result (Study CP-4-006)



Source: Integrated Summary of Immunogenicity BLA Resubmission, Figure 4.
Abbreviations: ADA, antidrug antibodies; OLE, open label extension

Most (97% in somatrogon/somatrogon and 77% in Genotropin/somatrogon arm) subjects who developed ADA had persistent antibodies (Table 10). According to published criteria (Shankar et al. 2014), ADA persistence was defined as ≥ 2 ADA-positive samples at time points separated by a period of ≥ 16 weeks (irrespective of any ADA-negative samples in between), or ADA-positive sample only at the last time point of the study treatment period, or at a time point < 16 weeks before an ADA-negative last sample.

Table 10. Summary of ADA Status During Study CP-4-006

Antibody Status	Somatrogon/somatrogon (N = 106) n (%)	Genotropin/somatrogon (N = 107) n (%)	Total (N = 213) n (%)
ADA-positive	91 (86%)	60 (56%)	151 (71%)
Persistent	88 (97%[a])	46 (77% [a])	134 (89% [a])
Transient	3 (3% [a])	14 (23% [a])	17 (11% [a])
ADA-negative	15 (14%)	47 (44%)	62 (29%)

Source: Data excerpted from Table 3.1.12 ISI-appendix tables CP-4-006 Integrated Summary of Immunogenicity BLA Resubmission
[a] Percent calculated using ADA-positive subjects as denominator
Abbreviations: ADA, anti-drug antibody

Antibody Titers

The median ADA titers for subjects originally randomized to somatrogon remained stable during the open-label extension period of Study CP-4-006. For subjects originally randomized to Genotropin, the median ADA titer was lower (Table 11).

Table 11. Summary of ADA Titer, Study CP-4-006

ADA Titer by Time Point	Originally Randomized to Somatrogon (N = 109)	Originally Randomized to Genotropin (N = 108)
Month 6		
N	73	
Median	250	
Range (minimum, maximum)	(10, 6250)	
Month 12		
N	83	
Median	50	
Range (minimum, maximum)	(10, 6250)	
OLE month 6		
N	68	21
Median	250	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)
OLE month 12		
N	57	24
Median	250	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)
OLE month 18		
N	56	26
Median	150	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)
OLE month 24		
N	60	31
Median	250	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)
OLE month 30		
N	59	33
Median	50	50
Range (minimum, maximum)	(10, 1250)	(10, 6250)

Source: Data excerpted from Table 10 Integrated Summary of Immunogenicity BLA Resubmission.
For titer values, 6250 was the highest dilution possible and was used to represent values >6250.
Gray text indicates data provided with previous BLA submission.
Abbreviations" ADA, anti-drug antibody; OLE, open-label extension

Neutralizing Antibodies

Neutralizing antibodies (NAbs) are ADAs that directly block the binding of drug to its receptor (i.e., hGH receptor). The presence of NAbs may reduce both drug efficacy and endogenous/ native GH activity. NAbs are more likely to be present when the incidence and prevalence of ADA is high.

Eight subjects in Study CP-4-006 (in main and OLE period; until data cutoff of March 31, 2022) developed neutralizing antibodies; 3 of them were newly identified since the original submission (Table 12, also refer to Integrated Review in DARRTS, dated January 21, 2022, Section 6.3.1, for details). Six of the 8 subjects with positive NAbs were originally randomized to somatrogon during the main period. All but one (subject (b) (6) in whom follow up testing was not performed) had documented resolution of their NAbs. Six of the 8 subjects had positive NAbs at one assessment only and correlated with the peak ADA titer (Table 12). There was no correlation between time of development of neutralizing antibodies and the duration of

exposure to somatrogon, with 3 subjects having positive neutralizing antibodies during year 1, 3 subjects during year 2, and 2 subjects during year 3 of exposure to somatrogon, respectively.

Table 12. Summary of Neutralizing Antibodies During Study CP-4-006

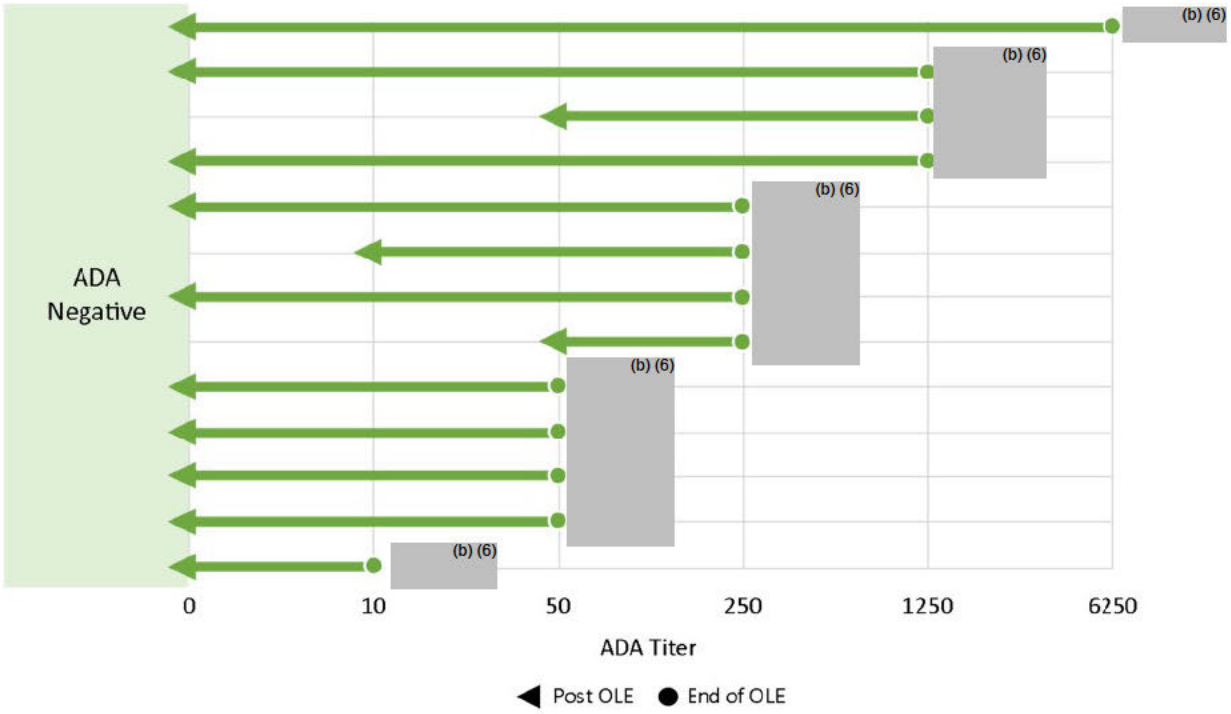
Subject ID	Gender/Age (Years)	Time(s) of NAb Positivity During Study	ADA Titer at Time of NAbs
(b) (6)	Male/7.3	Month 21	1250
		Month 24	250
		Month 30	>6250
	Male/9.5	Month 24	1250
	Male/6.0	Month 36	>6250
	Male/8.6	Month 36	1250
	Female/9.5	Month 12	250
	Male/6.3	Month 12	10
	Male/3.0	Month 6	>6250
		Month 12	>6250
		Month 24	1250
	Female/6.0	Month 15	>6250

Source: Data excerpted from Table 3.1.13a ISI-appendix tables CP-4-006 Integrated Summary of Immunogenicity BLA Resubmission
Gray text indicates data provided with previous BLA submission
Abbreviations: Nab, neutralizing antibody; ADA, anti-drug antibody

Immunogenicity Results in Subjects Who Discontinued Somatrogon during Study CP-4-006

Given the homology in amino acid sequence between somatrogon, native growth hormone and other recombinant hGH products, there is concern that anti-somatrogon-antibodies may cross-react with other growth hormone products, and if persistent, they may also result in non-responsiveness to other hGH replacement therapy. As such, the Agency asked the Applicant to provide follow up data on the immunogenicity status in subjects who discontinued somatrogon and had positive ADA at the time of study drug discontinuation, as well as growth data in those subjects who have started other hGH products. There were 46 subjects who discontinued somatrogon treatment during the OLE period; 22 subjects completed the study after OLE Year 1 (per country specific protocol in India) and 24 subjects discontinued the study prematurely (refer to Table 7. Subjects Disposition, Study CP-4-006, OLE, Section 8.1.1.1). Of the 46 subjects, 21 had positive ADA at their last assessment before treatment discontinuation. Of the 21 subjects, the Applicant was able to collect and report follow-up data on the immunogenicity status after somatrogon discontinuation and the use of other hGH therapies in 13 subjects (Figure 4).

Figure 4. Immunogenicity Status in Subjects Who Discontinued Somatrogon in Study CP-4-006, OLE



Source: Figure 11, Integrated Summary of Immunogenicity BLA Resubmission.
End of OLE: last assessment during OLE; Post OLE: unscheduled visit post study discontinuation
Abbreviations: ADA, anti-drug antibody; OLE, open-label extension

Of the 13 subjects with positive ADA at the end of OLE period while on treatment, 3 remained ADA-positive after the drug discontinuation at the time of the post-OLE sample assessment. The ADA titer in these 3 subjects was lower compared to the end of OLE period (Figure 4). The median (range) time between the end of OLE and post OLE sampling time was 663 days (range 363 -1029 days). None of the 3 subjects who had positive ADA at the post OLE testing had neutralizing antibodies.

Four out of the 13 subjects with positive ADA at the end of OLE period reported taking another hGH product (Table 13).

Table 13. Immunogenicity Data in the 4 Subjects Who Discontinued Somatrogon and Started Other hGH Therapy

Subject ID	Days After Somatrogon Discontinuation	Days on Non-Somatrogon hGH	ADA Status	ADA Titer
(b) (6)	363	133	Negative	
	1029	612	Positive	10
	675	369	Positive	50
	819	131	Negative	

Source: Data excerpted from ISI Supplement (BLA Resubmission) Listings 1 and 2
Abbreviations: ADA, anti-drug antibody; hGH, human growth hormone

Of these 4, 2 subjects (b) (6) had growth data available (data received from the Applicant on January 4, 2023, following an Information Request submitted by the Agency on December 21, 2022):

- Subject (b) (6) had a height SDS of -1.24 at the time of end of OLE, and -0.90 at the time of the unscheduled visit, 675 days after somatrogon discontinuation and 369 days after starting daily hGH therapy, respectively, suggestive of continued growth while on daily hGH therapy. This subject had positive NAbs while on somatrogon therapy (at Months 6 and 12 of the main study and at OLE Month 15).
- Subject (b) (6) had a height SDS of -1.56 at the time of end of OLE, and -2.92 at the time of the unscheduled visit, 819 days after somatrogon discontinuation, and 131 days after starting daily hGH therapy, respectively. The growth response to initiation of daily hGH therapy cannot be assessed in this subject due to lack of height data prior to start of hGH therapy, however, decrease in height SDS may be due to interruption of treatment with hGH for > 1 year.

In summary, the longer-term data (i.e., up to 4 years) from Study CP-4-006 show persistence of ADAs in the majority of subjects with continued somatrogon exposure. Most ADA positive samples showed specificity to hGH. NAbs developed in 8 subjects, with new 3 subjects reported in the resubmission. The presence of NAbs was transient (i.e., at a single timepoint) in most subjects, and all subjects tested negative for NAbs even with continued somatrogon treatment. Data from subjects who were ADA positive and discontinued somatrogon suggest that the antibodies resolve over time.

Study CP-4-004, **OLE**

The incidence of ADA during OLE Pen Years 3 and 4 was 38.7% and 42.3%, respectively, which is similar to the incidence observed during OLE Pen Years 1 and 2 (38% and 37%, respectively). No NAbs were reported during Study CP-4-004 (main and OLE periods) until data cutoff of March 31, 2022.

In summary, immunogenicity data from the OLE Pen Years 3 and 4 showed persistence of ADA at similar incidence as observed during previous years. No NAbs were reported during Study CP-4-004.

Study CP-4-009

The immunogenicity profile of subjects in this study was consistent with Study CP-4-006. During the main period, 81% (18 out of 22) of the subjects randomized to somatrogon and 18 % (4 out of 22) subjects randomized to Genotropin developed ADA. Seroconversion developed between months 3 to 6 and the antibodies were persistent in all cases. Two (9%) of the 22 subjects had transient neutralizing antibodies to somatrogon at one time point only during the main study period (1 subject at month 6 and 1 subject at baseline, pre-dose). During the OLE period of 1 year duration, 15 out of the 18 subjects originally randomized to somatrogon who were ADA positive in the main period continued to be ADA positive. Of the subjects originally randomized

to Genotropin during main study period, 60% (12 out of 20) developed positive ADA during the OLE period. No subjects had positive neutralizing antibodies during the OLE period. Most subjects who tested ADA positive to somatrogon showed specificity to hGH component of the molecule.

In summary, the immunogenicity data in Study CP-4-009 showed similar findings with those from Study CP-4-006, with high incidence and persistence of ADA and transient NAbs in a few subjects.

Conclusions

The immunogenicity data from the somatrogon clinical development program shows a high rate of ADA formation (71% of subjects tested ADA-positive during Study CP-4-006 overall) with specificity to hGH. The incidence of ADA after 2 years of treatment was higher in subjects originally randomized to somatrogon vs Genotropin (i.e., 84% of subjects originally randomized to somatrogon developed ADA vs 55% of subjects originally randomized to Genotropin). The long-term data (i.e., up to 4 years of exposure in Study CP-4-006 and up to 8 years of exposure in Study CP-4-004) suggest that ADA persist overtime in the majority of subjects, and ADA titers remained stable. While NAbs developed in a few subjects (8 out of 212 subjects exposed to somatrogon in Study CP-4-006 and 1 out of 43 subjects exposed to somatrogon in Study CP-4-009), they were detected at one timepoint only in majority (7 out of 9) of NAbs-positive subjects, were transient in all subjects, and were not dependent on the duration of exposure to somatrogon. Data from subjects who were ADA positive and discontinued somatrogon suggest that the ADA resolve/decrease in titer over time. There are very limited data on subjects who initiated other GH products after somatrogon discontinuation (4 subjects, and only 2/4 subjects had growth assessment), therefore an assessment of the impact of anti-somatrogon antibodies on growth when transitioning to other GH products could not be assessed. The risk of a potential increase in immunogenicity beyond what was observed up to the cut-off date is considered to be low based on the long-term immunogenicity assessment.

Lastly, epitope spreading during continuous administration of an immunogenic protein such as somatrogon may lead to the development of ADA against new epitopes in the molecule over time, including neutralizing and non-neutralizing antibodies. These are antibodies to epitopes of the protein that were not immunogenic in the first place. Moreover, environmental or physiological factors such as infection or hormonal changes can exacerbate epitope spreading. The risk of epitope spreading that could impact efficacy or safety of somatrogon is low. This is based on the fact that most patients who seroconverted did so within the first 6-12 months of treatment and ADA titers plateaued or decreased thereafter. Furthermore, subjects were most likely exposed to the mentioned enhancing factors during the course of the clinical trial. Epitope mapping to determine the extent of epitope spreading in somatrogon is thus not justified given such a low-risk impact.

8.1.1.3. Impact of Immunogenicity on Efficacy

Study CP-4-006, OLE

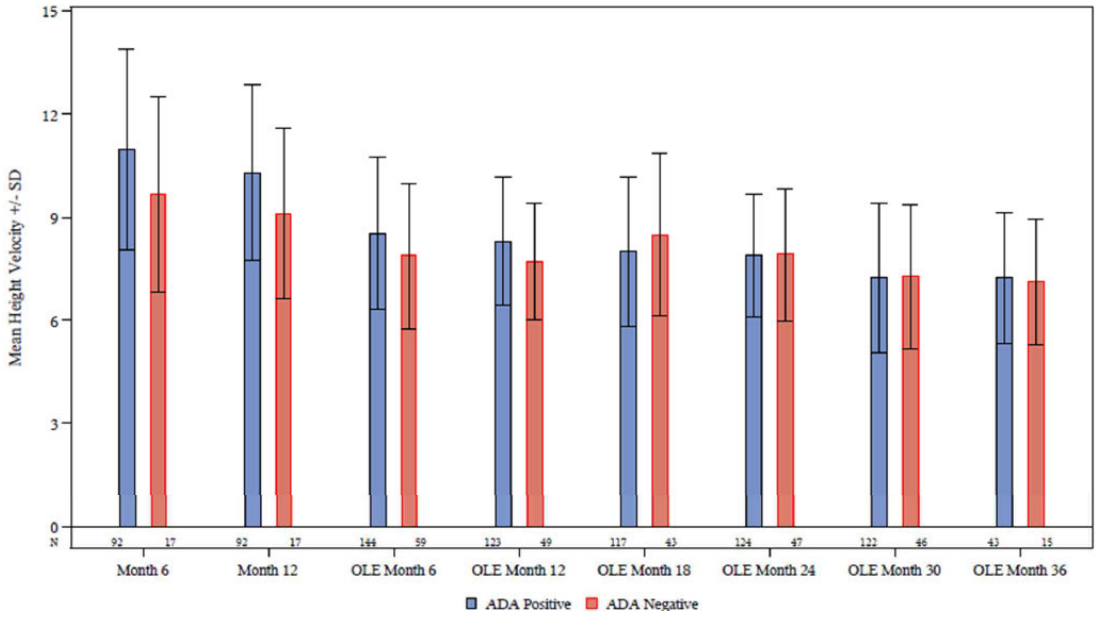
During the 12-month main period of Study CP-4-006, there were no meaningful differences in growth parameters (AHV and height SDS) between ADA-positive and ADA-negative subjects in somatrogon-treated subjects, with growth also being comparable to the growth observed in the Genotropin arm (refer to Section 6.3.1., Integrated Review, dated January 21, 2022).

The additional long-term growth data included in the re-submission show that during the OLE of this study up to Month 36, subjects continued to show improvement in growth measures. (Figure 5 and Figure 6). There was a slight decline in growth velocity after the first year of treatment that is consistent with growth patterns observed with daily hGH products. Children with GHD treated with daily hGH products typically have a growth acceleration from a pre-treatment growth velocity of 3-4 cm/year to 10-12 cm/year during first year of treatment, followed by a slight decline to 7-9 cm/year during the following years (Ali and Cohen 2009). Similar growth velocity values were observed following treatment with somatrogon (Figure 5), but growth velocity remained above the pre-treatment values.

During the OLE period, there was also no observed difference in growth between the ADA-positive and ADA-negative subjects. At OLE Months 24 and 36, the AHV (SD) was 7.87 (1.79) cm/year and 7.23 (1.90) cm/year in ADA-positive subjects, respectively, and 7.9 (1.93) cm/year and 7.10 (1.83) cm/year in ADA-negative subjects, respectively.

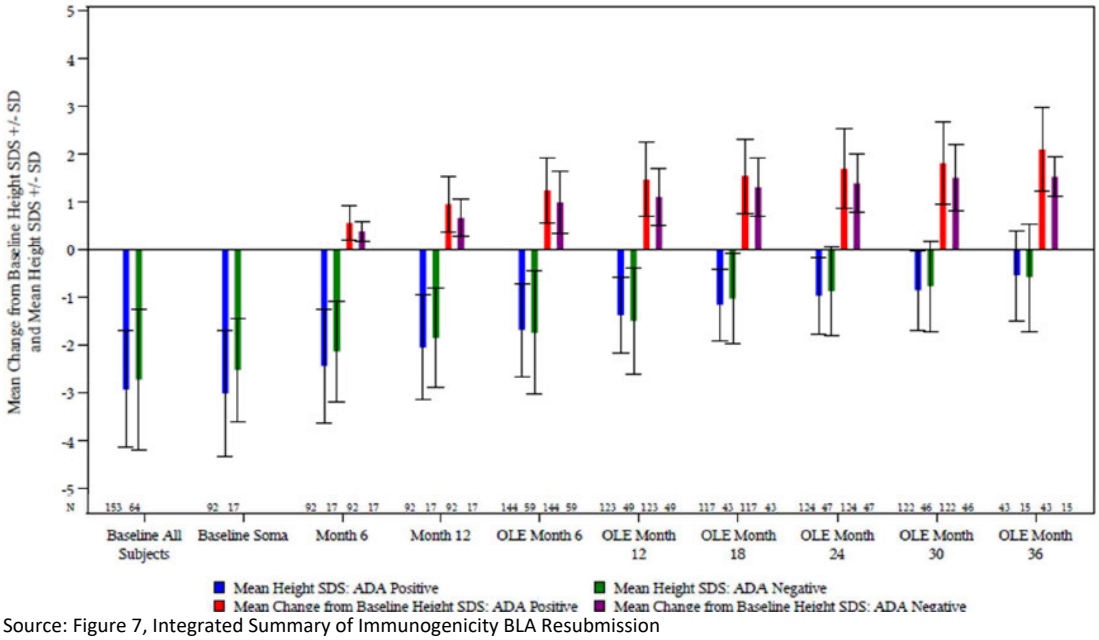
The height SDS data were also supportive of AHV findings and demonstrated continued improvement over time, reaching a value close to zero by OLE Month 36 (Figure 6). Subjects who were ADA-positive, including OLE Years 2 (Month 24) and 3 (Month 36), had values for height SDS similar to ADA-negative subjects. At OLE Months 24 and 36, height SDS (SD) was -0.97 (0.81) and -0.54 (0.95) for ADA-positive subjects, respectively, and -0.88 (0.93) and -0.59 (1.13) for ADA-negative subjects (Figure 6).

Figure 5. Mean Height Velocity Over Time by ADA Status, Study CP-4-006, Main and OLE, Full Analysis Set



Source: Figure 5, Integrated Summary of Immunogenicity BLA Resubmission
ADA-positive defined as the subjects who tested positive after receiving drug at any time during the study.
Main study visits (Month 6 and Month 12) are only presented for somatrogon/somatrogon group since subjects in "Genotropin/somatrogon" group are not tested for Somatrogon ADA in the main study period.
Height Velocity is calculated on an annual basis, with height at Month 12 of the previous year serving as reference value.
Abbreviations: ADA, anti-drug antibody; OLE, open-label extension; SD, standard deviation

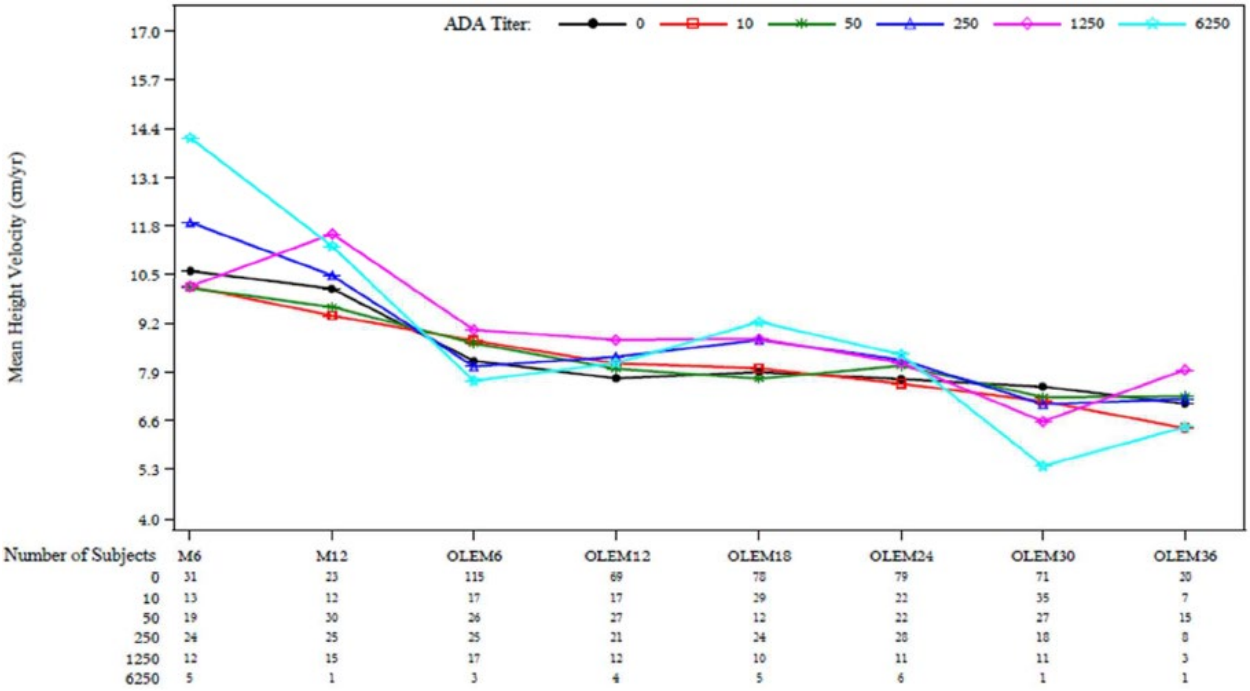
Figure 6. Mean Height SDS and Mean Change From Baseline in Height SDS Over Time by ADA Status, Study CP-4-006, Main and OLE, Full Analysis Set



Source: Figure 7, Integrated Summary of Immunogenicity BLA Resubmission
ADA-positive defined as the subjects who tested positive after receiving drug at any time during the study.
Main study visits (Month 6 and Month 12) are only presented for somatrogon/somatrogon group since subjects in "Genotropin/somatrogon" group are not tested for Somatrogon ADA in the main study period.
Change in height SDS is calculated cumulatively from main study baseline to end of each study year.
Abbreviations: ADA, anti-drug antibody; OLE, open-label extension; SD, standard deviation; SDS, standard deviation scores

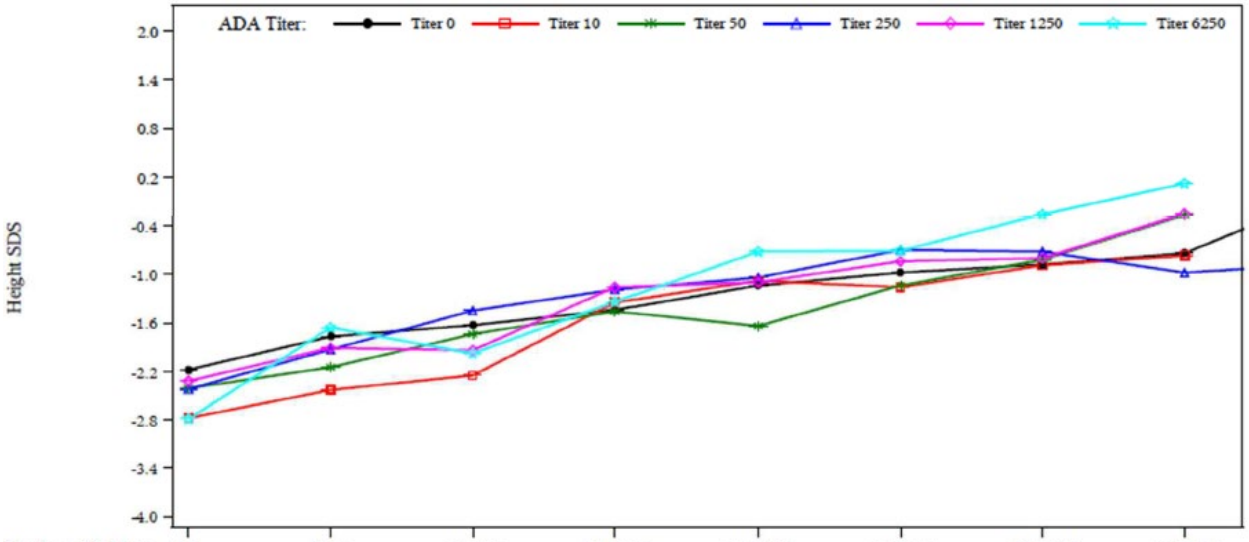
Additionally, there was no correlation between ADA titer and AHV (Figure 7) or height SDS (Figure 8) during OLE Years 2 and 3, which is consistent with findings from the main period and OLE Year 1.

Figure 7. Mean AHV Over Time in ADA-Positive Subjects by ADA Titer, Study CP-4-006 (Main and OLE), Full Analysis Set



;
Source: Figure 6, Integrated Summary of Immunogenicity BLA Resubmission
Abbreviations: ADA, anti-drug antibodies; AHV, annualized height velocity; OLE, open-label extension

Figure 8. Mean Height SDS Over Time in ADA-Positive Subjects by ADA Titer, Study CP-4-006 (Main and OLE), Full Analysis Set



Number of Subjects	M6	M12	OLEM6	OLEM12	OLEM18	OLEM24	OLEM30	OLEM36
Titer 0	31	23	115	69	78	79	71	20
Titer 10	13	12	17	17	29	22	35	7
Titer 50	19	30	26	27	12	22	27	15
Titer 250	24	25	25	21	24	20	10	8
Titer 1250	12	15	17	12	10	11	11	3
Titer 6250	5	1	3	4	5	6	1	1

Source: Figure 6, Integrated Summary of Immunogenicity BLA Resubmission
Abbreviations: ADA, anti-drug antibodies; SDS, standard deviation score; OLE, open-label extension

Neutralizing antibodies (NAbs) Effect on Growth

Because NAbs block the binding of the drug to the hGH receptor, there is concern that they can reduce both drug efficacy and endogenous GH activity.

During the previous submission review cycle, one (# (b) (6)) of the five subjects who developed NAbs was noted to have a significant decrease in AHV (from 11.8 to 3.0 cm/year) at Month 18 (OLE Month 6) after testing positive for NAb at Month 12 (refer to Integrated Review, Section 6.3.1, for details). The observed decline in AHV remained unexplained at the end of the first cycle review because of insufficient follow up time, and an immunogenic effect on growth could not be ruled out. With the current submission, the Applicant included additional information regarding this subject.

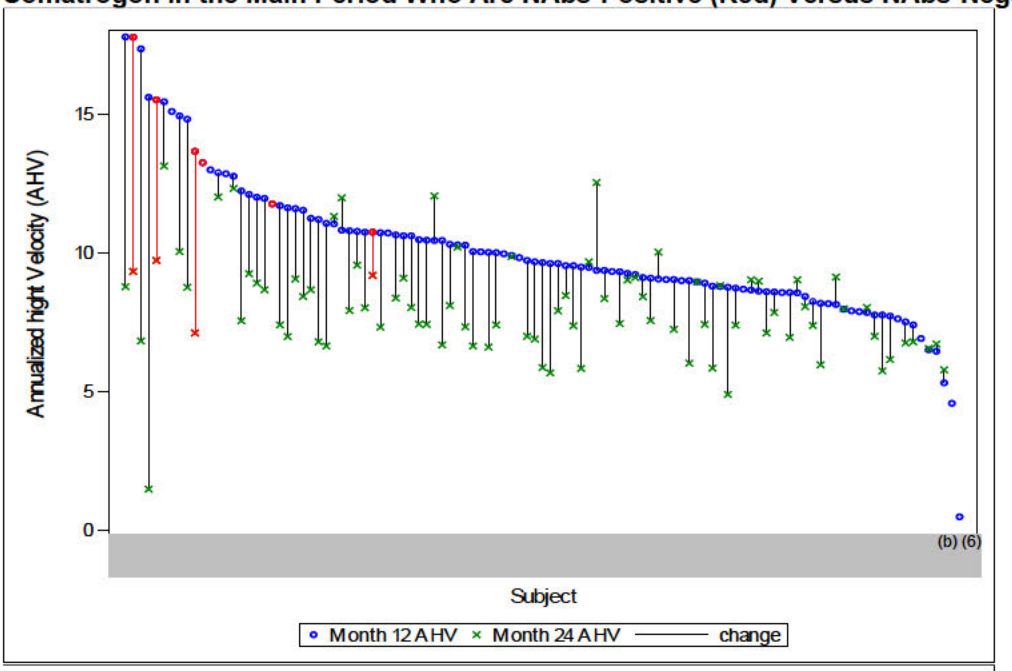
He was a 6-year-old boy from India who was randomized to somatrogon 0.66 mg/kg/week in Study CP-4-006. Following the main phase, he had a drug interruption of 116 days before enrolling in the OLE phase due to delay in regulatory approval of the OLE protocol. His last study visit in the OLE was Month 9 (12 months after completing the main period). According to country-specific protocol requirements, he completed study at the end of OLE Month 12 (the India-specific protocol allowed participants to enroll in the OLE period of the study for only 1 year). Of note, he had severe short stature (height/ heigh SDS: 79.5 cm/-7.48) and weight deficit (9 kg) at baseline. During the first year of treatment with somatrogon, he had a significant improvement in growth velocity at approximately 12 cm/year, followed by a significant decline in growth velocity to 3 cm/year at OLE Month 6; height SDS also showed

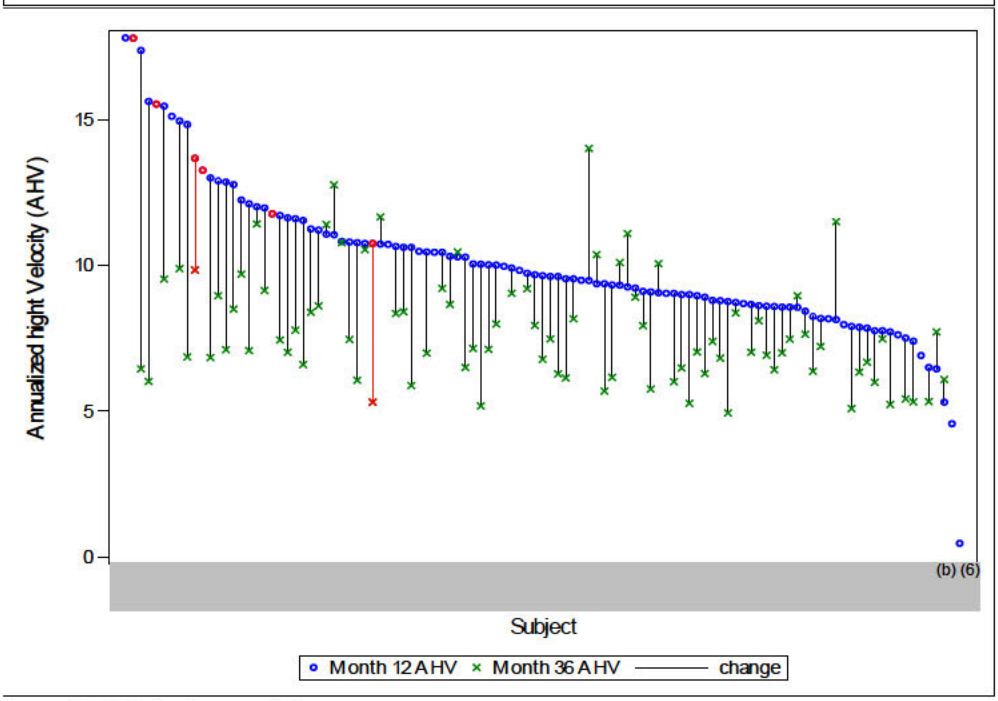
continued decrease. The new data included with the current submission provided further evidence of decreased growth velocity at 3 cm/year at OLE Month 9 (in addition to OLE Month 6), raising the question of whether there was lack of drug efficacy (Table 14). He had a low ADA titer from Month 6 until OLE Month 15, and positive NAbs at Month 12, as previously noted. Follow up immunogenicity data demonstrated negative ADAs and NAbs at OLE Months 18 and 21, respectively. An additional sample collected at what would have been OLE Month 40 was also ADA negative. At this time, the subject underwent genetic testing, which revealed homozygous whole gene deletion of the GH1 gene, consistent with a diagnosis of isolated GHD (IGHD) type 1A, a rare autosomal recessive form of GHD (Keselman et al. 2012). Individuals with this diagnosis have severe GHD and early-onset growth attenuation with severe short stature throughout their lifetime. Because of complete lack of GH, exposure to hGH does not occur during fetal life, resulting in postnatal immunological intolerance to GH and development of anti-GH antibodies following exposure to treatment with any GH products. Whereas the cause of the growth attenuation in this condition is believed to be due to the development of NAbs to exogenous hGH, immunogenicity and clinical responses to exogenous hGH containing products has been reported to be quite variable. As such, the significant decline in growth velocity in this subject is believed to be the result of the underlying diagnosis of IGHD, and not a direct effect of somatrogon-induced immunogenicity.

The effect of the drug on growth was further evaluated in the remaining 7 subjects who developed neutralizing antibodies during Study CP-4-006 (the 3 subjects newly identified with the current submission, and the 4 subjects identified during previous submission, in whom additional data were provided).

Growth velocity evaluation using 12-month (i.e., from Month 12 to Month 24), and 24-month (i.e., from Month 12 to Month 36) interval data showed improvement in growth and changes were of similar magnitude in both NAbs-positive and NAbs-negative subjects (Figure 9 and Figure 10).

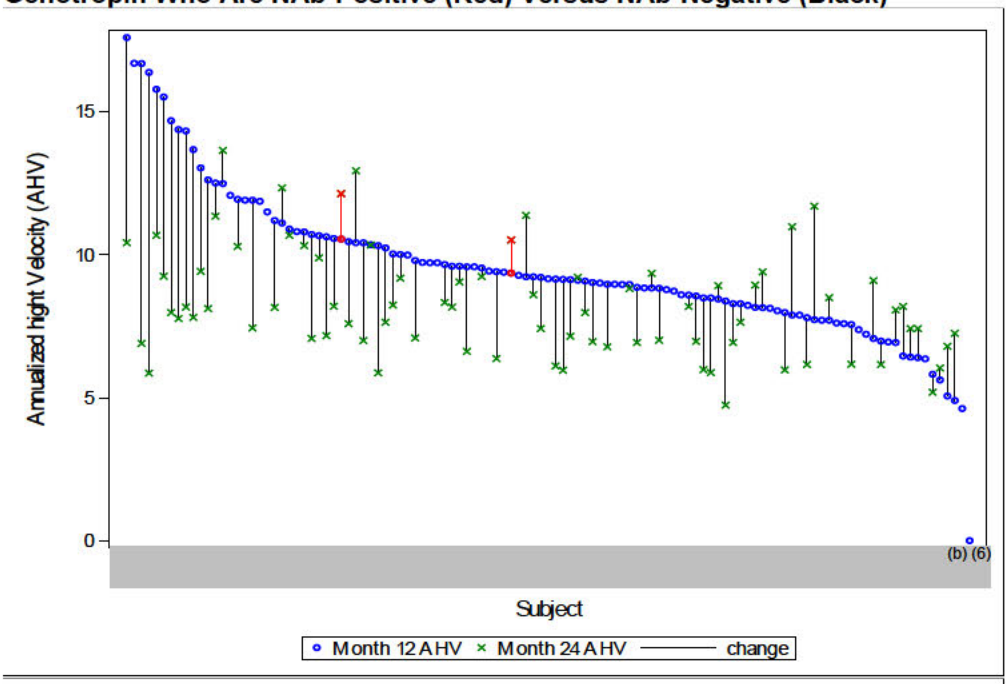
Figure 9. Waterfall Plots of Change in AHV in Individual Subjects Originally Randomized to Somatrogon in the Main Period Who Are NAbs-Positive (Red) Versus NAbs-Negative (Black)

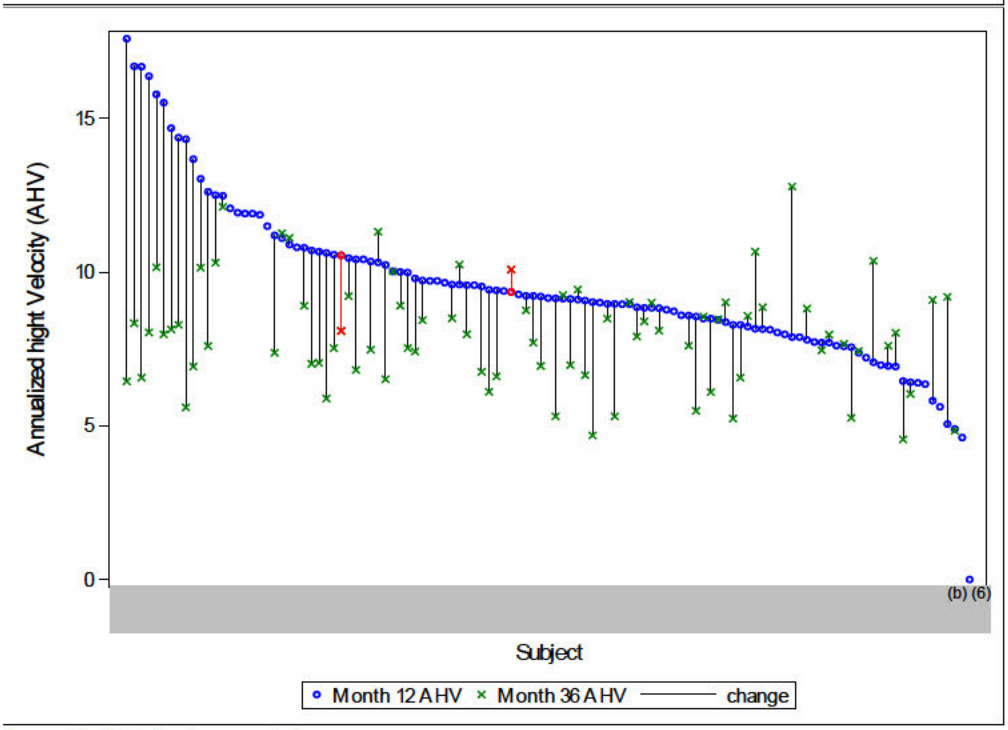




Source: Statistical reviewer analysis
Notes: The graph on top shows change in AHV from Month 12 to Month 24.
The graph at the bottom shows change in AHV from Month 12 to Month 36.
Red: subjects who were NAb-positive between Month 12 to Month 36
Black: subjects who were NAb-negative during the study
Abbreviations: ADA, anti-drug antibodies; AHV, annualized height velocity; NAbs, neutralizing antibodies; SDS, standard deviation score

Figure 10. Waterfall Plots of Change in AHV in Individual Subjects Originally Randomized to Genotropin Who Are NAb-Positive (Red) Versus NAb-Negative (Black)





Source: Statistical reviewer analysis
Notes: The graph on top shows change in AHV from Month 12 to Month 24.
The graph at the bottom shows change in AHV from Month 12 to Month 36.
Red: subjects who were NAb-positive between Month 12 to Month 36
Black: subjects who were NAb-negative during the study
Abbreviations: ADA, anti-drug antibodies; AHV, annualized height velocity; NAbs, neutralizing antibodies; SDS, standard deviation score

Table 14 presents growth data by study month in subjects with positive NAbs. Bolded rows indicate timepoints when neutralizing antibodies were positive. Gray text indicates data

provided with previous BLA submission. A decline in AHV that correlated with the timepoints during which Nabs were positive was observed when looking at the AHV data by study month (Table 14). However, there were other factors that could explain the short-term decline in AHV, including: a) temporary dose interruption (subjects [redacted]); b) dose reduction (subject [redacted]); c) algorithm used for growth velocity calculation, which may overestimate a growth decline if growth is measured at frequent intervals (subjects [redacted]), or a combination of above-mentioned factors.

In addition, height SDS continued to improve in all 7 subjects with positive NAbs until last assessment, suggesting continued study drug benefit on growth, despite presence of NAbs (Table 14).

Table 14. ADA Titers and Growth Measurements in Subjects With Positive NAbs Over Time, Study CP-4-006 (Main and OLE)

Subject ID	Gender/Age (Years) at Entry	Timepoint From Entry	ADA Titer	NAb	AHV (cm/year)	HT SDS	IGF-1 SDS
[redacted]	Male/ 7.3	Baseline		N	NA	-3.745	-3.54
		Month 3	50	N	17.8	-3.19	-0.80
		Month 6	250	N	15.9	-2.66	0.07
		Month 12	250	N	13.7	-2.14	NA
		Month 18	250	N	9.8	-1.62	-2.38
		Month 24	250	N	7.1	-1.68	-0.03
		Month 30	>6250	Pos	7.2	-1.46	-2.69
		Month 36	50	N	9.8	-0.86	0.25
		Month 42	10	N	15.3	-0.04	-0.12
		Month 48	NA	NA	12.44	0.22	0.46
[redacted]	Male/ 9.5	Baseline	N	N	NA	-3.66	-3.50
		Month 6	10	N	10.9	-3.04	1.33
		Month 12	50/250	N	10.8	-2.50	2.61
		Month 18	1250	N	10.8	-1.98	1.54
		Month 24	1250	Pos	9.2	-1.81	2.28
		Month 30	250	N	6.15	-1.71	1.46
		Month 36	250	N	5.31	-1.82	0.77
		Month 42	250	N	7.98	-1.80	1.73
		Month 48	250	N	8.70	-1.67	1.96
[redacted]*	Female/ 9.5	Baseline	N	N	NA	-6.86	-3.54
		Month 6	250	N	15.4	-5.52	-3.21
		Month 12	250	Pos	15.5	-4.33	0.63
		Month 18	10	N	8.3	-3.79	1.41
		Month 24/EOS	50	N	9.7	-3.41	1.28
[redacted]*	Male/ 6.3	Baseline	N	N	NA	-7.48	-3.70
		Month 6	10	N	11.8	-6.95	-3.54
		Month 12	10	Pos	11.8	-6.40	-1.84
		Month 15	10	N	2.39	-6.74	-1.63
		Month 18	N	N	2.95	-6.75	-1.68
		Month 21	N	N	3.07	-6.76	-1.68
[redacted]*	Male/ 3.0	Baseline	N	N	NA	-6.18	-3.05
		Month 6	>6250	Pos	20.1	-3.73	0.27
		Month 12	1250	Pos	17.8	-2.25	1.19
		Month 18	1250	N	9.7	-1.68	2.13

Subject ID	Gender/Age (Years) at Entry	Timepoint From Entry	ADA Titer	NAb	AHV (cm/year)	HT SDS	IGF-1 SDS
		Month 27/EOS	1250	Pos	9.3	-1.24	3.02
(b) (6)*	Female/6.0	Baseline	N	N	NA	-5.20	-2.93
		Month 6	1250	N	14.57	-4.12	0.74
		Month 12	250	N	13.26	-3.27	0.87
		Month 15	>6250	Pos	6.51	-3.26	-3.03
		Month 18	1250	N	8.73	-2.91	0.22
(b) (6)	Male/6.0	Baseline	NA	NA	NA	-1.87	-2.81
		Month 6	NA	NA	13.45	-1.06	-0.11
		Month 12	N*	NA	10.55	-0.91	-0.60
		Month 18	1250	N	14.13	-0.12	2.68
		Month 24	NA	NA	12.14	0.15	2.90
		Month 36	>6250	Pos	8.09	0.49	1.43
		Month 42	1250	N	8.91	0.82	1.74
		Month 48	1250	N	7.58	0.79	1.18
(b) (6)	Male/8.6	Baseline	NA	NA	NA	-3.25	-3.75
		Month 6	NA	NA	10.46	-2.72	-3.31
		Month 12	N	NA	9.36	-2.39	-0.57
		Month 18	10	N	10.62	-1.85	-1.15
		Month 24	NA	NA	10.52	-1.32	0.15
		Month 30	1250	N	10.17	-0.88	0.09
		Month 36	1250	Pos	10.09	-0.51	-3.53
		Month 42	50	N	3.99	-0.58	2.27
		Month 45	NA	NA	6.43	-0.41	NA
		Month 48	NA	NA	6.5	-0.40	NA
		Month 51	NA	NA	7.7	-0.33	NA

Source: Prepared by the Medical Officer with data excerpted from the Integrated Summary of Immunogenicity, BLA Resubmission, Table 3.1.13a and Applicant's response to Agency's Information Request, dated December 21, 2022.
*Subjects completed the study as per protocol in India, and no further data are available on these subjects.
Abbreviations: ADA, anti-drug antibodies; AHV, annualized height velocity; HT, height; IGF-1, insulin-like growth factor-1; N, negative; NA, not available; NAbs, neutralizing antibodies; OLE, open-label extension; Pos, positive; SDS, standard deviation score

In summary, the additional growth data during OLE Years 2 and 3 in Study CP-4-006 do not suggest that either ADAs or NAbs meaningfully impact height velocity. In the single case identified during the previous submission in which growth velocity abruptly declined, an alternative valid explanation was identified. Transient decreases in height velocity observed in subjects who developed NAbs are unlikely to be related to NAbs, because similar patterns of growth attenuations are seen in Nab positive and NAb negative subjects. In addition, alternative valid explanations were identified for the transient decline in AHV, and height SDS continued to improve in all subjects.

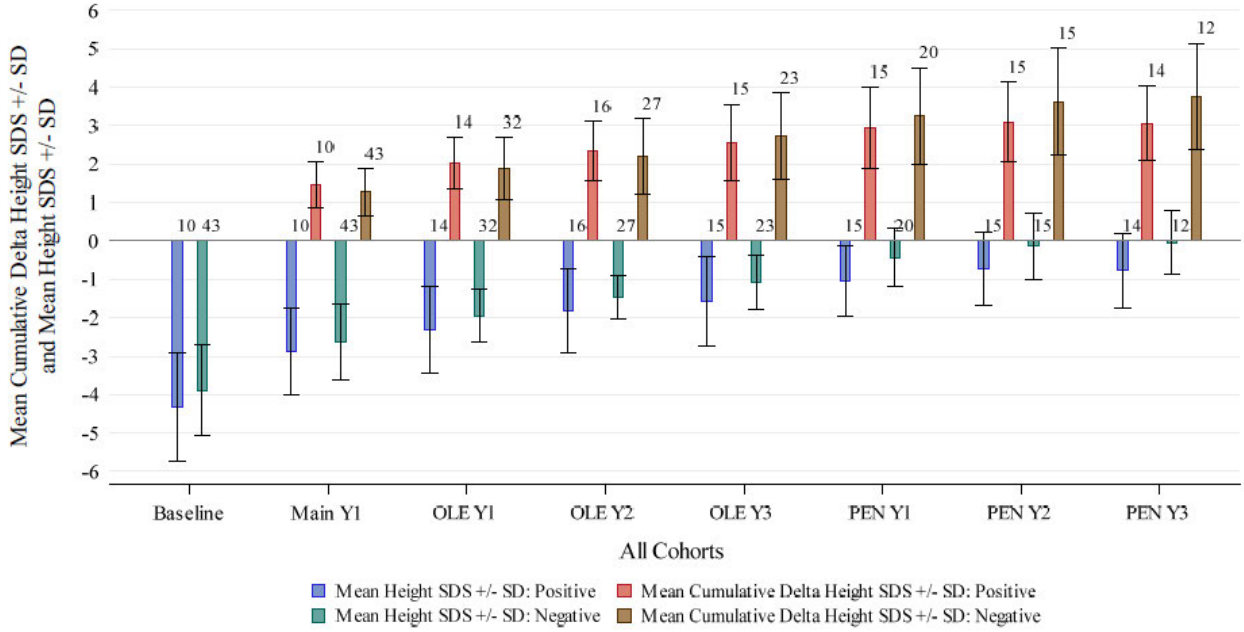
Study CP-4-004, OLE

In Study CP-4-004, the improvements in AHV and height SDS were similar between ADA-positive and ADA-negative subjects in all dose groups at the end of the 12 month dose-finding study period, as well as during the extension period of up to 5 years (Years 1-3 and Pen Years 1 and 2) (refer to Section 6.3.1., Integrated Review, and Figure 11 below). During the OLE PEN Year 3, subjects continued to show improvement in growth measures, as evaluated by AHV and height SDS, with no difference observed between the ADA-positive and ADA-negative subjects.

At OLE PEN Year 3, the AHV (SD) was 5.42 (1.52) cm/year in ADA-positive subjects and 5.42 (1.91) cm/year in ADA-negative subjects, respectively. These growth velocities were of similar magnitude as observed during previous years of exposure to somatrogon in Study CP-4-004.

Similarly, height SDS continued to improve over time, reaching a value close to zero by OLE Pen Year 3, with no difference between ADA-positive and ADA-negative subjects observed each year (Figure 11). At OLE PEN Year 3, height SDS (SD) was -0.77 (0.96) for ADA-positive subjects and -0.05 (0.83) for ADA-negative subjects.

Figure 11. Height SDS and Mean Change From Baseline in Height SDS Over Time by ADA Status, Study CP-4-004 (All Cohorts Combined)



Source: Figure 2, Integrated Summary of Immunogenicity BLA Resubmission
ADA-positive defined as the subjects who tested positive after receiving drug at any time during the study.
Change in height SDS is calculated cumulatively from baseline to end of each study year.
Abbreviations: ADA, anti-drug antibodies; PEN, prefilled pen device; OLE, open-label extension; SDS, standard deviation score; SD, standard deviation

Final Adult Height

Four subjects, all boys, achieved final adult height during the Study CP-4-004; no other subjects in the clinical program achieved final adult height yet. Their median final height was 173.85 cm (range: 168.7 to 179.5 cm), consistent with normal average adult height. Three of the subjects were ADA negative and one subject was ADA positive (final height 174.5 cm).

In summary, no apparent effect of immunogenicity on growth was noted with continued exposure to somatrogon during OLE Pen Year 3, and for a total of up to 8 years of exposure in Study CP-4-004.

Study CP-4 009

Similar to Study CP-4-006, no meaningful differences in mean AHV (Table 15) and heigh SDS (Table 16) were noted between ADA-positive subjects and ADA-negative subjects during the 12-month active controlled period, as well as during the 12-month open label extension period. The overall effect of somatrogon on growth parameters was similar to that observed in Study CP-4-006. There was no evidence of growth decline in the one subject who had transient NAbs after 6 months of exposure to somatrogon during Study CP-4-009, based on growth data available for up to 21 months of exposure to somatrogon.

Table 15. Summary of Mean AHV vs ADA Status, Study CP-4-009 (Main and OLE), Full Analysis Set

Visit Time Point (n)	Somatrogon (N = 22)		Genotropin (N = 22)	
	ADA +	ADA -	ADA +	ADA -
Month 6	18	4	4	17
Mean (SD)	10.02 (2.9)	8.82 (2.2)	8.61 (2.6)	8.28 (1.7)
Month 12	18	4	4	17
Mean (SD)	9.93 (1.5)	9.10 (1.9)	7.89 (1.0)	7.75 (1.2)
	Originally Randomized to Somatrogon (N = 22)		Originally Randomized to Genotropin (N = 20)	
	ADA +	ADA -	ADA +	ADA -
Month 18	18	2	12	8
Mean (SD)	8.07 (1.0)	6.90 (1.1)	8.09 (1.1)	8.02 (1.6)
Month 24	20	2	12	7
Mean (SD)	7.61 (1.1)	6.89 (0.7)	7.94 (0.9)	7.95 (1.3)

Source: Prepared by Medical Officer with data excerpted from the Integrated Summary of Immunogenicity Table 32 and CP-4-009 CSR, Table 14.2.7.1.s1.
Abbreviations: ADA, anti-drug antibodies; AHV, annualized height velocity; OLE, open-label extension; SD, standard deviation

Table 16. Mean Height SDS by ADA Status, Study CP-4-009 (Main and OLE), Full Analysis Set

Visit Time point (n)	Somatrogon (N = 22)		Genotropin (N = 22)	
	ADA +	ADA -	ADA +	ADA -
Baseline	20	2	12	10
Mean (SD)	-2.58 (0.4)	-2.89 (0.1)	-2.57 (0.4)	-2.48 (0.4)
Month 6	20	2	12	9
Mean (SD)	-1.95 (0.4)	-2.66 (0.3)	-2.28 (0.4)	-2.16 (0.4)
Month 12	20	2	12	9
Mean (SD)	-1.56 (0.3)	-2.48 (0.3)	-2.05 (0.5)	-2.0 (0.5)
	Originally Randomized to somatrogon (N = 22)		Originally Randomized to Genotropin (N = 20)	
	ADA +	ADA -	ADA +	ADA -
Month 18	20	2	12	8
Mean (SD)	-1.27 (0.4)	-2.35 (0.4)	-1.78 (0.4)	-1.83 (0.4)
Month 24	20	2	12	7
Mean (SD)	-1.16 (0.4)	-2.24 (0.3)	-1.58 (0.5)	-1.54 (0.5)

Source: Prepared by Medical Officer with data excerpted from CP-4-009 CSR, Table 14.2.7.1.1.s1.
Abbreviations: ADA, anti-drug antibodies; OLE, open-label extension; Pos, positive; SD, standard deviation; SDS, standard deviation score

In summary, no immunogenicity effect on growth was noted after 2 years of exposure to somatrogon in Study CP-4-009, consistent with results from Studies CP-4-006 and CP-4-004.

Conclusions

Despite high ADA formation in the somatrogon clinical development program, there was no apparent impact of immunogenicity, including Nabs, on growth. This conclusion was supported by long-term exposure data of up to 4 years in Study CP-4-006 and up to 8 years in Study CP-4-004. In addition, the 2-year data from Study CP-4-009 showed no effect of ADA on growth, consistent with results observed in Studies CP-4-006 and CP-4-004.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety data are derived from two studies in pediatric subjects, age 3 to 11 years, with GHD: phase 3, CP-4-006 and phase 2, CP-4-004. The data from CP-4-006 (main period and OLE Year 1 period) and CP-4-004 (main period and up to 5 years of follow up [OLE Years 1-3, and OLE PEN Years 1 and 2]) with a cutoff date of December 21, 2020, has been reviewed during the original submission (refer to Integrated Review in DARRTS, dated January 21, 2022).

This review focuses on new safety data not previously reviewed from the open-label extension studies, CP-4-006 and CP-4-004 covering the period December 22, 2020, through March 31, 2022 (i.e., CP-4-006 OLE Year 2 and OLE Year 3, and CP-4-004 OLE Year 6 [PEN Year 3] and OLE Year 7 [PEN Year 4]). These data are presented for each year of the OLE in tabular format where appropriate. This review also covers safety data from CP-4-009, the phase 3 Japanese study not previously submitted.

Safety data were considered from all subjects who continued treatment on somatrogon in the above-mentioned studies beyond the original cutoff date (December 22, 2020). Considering the differences in trial designs, including randomization, use of control arms, duration, doses studied, and previous exposures to Genotropin, the clinical reviewer analyzed and presented the safety data separately for each individual trial. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Lastly, the primary source for safety assessment of somatrogon originates from the main phase of Study CP-4-006, which was previously reviewed by the Division [refer to Integrated Review in DARRTS, dated January 21, 2022] and will be used for labeling purposes. The safety data from the OLE period of studies CP-4-006 and CP-4-004 are considered supportive, given absence of a control arm and the potential confounding effect of previous exposure to Genotropin. As such, these data will not be included in the label, unless new safety signals are identified.

8.2.2. Review of the Safety Database

Overall Exposure

The overall exposure to somatrogon in Studies CP-4-006 and CP-4-004 is summarized below. With the current submission, the Applicant provided an additional 15 months of safety data from studies CP-4-006 and CP-4-004 from the previous submission.

Study CP-4-006

Until the data cut-off of March 31, 2022, the mean (SD) and median duration of exposure to somatrogon in Study CP-4-006 were 36.1 (12.34) months, and 38.4 months, respectively (Table 17). The number of subjects with 36 months, 48 months, and > 48 months of exposure to somatrogon were 174 subjects, 87 subjects and 33 subjects, respectively.

Table 17. Duration of Exposure to Somatrogon, Study CP-4-006 (Main and OLE Period Combined, Safety Population)

Subjects Treated by Duration (months/years)	Total (N = 217) n (%)
Completed 12 months (1 year)	204 (94)
Completed 24 months (2 years)	186 (86)
Completed 36 months (3 years)	174 (80)
Completed 48 months (4 years)	87 (40)
Completed > 48 – 54 months (> 4 years)	33 (15)
Duration (months)	
Mean (SD)	36.1 (12.3)
Median (min, max)	38.4 (2.1, 54.0)

Source: Excerpted from Applicant's Safety Update Resubmission, Table 1
Abbreviations: OLE, open-label extension; SD, standard deviation

Study CP-4-004

Until the data cut-off of March 31, 2022, the mean (SD) and median duration of exposure to somatrogon in Study CP-4-004 were 74.4 (31.08) months, and 86.5 months, respectively, with 24 subjects completing 7 years of treatment with somatrogon. (Table 18)

Table 18. Duration of Exposure to Somatrogon 0.066 mg/kg/week, Study CP-4-004 (Main and OLE Periods Combined, Safety Population)

Subjects treated by duration (months/years)	Total (N = 52) n (%)
Completed 72 months (5 years)	38 (73)
Completed 84 months (6 years)	32 (62)
Completed 96 months (7 years)	24 (46)
Completed 108 months (8 years)	5 (10)
Duration (months)	
Mean (SD)	74.4 (31.08)
Median (min, max)	86.5 (10.8, 108.0)

Source: Excerpted from Applicant's Safety Update Resubmission, Table 1
Abbreviations: OLE, open-label extension; SD, standard deviation

Study CP-4-009

The mean (SD) duration of exposure to somatrogon in Study CP-4-009 were 732 (15.3) days for subjects originally randomized to somatrogon, and 370.9 (8.1) days for subjects originally randomized to Genotropin and switched to somatrogon in OLE period.

8.2.3. Safety Results

8.2.3.1. Deaths

No deaths were reported in studies CP-4-006, CP-4-004, and CP-4-009 at any time.

8.2.3.2. Serious Adverse Events

Study CP-4-006, OLE

There were 2 new serious adverse events (SAEs) of urticaria (OLE Year 2, subject (b) (6)) and delayed puberty (OLE Year 3, subject (b) (6)). Both events unlikely related to the drug and are summarized:

Urticaria

Subject (b) (6) was a 9.7-year-old boy with growth hormone deficiency who started somatrogon therapy in Study CP-4-006 on (b) (6) His past medical history included seasonal allergy (since (b) (6)) and house dust mite allergy (unknown date), while concomitant medications included cetirizine hydrochloride and montelukast sodium (both since (b) (6)) for allergy prophylaxis. The subject entered the long-term OLE phase of the study on (b) (6) On (b) (6) (study Day 774), the subject experienced urticaria, 3 days after the last dose of somatrogon. The adverse event manifested as itchy urticarial lesions on the back, face, torso, upper and lower limbs, and groin, and was graded as mild in severity. The event occurred after the subject had tomatoes and a soft drink. He was seen by a physician and treated with intravenous dexamethasone 3 mg and was admitted to the hospital. He was treated with oral cetirizine hydrochloride 5 mg twice daily from Day 774 to

Day 783. The physical exam and vital signs were normal during the hospital admission. The laboratory investigations in the hospital showed normal complete blood cell count and chemistry panel. Immunoglobulin E was slightly elevated at 126.3 U/mL (normal range < 90 U/mL). No action was taken with the study drug. The skin lesions resolved with treatment and did not recur. On study Day 776 the event of urticaria was considered resolved and the subject was discharged from the hospital. The subject had no other related adverse events. The subject's blood eosinophil levels were normal during the OLE period, except for mild elevation noted on study Day 1103 (0.46×10^9/L, normal range 0-0.3×10^9/L). The subject had intermittent positive antidrug antibodies (ADA) to somatrogon and human growth hormone (hGH), starting at month 3 of the OLE, until OLE month 36, with titer ranging between 10-50. The ADA were positive at OLE month 12, 38 days prior to the event of urticaria, but they were negative at OLE month 21, 8 months post-event, with no other ADA testing performed in between. He was negative for neutralizing antibodies (NAbs) to somatrogon and hGH.

While a positive causal relationship between the event of urticaria and study drug-induced adverse reaction is possible, in the setting of exposure to study drug, as well as positive ADA prior to the event, confounding factors exist, such as underlying history of allergies and presence of food-related trigger (i.e., ingestion of tomatoes right before the event). In addition, the event resolved with treatment and did not recur, despite continuous exposure to somatrogon and presence of ADA. As such, this medical reviewer considers the event of urticaria as unlikely to be related to somatrogon.

Delayed puberty

Subject (b) (6) was a 9.5-year-old (at the time of enrollment) boy with delayed puberty 40 months after somatrogon initiation that required hospitalization for diagnostic evaluation. Past medical history included phimosis, brain malformation and pituitary hypoplasia, secondary hypothyroidism, astigmatism, congenital eye disorder, congenital optic nerve anomaly, myopia and strabismus, secondary adrenocortical insufficiency, dwarfism, hyperprolactinemia, and growth hormone deficiency. Concomitant medications included hydrocortisone and levothyroxine. The hospital work up revealed testicular hypoplasia, borderline low normal levels of LH, FSH and testosterone, but adequate response in FSH, LH and testosterone level post stimulatory tests with diphereline and human chorionic gonadotropin.

After reviewing the case narrative, this medical reviewer determined that a causal relationship between somatrogon and delayed puberty was unlikely, but rather related to subject's underlying pituitary insufficiency.

Study CP-4-004, OLE

No SAEs were reported during OLE periods PEN Year 3 and PEN Year 4.

Study CP-4-009

A total of 6 SAEs were reported in 4 subjects (9.1%) during main study: 2 subjects in somatrogon arm (hypoparathyroidism, influenza, traumatic fracture, and febrile convulsion), and 2 subjects (9.1%) in Genotropin arm (craniopharyngioma and asthma). During the OLE, 3 SAEs were reported in 2 subjects (4.8%): gastroenteritis, epilepsy, and upper respiratory tract inflammation. After reviewing the case narratives, none of the SAEs occurring in somatrogon-treated subjects were considered related to somatrogon; the occurrences represent common events in this age group.

Overall, no SAEs were considered related to somatrogon, and no subject discontinued study drug due to the SAE.

8.2.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study CP-4-006, OLE

Since the last cutoff date of December 22. 2020, 9 subjects discontinued somatrogon due to AEs including: injection site reaction (5 subjects), lysinuric protein intolerance, chronic recurrent multifocal osteomyelitis (CRMO), anxiety and irritability (1 subject, each). A causal relationship between the study drug and the AEs of injection site reactions is probable. The AEs of anxiety and irritability are likely related to fear associated with the injection, and not a direct effect of somatrogon. The narrative for the case of lysinuric protein intolerance was not provided by the Applicant. However, a causal relationship between somatrogon and the AE is unlikely, since lysinuric protein intolerance is an autosomal recessive inborn error of lysine metabolism, manifested as severe hyperammonemia and lysinuria after protein intake secondary to l-arginine deficiency. Because CRMO is an autoimmune condition that could plausible be triggered by ADA, the case narrative was further reviewed below.

<u>Chronic recurrent multifocal osteomyelitis (CRMO)</u>

Subject (b) (6) was a 7.6-year-old white girl with growth hormone deficiency who started somatrogon in Study CP-4-006 on (b) (6) and continued in the OLE period on (b) (6) (b) (6) Her past medical history included abnormal nuclear magnetic resonance imaging brain (ectopic pituitary bright spot located just posterior to the optic chiasm; thinning of the pituitary stalk), since (b) (6) and hypothyroidism. Concomitant medications during the study include levothyroxine and intermittent antibiotic and antiviral therapy for various transient respiratory infections, and left toe infection.

On OLE Day 658 the subject reported AEs of right foot and left hip pain. On OLE Day 701 the AE of pain in right foot resolved, while the AE of left hip pain remained unresolved and a new diagnosis of chronic recurrent multifocal osteomyelitis (CRMO) was reported on the same day, following evaluation by rheumatologist. The diagnosis of CRMO was made based on clinical presentation, hip magnetic resonance imaging, which showed “patchy areas of signal

abnormality in the left hip affecting the acetabulum, ischium and left superior ramus of the pubis at the anterior acetabular pillar. Similar but less apparent patchy bright signal is seen around the right acetabulum. All these areas enhance on post-contrast imaging" and elevated inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]). On OLE Day 701, the subject started prednisone, followed by methotrexate on OLE Day 711, and adalinumab OLE Day 750. On OLE Day 928, study drug was discontinued due to the AE of CRMO. The subject permanently discontinued from the study on (b) (6) The AE was listed as not resolved at the last study visit. The subject had positive antidrug antibodies (ADA) to somatrogon and human growth hormone (hGH) from baseline (i.e., before initiation of somatrogon) and remained positive throughout the entire duration of study until discontinuation of study drug, when antibodies became negative. Neutralizing antibodies (NAbs) to somatrogon and hGH were negative. The peak ADA titer of 1250 was noted on (b) (6) (OLE Day 542). Additional information regarding the case was obtained from the Applicant following an Information request; the condition was described as ongoing, and he was restarted on daily growth hormone therapy on (b) (6) due to growth attenuation following somatrogon discontinuation, which resulted in an improvement in growth following initiation of daily hGH treatment.

Chronic recurrent multifocal osteomyelitis (CRMO) is a skeletal disorder occurring primarily in children and adolescents, and it is considered a noninfectious inflammatory disorder of unknown cause (Iyer et al. 2011). Some hypothesize that CRMO represents an autoimmune disorder (Jurik 2004), while others consider it as an auto-inflammatory condition, which is distinct from autoimmune disorders in that it is due to over-activation of the innate immune system, rather than the humoral immune system, which is typical of autoimmune conditions (Hofmann et al. 2017).

Based on the fact that CRMO is autoimmune disorder, a causal relationship between the study drug and the autoimmune event of CRMO is possible, given the positive temporal relationship and persistence of ADA during the study period, with peak titer corresponding to the diagnosis of disease. High titers of ADA and sustained antibody in circulation could potentially induce immune responses. However, the presence of ADA at baseline (i.e., before somatrogon initiation) makes a causal association between presence of antibodies and drug-induced immunogenic adverse reaction less likely, although it cannot be excluded completely. To further evaluate the potential risk of drug-induced immunogenic autoimmune adverse reactions, the Applicant was asked in an Information Request to provide a summary and case narratives (including antibody status) of any other AEs of autoimmune etiology that occurred in somatrogon clinical development program until the data cutoff. The Applicant submitted all the events included in the standardized Medical Dictionary for Regulatory Activities (MedDRA) Query of "immune mediated autoimmune disorders' from Studies CP-4-006 and CP-4-004 [hypothyroidism (14), enteritis (4), dermatitis (3), Raynaud's phenomenon (1), Henoch-Schonlein purpura (1) and cranial nerve disorder (1)], which were reviewed by the Agency and determined that none of them were likely autoimmune in etiology, nor were they likely related to study drug and/or antibody status. Because the event of CRMO is the single autoimmune event observed in the clinical development program of somatrogon and for which a definitive

causal relationship could not be established, the potential risk of drug-induced immunogenic autoimmune adverse reactions remains theoretical at this time. As such, its inclusion in the label is not justified at this time.

Study CP-4-004, OLE

None of the subjects discontinued somatrogon due to AEs during Study CP-4-004, PEN Years 3 and 4.

Study CP-4-009

No study drug discontinuations due to AEs were reported in somatrogon-treated subjects in Study CP-4-009.

8.2.3.4. Treatment Emergent Adverse Events and Adverse Reactions

Study CP-4-006, OLE

No new safety signals were reported. Treatment-emergent AE (TEAE) during OLE Years 2, 3 and 4 occurred at a lower incidence compared to OLE Year 1 (Table 19) and the main study period [refer to Section 7.6.6, Integrated Review, dated January 21, 2022], except for Coronavirus infection which is correlated to the COVID19 Pandemic timeline.

Table 19. Summary of AEs Occurring in >= 5% of Subjects Exposed to Somatrogon (Study CP-4-006, OLE Period)

System Organ Class (SOC) [a] Preferred Term (PT)	OLE Year 1 (N = 212)	OLE Year 2 (N = 176)	OLE Year 3 (N = 170)	OLE Year 4 (N = 30)
Any event	153 (72.2)	126 (71.6)	108 (63.5)	13 (43.3)
Infections and infestations	92 (43.4)	48 (27.3)	58 (34.1)	8 (26.7)
Nasopharyngitis	44 (20.8)	19 (10.8)	21 (12.4)	4 (13.3)
Coronavirus infection	1 (0.5)	3 (1.7)	19 (11.2)	3 (10.0)
General disorders and administration site conditions	89 (42.0)	51 (29.0)	42 (24.7)	4 (13.3)
Injection site pain	55 (25.9)	35 (19.9)	22 (12.9)	3 (10.0)
Injection site erythema	10 (4.7)	2 (1.1)	0	0
Injection site pruritus	3 (1.4)	2 (1.1)	1 (0.6)	0
Pyrexia	28 (13.2)	10 (5.7)	14 (8.2)	1 (3.3)
Respiratory, thoracic and Mediastinal disorders	30 (14.2)	17 (9.7)	12 (7.1)	1 (3.3)
Cough	13 (6.1)	4 (2.3)	7 (4.1)	0
Nervous system disorders	25 (11.8)	14 (8.0)	12 (7.1)	2 (6.7)
Headache	20 (9.4)	13 (7.4)	12 (7.1)	2 (6.7)
Gastrointestinal disorders	37 (17.5)	20 (11.4)	18 (10.6)	2 (6.7)
Vomiting	15 (7.1)	6 (3.4)	5 (2.9)	2 (6.7)
Abdominal pain [b]	9 (4.2)	6 (3.4)	5 (2.9)	1 (3.3)

Source: Excerpted from Applicant's Safety Update Resubmission, Tables 5 and 6

[a] The total number of subjects in System Organ Class is not the sum of the preferred terms in the respective category, since only the PTs occurring with an incidence of >= 5% were included in the table, and also a subject may report two or more different AEs by PT within the respective SOC category.

[b] includes the PTs of abdominal pain and abdominal pain upper

Abbreviations: AEs, adverse events; OLE, open-label extension; SOC, system organ class; PT, preferred term

Study CP-4-004, OLE

No new safety signals were reported. The incidence of TEAEs was also noted to decline during PEN Years 3 and 4 compared to previous years and consisted of primarily single AEs, similar to the ones observed in Study CP-4-006. No new safety signals were observed with long-term (i.e., up to 8 years) exposure to somatrogon during Study CP-4-004.

Study CP-4-009

No new safety signals were reported. The incidence and type of TEAEs during Study CP-4-009 was similar to those observed during Study CP-4-006 and consisted primarily of injection site reactions (73%) and upper respiratory tract infections (54%).

8.2.3.5. Laboratory Findings

No additional laboratory findings for studies CP-4-006, OLE and CP-4-004, OLE were included with the current submission.

8.2.3.6. Vital Signs

No additional vital signs for studies CP-4-006 and CP-4-004 were included with the current submission.

8.2.3.7. Electrocardiograms (ECGs)

No additional electrocardiograms were included with the current submission.

8.2.3.8. Immunogenicity

Refer to Section 8.1.1.2 for immunogenicity results from studies CP-4-006, CP-4-004, and CP-4-009.

Anti-carboxy terminal peptide (CTP) antibodies were detected in several subjects during somatrogon clinical development program. The potential risk of anti-CTP antibodies is interference with hCG-based diagnostic tests. This risk was evaluated in the original review of the BLA (refer to Section 7.7.4 of the Integrated Review in DARRTS dated January 21, 2022, for details). The Applicant did not provide any new information regarding this risk assessment with the current submission.

8.2.4. Analysis of Submission-Specific Safety Issues

8.2.4.1. Immunogenicity and Safety

The team considered whether high titers and persistent circulating antibodies are associated with immune responses and immune complex deposition in the long-term. Immunogenicity-related safety concerns include ADA-related adverse reactions (e.g., injection site reactions, hypersensitivity reactions, and autoimmune syndromes) and ADA-related decrease in drug

clearance which increases exposure to drug and thus may affect the safety profile of the drug [e.g., increase in frequency or severity of drug class adverse reactions (i.e., adverse event of special interest [AESI]), such as tumorigenesis, intracranial hypertension, slipped capital epiphysis, glucose intolerance and diabetes mellitus, pancreatitis, adrenal insufficiency, hypothyroidism, fluid retention (manifested by arthralgia, myalgia, and nerve compression), scoliosis etc.]. As such, evaluation of ADA-related adverse reactions) was further reviewed in the context of ADA status.

8.2.4.2. ADA-related Adverse Reactions

Study CP-4-006, OLE

Evaluation of AEs by ADA status during the OLE period of Study CP-4-006 showed no difference between ADA-positive and ADA- negative subjects. These results are consistent with the findings during the main study period. Specifically, during OLE Years 1, 2 and 3, AEs were reported in 72%, 69.5% and 62.6% ADA-positive subjects, and 72.6%, 77.1% and 66% ADA-negative subjects, respectively (Table 20).

Table 20. Summary of AEs by ADA Status, Study CP-4-006, OLE Period

Adverse Event	OLE Year 1 (N = 212)		OLE Year 2 (N = 176)		OLE Year 3 (N = 170)		OLE Year 4 (N = 30)	
Preferred Term	ADA+ (N=150) n (%)	ADA- (N=62) n (%)	ADA+ (N=128) n (%)	ADA- (N=48) n (%)	ADA+ (N=123) n (%)	ADA- (N=47) n (%)	ADA+ (N=18) n (%)	ADA- (N=12) n (%)
Any AE	108 (72)	45 (72.6)	89 (69.5)	37 (77.1)	77 (62.6)	31 (66)	8 (44.4)	5 (41.7)
Serious AEs	6 (4)	4 (6.5)	1 (0.8)	0	1 (0.8)	0	0	0
AEs leading to study drug discontinuation	5 (3.3)	2 (3.2)	1 (0.8)	1 (2.1)	0	0	0	0

Source: Data excerpted from Tables 19, 20 and Appendix 1 Table 3.1.2b, Integrated Summary of Immunogenicity.
Abbreviations: ADA, anti-drug antibodies; AE, adverse events; OLE, open-label extension

ADA status did not have any impact on AEs reporting when evaluated by System Organ Class (SOC), common AEs, drug class adverse reactions (i.e., AESI), SAEs, or AEs leading to study drug discontinuation. Similarly, there was no association between ADA titer and incidence of AEs reporting by SOC, common AEs, AESI, SAEs, or AEs leading to study drug discontinuation.

Given the potential impact of immunogenicity on hypersensitivity reactions and/or certain injection site reactions with long-term use of the drug, these AEs were evaluated in more details below.

Hypersensitivity reactions

An analysis of all AEs reported by Preferred Terms suggestive of potential hypersensitivity reactions was performed under the grouped query (GQ) Hypersensitivity. Although certain

injection site reactions might be related to hypersensitivity, they were not included in the GQ Hypersensitivity, but they are discussed in a separate subsection below.

During the main period of Study CP-4-006, there were no meaningful differences in the incidence or type of hypersensitivity reactions between somatrogon and Genotropin treatment arms, or between ADA-positive vs ADA-negative subjects in each treatment arm [refer to Integrated Review dated January 21, 2022, Section 7.7.3]. The frequency of hypersensitivity adverse reactions was low (< 10%) during the OLE period of Study CP-4-006 and similar between the ADA-positive and ADA-negative subjects (Table 21). During OLE Years 1, 2 and 3, hypersensitivity reactions were reported in 9.3%, 6.2% and 9.7% ADA-positive subjects, and 8.1%, 4.2% and 0 ADA-negative subjects, respectively (Table 21). A slight imbalance between the incidence of hypersensitivity reactions was observed during OLE Year 3 (8.9% vs 0). This likely has no clinical significance but can be attributed to the small sample size and imbalance in the number of subjects per each group, with more ADA+ subjects than ADA-negative subjects. The higher incidence was driven by more events of dermatitis [4 (3.2%) ADA+ subjects vs 0 ADA- subjects). Aside from dermatitis, no other AE under GQ "hypersensitivity" occurred in more than 2 subjects. All AEs but one (urticaria occurring during OLE Year 2 in an ADA+ subject, refer to SAE reported in Section 8.2.3above) were nonserious, mild, or moderate, majority were self-limiting, and none required drug discontinuation.

Table 21. Incidence of AEs of Hypersensitivity Reactions by ADA Status, Trial CP-4-006 (Extension Period)

Adverse Event	OLE Year 1 (N = 212)		OLE Year 2 (N = 176)		OLE Year 3 (N = 170)		OLE Year 4 (N = 30)	
Grouped Query Preferred Term/FMQ*	ADA+ (N=150) n (%)	ADA- (N=62) n (%)	ADA+ (N=128) n (%)	ADA- (N=48) n (%)	ADA+ (N=123) n (%)	ADA- (N=47) n (%)	ADA+ (N=18) n (%)	ADA- (N=12) n (%)
Hypersensitivity	14 (9.3)	5 (8.1)	8 (6.2)	2 (4.2)	11 (8.9)	0	0	0
Rash*	2 (1.3)	1 (1.6)	1 (0.8)	1 (2.1)	2 (1.6)	0	0	0
Rhinitis allergic	1 (0.7)	1 (1.6)	2 (1.6)	0	2 (1.6)	0	0	0
Conjunctivitis allergic	2 (1.3)	0	0	0	0	0	0	0
Urticaria*	2 (1.3)	3 (4.8)	1 (0.8)	1 (2.1)	1 (0.8)	0	0	0
Eyelid edema	1 (0.7)	0	0	0	0	0	0	0
Bronchospasm	0	0	1 (0.8)	0	1 (0.8)	0	0	0
Dermatitis *	4 (2.6)	0	2(1.6)	0	4 (3.2)	0	0	0
Hypersensitivity	1 (0.7)	0	0	0	1 (0.8)	0	0	0
Eye allergy	0	0	1 (0.8)	0	0	0	0	0
Multiple allergies	1 (0.7)	0	0	0	0	0	0	0

Source: Adapted from Table 21, Integrated Summary of Immunogenicity
*FMQ (: groups together synonymous preferred terms.
Rash includes: rash, rash erythematous, rash pruritic, exfoliative rash;
Dermatitis includes: dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, eczema;
Urticaria includes: urticaria, idiopathic urticaria, urticaria physical.
Abbreviations: ADA, anti-drug antibodies; AE, adverse events; FMQ, FDA medical queries; OLE, open-label extension

Injection -site reactions

Similar to the main period of Study CP-4-006 (refer to Integrated Review dated January 21, 2022, Section 7.7), antibody status did not appear to impact the incidence of injection site reactions during the OLE period (Table 22).

Table 22. Incidence of AEs of Injection Site Reactions by ADA Status, Trial CP-4-006 (Extension Period)

Adverse Event	OLE Year 1 (N = 212)		OLE Year 2 (N = 176)		OLE Year 3 (N = 170)		OLE Year 4 (N = 30)	
Grouped Query Preferred Term	ADA+ (N=150) n (%)	ADA- (N=62) n (%)	ADA+ (N=128) n (%)	ADA- (N=48) n (%)	ADA+ (N=123) n (%)	ADA- (N=47) n (%)	ADA+ (N=18) n (%)	ADA- (N=12) n (%)
Local administration reactions	60 (40)	20 (32.3)	29 (22.6)	12 (25)	18 (14.6)	7 (14.9)	1 (5.5)	2 (16.6)
Injection site pain	38 (25.3)	17 (27.4)	26 (20.3)	9 (18.8)	16 (13.0)	6 (12.8)	1 (5.6)	2 (16.7)
Injection site erythema	9 (6.0)	1 (1.6)	1 (0.8)	1 (2.1)	0	0	0	0
Injection site pruritus	6 (4.0)	0	0	0	0	0	0	0
Injection site swelling	2 (1.3)	1 (1.6)	1 (0.8)	1 (2.1)	1 (0.8)	0	0	0
Injection site induration	2 (1.3)	0	0	0	0	0	0	0
Injection site hemorrhage	0	0	0	0	1 (0.8)	0	0	0
Injection site bruising	1 (0.7)	1 (1.6)	0	0	0	0	0	0
Injection site hypertrophy	0	0	1 (0.8)	0	0	0	0	0
Injection site urticaria	2 (1.3)	0	0	0	0	1 (2.1)	0	0
Injection site atrophy	0	0	0	1 (2.1)	0	0	0	0

Source: Adapted from Table 21, Integrated Summary of Immunogenicity
Abbreviations: ADA, anti-drug antibodies; AE, adverse events; FMQ, FDA medical queries OLE, open-label extension

Study CP-4-004, OLE

Evaluation of AEs by ADA status during the OLE Pen Years 3 and 4 of Study CP-4-004 showed no difference between ADA-positive and ADA- negative subjects. ADA status did not have any impact on AEs reporting when evaluated by SOC, common AEs, drug class adverse reactions (i.e., AESI), SAEs, or AEs leading to study drug discontinuation. No hypersensitivity, or injection site reactions were reported in any subject regardless of ADA status during Pen Years 3 and 4 of Study CP-4-004.

Study CP-4-009

Evaluation of AEs by ADA status during the main and OLE period of Study CP-4-004 revealed no meaningful differences between ADA-positive and ADA- negative subjects.

Evaluation of all AEs suggestive of potential hypersensitivity reactions under the GQ hypersensitivity (refer to Table 21 above for all Preferred Terms evaluated) was also performed for subjects exposed to somatrogon during Study CP-4-009, main and OLE periods (Table 23). Potential hypersensitivity reactions were reported in 33% (6 out of 18) ADA-positive subjects vs 50 % (2 out of 4) ADA-negative subjects during the main study period, and 25% (8 out of 21) ADA-positive subjects vs none (0 out of 10) ADA-negative subjects during the OLE period. The

higher incidence of the hypersensitivity reactions observed during OLE Year 1 in the ADA+ subjects can be attributed to the imbalance between number of ADA-positive and ADA-negative subjects, as well as the small number of ADA-negative subjects.

Table 23. Incidence of AEs of Hypersensitivity Reactions, Trial CP-4-009 (Main and Extension Period)

Adverse Event	Main Period		OLE Year 1	
Grouped Query Preferred Term*	ADA+ N = 18 n (%)	ADA- N = 4 n (%)	ADA + N = 32 n (%)	ADA- N = 10 n (%)
Hypersensitivity	6 (33.3)	2 (50)	8 (25)	0
Rhinitis allergic	1 (5.5)	0	2 (6.2)	0
Conjunctivitis allergic	1 (5.5)	1 (25)	2 (6.2)	0
Urticaria*	2 (11.1)	0	0	0
Dermatitis *	2 (11.1)	1 (25)	4 (12.4)	0

Source: Adapted from Tables 34 and 35, Integrated Summary of Immunogenicity
*FMQ: groups together synonymous preferred terms.
Dermatitis includes: dermatitis, dermatitis allergic, dermatitis atopic, dermatitis contact, eczema
Urticaria includes: urticaria, idiopathic urticaria, urticaria physical.
Abbreviations: ADA, anti-drug antibodies; AE, adverse events; FMQ, FDA medical queries; OLE, open-label extension

Similar to results from Studies CP-4-006 and CP-4-004, ADA status did not appear to play a role on the incidence of injection site reactions during Study CP-4-009, with majority of ISRs being related to pain at the injection site (Table 24).

Table 24. Incidence of AEs of Injection Site Reactions, Trial CP-4-009 (Main and Extension Period)

Adverse Event	Main Period		OLE Year 1	
Grouped Query Preferred Term	ADA+ (N = 18) n (%)	ADA- (N = 4) n (%)	ADA + (N = 32) n (%)	ADA- (N = 10) n (%)
Local administration reactions	14 (77.8)	2 (50)	18 (56.2)	5 (50)
Injection site pain	14 (77.8)	2 (50)	19 (56.2)	5 (50)
Injection site erythema	2 (11)	0	0	0
Injection site pruritus	1 (5.6)	0	0	0
Injection site swelling	1 (5.6)	0	0	0

Source: Adapted from Tables 36 and 37, Integrated Summary of Immunogenicity
Abbreviations: ADA, anti-drug antibodies; AE, adverse events; OLE, open-label extension

Other Adverse Event of Special Interest (AESI)

Other AESI that are class-specific labeled adverse events for all approved hGH labels include tumorigenesis, intracranial hypertension, slipped capital epiphysis, glucose intolerance and diabetes mellitus, pancreatitis, adrenal insufficiency, fluid retention (manifested by arthralgia, myalgia, and nerve compression). The Applicant included the AESI that occurred during the period December 22, 2020, through March 31, 2022. The AESI that are included in this re-submission are briefly summarized below. AESI that occurred prior to the cutoff date of December 21, 2020, of the original submission were analyzed in detail in the original review of BLA (refer to the Integrated Review dated January 21, 2022) and are not discussed in this review.

Study CP-4-006 OLE

A low incidence of AESI was similar to main period during the open-label extension period as follows: adrenal insufficiency [2 (1.9%) and 1 (0.9%) subjects during OLE Years 2 and 3, respectively], scoliosis [3 (1.7% and 3 (1.8%) subjects during OLE Years 2 and 3, respectively], benign skin neoplasms (skin papilloma, melanocytic nevus) [1 (0.6%) subject each during OLE Years 2 and 3], thyroid function impairment [6 (3.4%) and 5 (3%) subjects during OLE Years 2 and 3, respectively], and arthralgia [6 (3.4%) and 1 (0.6%) subjects during OLE Years 2 and 3, respectively]. No AESI were reported during OLE Year 4, possibly due to short follow up period. There was no difference in the incidence of AESI between ADA-positive versus ADA-negative subjects (Table 25). No AESI of intracranial hypertension, slipped capital epiphysis, pancreatitis, diabetes were reported to date.

Table 25. Incidence of AESI by ADA Status, Trial CP-4-006 (Extension Period)

Adverse Event	OLE Year 1 (N = 212)		OLE Year 2 (N = 176)		OLE Year 3 (N = 170)		OLE Year 4 (N = 30)	
Grouped Query Preferred Term	ADA+ (N=150) n (%)	ADA- (N=62) n (%)	ADA+ (N=128) n (%)	ADA- (N=48) n (%)	ADA+ (N=123) n (%)	ADA- (N=47) n (%)	ADA+ (N=18) n (%)	ADA- (N=12) n (%)
Adrenal insufficiency	2 (1.3)	0	0	1 (2.1)	0	0	0	0
Hyperglycemia	0	1 (1.6)	1 (0.8)	0	0	0	0	0
Neoplasia[a]	2 (1.3)	1 (1.6)	1 (0.8)	0	0	1 (2.1)	0	0
Scoliosis	0	0	3 (2.3)	0		1 (2.1)	0	0
Arthralgia	2 (1.3)	2 (3.2)	5 (3.9)	1 (2.1)	1 (0.8)	0	0	0
Thyroid function impairment	5 (3.3)	4 (6.5)	4 (3.1)	2 (4.2)	5 (4.1)	0	0	0

Source: Adapted from Table 21, Integrated Summary of Immunogenicity
[a] Neoplasia included the events of melanocytic nevus and skin papilloma
Abbreviations: ADA, anti-drug antibodies; AESI, adverse event of special interest; OLE, open-label extension

Study CP-4-004 OLE

Only 2 AESI of scoliosis and arthralgia, respectively, were reported during PEN Year 3. Both events occurred in subjects who were ADA-negative. No AESI was reported during PEN Year 4 in Study CP-4-004.

Study CP-4-009

During the main period of Study CP-4-009, there were one event of neoplasia reported in each treatment arm [melanocytic nevus (somatrogon) and skin papilloma (Genotropin)] and one event of arthralgia reported in each treatment arm. Only one event of skin papilloma was reported during OLE period of Study CP-4-009. No other significant AESI were reported during Study CP-4-009.

Conclusions:

The additional safety data from studies CP-4-006 OLE Years 2 and 3, CP-4-004, Pen Years 3 and 4, and CP-4-009, main and OLE Year 1 did not reveal any immunogenicity-related safety

concerns, such as injection site reactions, hypersensitivity reactions, autoimmune syndromes, or increased incidence of drug class-related adverse reactions (i.e., AESI). Despite high incidence of ADA formation observed during somatrogon clinical development program, there was no impact of immunogenicity on safety for up to 4 years of exposure in Study CP-4-006 and up to 8 years in Study CP-4-004. Thus, longer-term impact of immunogenicity on safety is expected to be low.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant included in this re-submission the results of the phase 3 trial assessing the subject's perception of treatment burden with use of somatrogon versus Genotropin (C0311002). (b) (4) (b) (4) However, (b) (4) it is not reviewed as part of this re-submission. In addition, the protocol including statistical analysis plan was not previously reviewed by the Agency and the clinical outcome assessment (COA) instrument used to assess treatment burden/ patient treatment preference has not been validated by the Agency for the use in the intended population.

(b) (4)

The design and the results of this trial are briefly summarized in Appendix, Section 15.3 for the completeness of the review, only.

8.2.6. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

On October 26, 2021, somatrogon was approved in the European Union. According to the Applicant, the cumulative worldwide exposure to somatrogon since the International Birth Date (26 October 2021) is estimated to be 263 standard units (SUs). One SU is equal to one pre-filled injection pen.

According to the European Medicines Agency, the Periodic Safety Update reports covering the reporting period 27 Oct 2021 to 26 Apr 2022, and 27 Apr 2022 to 26 Oct 2022 did not identify any immunogenicity-related adverse events. In total, there were 7 cases of non-serious AEs reported, as follows: urticaria (3 cases); injection site reactions (3 cases) [injection site urticaria and injection site erythema (2 events each), injection site pruritus, injection site warmth, injection site swelling, injection site pain (1 event each)]; drug specific antibody present (1 case). According to the European Medicines Agency, the case of "drug specific antibody present" was missing important supporting information such as the somatrogon indication, latency, and action taken in response to the event; event details; event outcome; and laboratory data.

8.3. Conclusions and Recommendations

The data provided with the current submission included an additional 1.25 years of uncontrolled data on growth, safety, and immunogenicity from the ongoing studies CP-4-006 and CP-4-004, beyond the data included during the previous review cycle. The additional data confirm the persistence and high incidence of ADA in majority of subjects with continued exposure to somatrogon, while ADA resolved, or decreased in the subjects who discontinued somatrogon therapy. Neutralizing antibodies (NAbs) developed in several subjects in somatrogon development program, but they were transient in all subjects. The additional data do not suggest a meaningful impact of ADAs or NAbs on height velocity. The significant growth decline observed in one of the somatrogon-treated subjects who developed NAbs was unlikely to be drug-related, but more likely attributed to an underlying rare genetic condition.

Finally, there was no evidence of impact of immunogenicity on safety during somatrogon clinical development program. Given the high incidence and persistence of anti-somatrogon antibodies during clinical development program without demonstrated effect on safety, or efficacy, further postmarketing evaluation of immunogenicity impact on safety and/or efficacy is not warranted. Routine pharmacovigilance will be used for further evaluation of adverse reactions during the post-marketing setting.

The current data, along with data provided with previous submission (refer to Integrated Review, dated October 21, 2021) demonstrate a favorable benefit-risk profile of somatrogon in pediatric subjects with growth hormone deficiency. Thus, the Division recommends approval of somatrogon for treatment of pediatric growth failure due to insufficient secretion of growth hormone. In addition, since no impact of immunogenicity on the efficacy or safety of the drug during the long-term treatment was observed in the clinical program and that there is an overall low risk of the impact of antibody on efficacy or safety (refer to the clinical and immunogenicity team conclusion in Section 8.1.1.2 above), the Division recommends presenting the information on immunogenicity in section 12 of the label only.

9 Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held, as this was not the first drug in class, the application did not raise significant public health questions on the role of the biologic, and there were no controversial issues that would benefit from advisory committee discussion. The data in the resubmission addressed the immunogenicity concerns and did not need external input.

10 Pediatrics

The proposed indication for somatrogon is treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone. A phase 3 efficacy and safety study was conducted in patients 3 years and above.

The Applicant proposes to indicate this drug for all pediatric patients with open epiphyses. However, subjects < 3 years of age were not included in the somatrogon clinical development program. The pharmacokinetic (PK) and pharmacodynamic (PD) profile of somatrogon is different from other approved rhGH formulations because of its long-acting profile. The PK/PD profile and safety of somatrogon is not known at this time in the younger patient population and there was no predictive model to evaluate the PK/PD profile in this age group. In addition, growth failure due to GHD is not often diagnosed in children <2 years of age and the most common causes of growth failure during the first year of life are small for gestational age or genetic causes. As such, approval of somatrogon is recommended in pediatric patients with growth failure due to GHD who are ≥ 3 years of age only.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing information

Agreement on the final labeling language has not been reached at the time this review was completed. Refer to the completed labeling in the approval letter. The following sections should be addressed in the label:

1. INDICATION AND USAGE:
    - The review team recommends that the proposed indication should be for pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous GH. The trial used for registrational purposes, CP-4-006, and the supportive trial CP-4-004 included subjects 3 to 11 years of age. Given that no subjects < 3 years of age were enrolled in the clinical development program of somapacitan, safety of this drug is not established in this patient population at this time. Efficacy in younger children cannot be extrapolated for a number of reasons. First, growth failure due to GHD is rarely diagnosed in children < 2 years old, and the most common causes of growth failure during the first year of life are small for gestational age or genetic causes. In addition, neonatal GHD manifests by hypoglycemia. The PK profile of this long-acting drug is different from other approved hGH formulations. It is therefore not clear if subjects younger than 3 would have a similar, greater, or lower IGF-1 response to somatrogon compared to subjects 3 years and older. If subjects under 3 years exhibit an exaggerated IGF-1

response with somatrogon, given that somatrogon has a longer half-life than the currently available daily GH therapies, any adverse events observed may not be easily reversible upon discontinuation of the drug. Lastly, binding of estimated IGF to insulin receptors may exaggerate hypoglycemia in neonates with GHD.

2. DOSAGE AND ADMINISTRATION:
   - We agree with the proposed language.

1. CONTRAINDICATIONS:
   - The drug should be contraindicated in pediatric patients with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment to the contraindications due to the known risk of sudden death with this pharmacological class.

2. ADVERSE REACTIONS:
   - The review team recommends reporting adverse reactions in this section based on the results of the FDA analyses using the MedDRA preferred terms FDA medical queries which were used to improve the capture of synonymous adverse event terms and to improve overall safety signal detection.
   - Adverse reactions that occurred at ≥5% frequency in pediatric patients treated with either the somatrogon or Genotropin in the main period of the phase 3 trial CP-4-006 should be included in the 'Clinical Trial Experience' subsection The ≥5% incidence threshold ensures class-related adverse reactions (e.g., hypothyroidism, arthralgia) are being captured in the label and it is also consistent with adverse reaction incidence reporting for the previous and recently approved growth hormone products (i.e., Sogroya, Skytrofa)[1] for pediatric GHD indication.

7. DRUG INTERACTIONS:
   - Edits were made to this section, so the information presented is consistent with other long-acting growth hormone products.

8. USE IN SPECIFIC POPULATIONS

   8.1 Pregnancy
   - Edits were made for clarity and to be consistent with the pregnancy and lactation labeling rule.

   8.3 Females and Males of Reproductive Potential
   - (b) (4)
   - Treatment with somatrogon was associated with development of anti-CTP antibodies that may potentially interfere with native hCG, leading to incorrect pregnancy tests. This risk was previously discussed in the original review of BLA. No new data was provided in this submission regarding the risk of drug interference with pregnancy tests. All disciplines agreed [Center for Devices and Radiological

[1] https://www.accessdata.fda.gov/scripts/cder/daf/

Health (CDRH), Division of Urology, Obstetrics and Gynecology, Office of Biotechnology Products, Division of General Endocrinology (DGE)l) that the risk is likely low, but it is not completely excluded since the Applicant did not demonstrate to date that there is no such interference (refer to Integrated Review in DARRTS, dated January 21, 2022, for details). Therefore, the original review team continues recommending to manage this potential risk through labeling only. This review team added the text regarding the hypothetical risk of interference of ADA with pregnancy in section 8.3.

12. CLINICAL PHARMACOLOGY:

- Edits were made to Section 12.2 Pharmacodynamics, Section 12.3 Pharmacokinetics and Section 12. 6 Immunogenicity mainly to 1) report values based on FDA's analysis and 2) delete figure/tables that do not provide additional information.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

- Edits were made for clarity, including to describe carcinogenesis, mutagenesis, and fertility in separate subsections.

(b) (4)

14. CLINICAL STUDIES:

- The review team recommends deleting information (b) (4) from this section. The information (b) (4) does not provide meaningful clinical information to prescribers (b) (4)
- The review team also recommends deleting information (b) (4)
- The review team also recommends deleting information (b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

No safety issues including the immunogenicity rising to the level of requiring a risk evaluation and mitigation strategy was identified in the application. Safety issues will be handled through appropriate labeling.

13 Postmarketing Requirements and Commitment

No safety findings prompt the need for Postmarketing Requirements.

Postmarketing Commitments:

Postmarketing commitment (b) (4): To perform commercial shipping studies to qualify the actual shipping conditions for the drug product (prefilled pen). The commercial shipping studies will include:

- Product quality assessment on commercial drug product in the commercial container closure system, fully packaged (primary and secondary packaging, etc.) before and after real-time shipping to evaluate the effect of handling and shipping conditions on product quality.
- Analytical testing to evaluate impact on critical quality attributes (CQAs) during shipping. Justification for the selected CQAs will be provided.
- Evaluation of container closure integrity to ensure the maintenance of sterile barrier using an appropriate method (e.g., dye ingress).
- Device functionality tests to demonstrate that the shipping conditions do not adversely impact the integrity and functionality of the device.
- Temperature monitoring of the shipping container (external and internal temperatures) recorded continuously throughout shipping from thermal couple probes placed inside and outside of the shipping container.

14 Office Director (or designated signatory authority) Comments

I agree with the conclusions of this review and the recommendation for regulatory action.

15 Appendices

15.1. References

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15.2. Financial Disclosure

The financial disclosure was reviewed, and no issues were identified.

Covered Clinical Study (Name and/or Number): CP-4-004, CP-4-006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 513		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: 1 Sponsor of covered study: 2		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. Additional Clinical Outcome Assessment Analyses

Study C0311002

Title**:** A phase 3, Randomized, Multicenter, Open-Label, Crossover Study Assessing Subject Perception of Treatment Burden With Use of Weekly Growth Hormone (Somatrogon) Versus Daily Growth Hormone (Genotropin®) Injections in Children With Growth Hormone Deficiency

Design: This study was a randomized, open-label, 2-period crossover study of 24 weeks duration conducted in 87 children 3 to <18 years of age with GHD evaluating the treatment burden and treatment experience with somatrogon versus Genotropin therapy. To be eligible for enrollment, subjects had to be on a stable regimen of daily Genotropin for a minimum of 3 months prior to enrollment. After enrollment, subjects were randomized in a 1:1 ratio to one of 2 sequences, either 12 weeks of treatment with daily Genotropin followed by 12 weeks of treatment with once weekly somatrogon, or 12 weeks of treatment with once weekly somatrogon followed by 12 weeks of treatment with daily Genotropin.

Subjects and caregivers (as a dyad) completed clinical outcome assessment questionnaires at baseline and at the end of each 12-week treatment period.

The Applicant developed a new tool called the Dyad Clinical Outcome Assessment (DCOA) to capture the patient and caregiver experience of the GH injection treatment regimen, with the goal of demonstrating the benefits of a weekly injection regimen using phase 3 trial data.

The primary endpoint was treatment burden assessed as the difference in mean overall life interference total scores between the weekly injection schedule and daily injection schedule using the Patient Life Interference Questionnaire (as part of DCOA 1). The secondary endpoints included: 1) treatment experience assessed as the difference in mean scores between the weekly injection schedule experience and daily injection schedule experience in each of the following variables within DCOA 1 Questionnaires completed at baseline and after subjects have experienced both treatment schedules: pen ease of use, ease of the injection schedule, satisfaction with overall treatment experience, willingness to continue injection schedule, caregiver life interference, including family life interference. 2) proportion of Subject/Caregiver Dyads that select the weekly injection schedule compared to the daily injection schedule in various outcome domains (e.g., choice of injection pen, preferred injection schedule, convenience, and ease of injection schedule) assessed by the DCOA2 Questionnaires completed at Week 24. 3) The Patient Global Impression Score at baseline and at the end of each period (Week 12 and Week 24).

Results

The proposed Dyad Clinical Outcome Assessment (DCOA) instrument used to assess treatment burden and other patient/caregiver treatment preference variables has not been previously evaluated and validated by the Agency for the use in the intended population. As such, the interpretability and clinical significance of the study results remain unknown at this time.

Signatures

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/Approved
Regulatory Project Manager	Sejal Kiani	ORO/DRO-CHEN	Authored: Section 3
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Immunogenicity Reviewer	Montserrat Puig, Ph.D.	OPQ/OBP/DBRRIII	Authored: Section 8
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Clinical Team Leader/ Cross-Discipline Team Leader	Marina Zemskova, MD	OCHEN/DGE	Authored: Section 1, 8, 9, 10, 11, 12, 13 Approved: All Sections
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Signatory Authority	Signature: (See appended electronic signature page)		

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/s/

MARINA ZEMSKOVA
06/26/2023 05:17:20 PM
I am also signing on behalf of Deputy Division Director, Naomi Lowy.

LISA B YANOFF
06/27/2023 05:35:51 PM

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	BLA
Application number(s)	761184
Priority or standard	Standard
Submit date(s)	10/22/2020
Received date(s)	10/22/2020
PDUFA goal date	1/22/2022
Division/office	Division of General Endocrinology (DGE)
Review completion date	See electronic signature page
Established/proper name	somatrogon
(Proposed) proprietary name	Ngenla
Pharmacologic class	Human growth hormone analog
Code name	MOD-4023
Applicant	Pfizer Ireland Pharmaceuticals C/O Pfizer Inc.
Dosage form(s)/formulation(s)	Prefilled pen (24 mg/1.2 mL and 60 mg/1.2 mL)
Dosing regimen	Once weekly
Applicant proposed indication(s)/ population(s)	Long-term treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone
Proposed SNOMED indication	Pituitary dwarfism
Regulatory action	Complete response
Approved dosage (if applicable)	Not Applicable
Approved indication(s)/ population(s) (if applicable)	Not Applicable
Approved SNOMED term for indication (if applicable)	Not Applicable

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Glossary

ADA	antidrug antibodies
AE	adverse event
AESI	adverse events of special interest
AHV	annualized height velocity
ALAG1	absorption lag time
AlkPhos	alkaline phosphatase
ANCOVA	analysis of covariance
AR	adverse reaction
AUC	area under the curve
BA	bone age
BASEIGF1	baseline IGF-1
BLA	biologics license application
BMI	body mass index
BUN	blood urea nitrogen
CA	chronological age
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CRF	case report form
CTP	carboxy-terminal peptide
DP	drug product
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ECL	electrochemiluminescence
ELISA	enzyme-linked immunosorbent assay
EOP2	End-of-Phase 2
FAS	full analysis set
FCS	fully conditional specification
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
GH	growth hormone
GHD	growth hormone deficiency
GLP	good laboratory practice
GOF	goodness-of-fit
hCG	human chorionic gonadotropin
hGH	human growth hormone
ICH	International Conference on Harmonisation
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin growth factor binding protein-3
IND	investigational new drug

IPRED	individual prediction
ISR	injection site reaction
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	missing not at random
MRHD	maximum recommended human dosage
NAb	neutralizing antibodies
NDA	new drug application
NI	noninferiority
NOAEL	no observed adverse effect level
OBP	Office of Biotechnology Products
OBL	OPKO Biologics Ltd.
OLE	open-label extension
PD	pharmacodynamic
PEN	period V
PK	pharmacokinetic
PopPK	population pharmacokinetic
PT	preferred term
QoLISSY	quality of life in short stature youth
rhGH	recombinant human growth hormone
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SDS	standard deviation score
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration

I. Executive Summary

1. Summary of Regulatory Action

Somatrogon is proposed for the treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone. This biologics licensing application (BLA) was reviewed by the multidisciplinary review team. The recommended regulatory action is Complete Response, and there was no dissent. I concur with the recommendation of the multidisciplinary review team. The deficiencies precluding approval and the recommended path forward are discussed below.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric growth hormone deficiency (GHD) is a well-characterized condition that may be idiopathic or secondary to congenital or acquired causes. • GHD results in inadequate circulating growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels which adversely affects linear growth and ultimately results in short stature. • Guidelines on the treatment of pediatric patients with GHD issued by professional societies (Growth Hormone Research 2000; Grimberg et al. 2016) recommend treating children with proven GHD with GH replacement therapy to normalize height during childhood and attain normal adult height.	• Pediatric GHD is a serious condition that, if not treated with GH replacement therapy, is associated with delayed growth and ultimately short final adult height. • Treatment with hGH is a replacement therapy that mimics the action of endogenous GH leading to an increase in IGF-1 levels, improvement of linear growth and final adult height.
Current Treatment Options	• Multiple human growth hormone (hGH; somatropin) products are Food and Drug Administration (FDA)-approved for the treatment of short stature associated with pediatric GHD and on the U.S. market. Most approved hGH products require daily or every other day injections via the subcutaneous (SC) route. A long-acting hGH (lonapegsomatropin) was recently approved for weekly SC injection. • Per current labeling, immunogenicity observed for approved products ranges from 0 to 6.3%.	• Multiple hGH products (short- and long-acting) are available for the treatment of pediatric GHD, including a recently approved long-acting GH therapy that requires once weekly injections (lonapegsomatropin-tcgd). • Immunogenicity is not an important risk with the available GH products.

Benefit	• The first approved hGH formulations were studied in clinical trials until final adult height was achieved and demonstrated that improved annualized height velocity (AHV) was sustained over the years of treatment and ultimately improved/normalized final adult height.
	• AHV at Week 52 was the primary endpoint in Trial CP-4-006. The effect of somatrogon on AHV at the end of 12-month treatment was noninferior to the effect of Genotropin (somatropin daily injection): the mean treatment difference between somatrogon and Genotropin was 0.34 cm/year (95% confidence interval -0.23, 0.91). Somatrogon was not superior to Genotropin (lower limit of 95% confidence interval was less than zero).
	• Similar changes in increase of mean height standard deviation score (HT SDS) at 12 months were observed in somatrogon and Genotropin groups: 0.91 and 0.86, respectively.
	• The proportion of subjects who underwent dose reduction during Study CP-4-006 was higher in the somatrogon group (24/109 subjects) than in the Genotropin group (9/105 subjects). Of the 24 subjects in somatrogon group, 12 had a dose according to pre-specified criteria of 2 consecutive measurements of IGF-1 SDS >2. Dose reductions were temporary, except for 3 subjects whose changes were close to the end of the study. The IGF-1 SDS levels decreased in all subjects following dose reduction. There were 5 subjects in the somatrogon group and 2 in the Genotropin group who had dose reductions due to adverse events and not related to IGF-1.
	• Confirmatory evidence consists of data from the 12-month main period of Trial CP-4-004. Changes in AHV and height SDS at the end of 12-month treatment in somatrogon 0.66 mg/kg group were similar to changes in growth parameters observed in trial CP-4-006:
	  ○ mean AHV was 11.4 cm/year
	  ○ mean change in height SDS was 1.35
	• A high and persistent incidence of antidrug antibodies (ADA) was observed in subjects treated with somatrogon compared to those treated with
		• FDA has accepted one-year changes in AHV that are noninferior to the active comparator (approved hGH with known effect on AHV) to support benefit of products with a native GH sequence for the treatment of short stature in pediatric patients with GHD.
		• An observed improvement in somatrogon-induced AHV at 52 weeks consistent with 12-month AHV seen with other hGH products suggests the benefit on final height of somatrogon may be similar to other available hGH therapies.
		• The cause of high immunogenicity and variability across studies remains unknown to date.
		• Given the formulation of NAbs and the concerning reduction in AHV in one subject with neutralizing antibodies, there is concern that ADA may adversely impact longer-term efficacy and final adult height.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Genotropin (see Risk summary below). A total of 5 subjects in the somatrogon group in Trial CP-4-006 developed neutralizing antibodies. Long-term efficacy data are limited: • Data beyond 12 months of treatment are uncontrolled in both trials. • Only 4 subjects were treated with somatrogon dose 0.66 mg/kg/week for up to 7 years in Trial CP-4-004. In addition, long-term data from this trial is confounded by various exposure to somatrogon, previous treatment with Genotropin and use of different delivery systems (vial versus pen injector). • Of 5 subjects with neutralizing antibodies, one subject had a significant reduction in AHV from 11.8 cm/year (at Month 12) to 3.0 cm/year (at Month 18). • No subjects reached final adult height up to the data lock date (12/21/2020) of the development program. • The etiology of the high immunogenicity with somatrogon is unclear, but one hypothesis that was explored was that immunogenicity was product presentation-dependent: the incidence of ADA was up to 77% with use of pen injector in Trial CP-4-006 compared to up to 36% observed with use of vial/syringes (in Trial CP-4-004). However, no CMC attributes could be identified that would explain higher immunogenicity with the pen.	
Risk and Risk Management	• No new safety signals were identified during the 12-month treatment with somatrogon in trials CP-4-006 and CP-4-004 followed by uncontrolled periods of these trials in a small number of subjects. • The most common (≥5%) adverse events (AEs) that occurred with higher frequency in the somatrogon group compared to Genotropin group were local administration reactions (43% versus 25 %), followed by nasopharyngitis (33% versus 29%) and pyrexia (17% versus 15%), respectively. • AEs of hypoadrenalism were observed in 4 subjects treated with somatrogon. No adrenal crisis was reported. • No AEs of hypothyroidism, pancreatitis, intracranial hypertension, slipped capital	• The safety of 12-month treatment with somatrogon was consistent with the known safety profile of hGH products, including injection site reactions, nasopharyngitis, rhinitis and pyrexia. However, an imbalance in AEs of injection site reactions between treatment groups was noted: 43% (somatrogon) versus 25% (Genotropin). There was no evidence that this difference was caused by immunogenicity. • Potential risks of tumorigenesis, intracranial hypertension, slipped capital epiphysis, pancreatitis are expected for the rhGH class of drugs and can be mitigated through the labeling. Like other drugs in the class, somatrogon should be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	femoral epiphysis or increase in tumorigenesis was reported with somatrogon treatment. • Non-serious hypersensitivity reactions were observed in 18/109 (16%) of somatrogon-treated subjects compared to 11/115 (10%) in the Genotropin group. All reactions resolved without drug discontinuation. No anaphylactic or Stevens-Jonson syndrome occurred in the clinical program. • Chronically elevated IGF-1 levels above the normal range are associated with potential risk for various AEs including headache, intracranial hypertension, edema, and tumors. In Trial CP-4-006, 24% of somatrogon-treated subjects had IGF-1 >2 SDS compared to 3% of Genotropin subjects. All elevated IGF-1 levels were not associated with symptoms and normalized either spontaneously or following a dose reduction. • There were no differences in frequency or severity of observed AEs between ADA-positive and ADA-negative subjects treated with somatrogon for 12 months in Trial CP-4-006. In the somatrogon group the number of subjects with any AE was 75/84 (89%) and 20/25 (80%) in ADA-positive and ADA-negative subjects, respectively; in the Genotropin group, 16/18 (89%) subjects with any AEs were ADA-positive and 81/97 (84%) subjects were ADA-negatives. The incidence of AEs by ADA titer in the somatrogon group was 14/17 (82%) with titer of 0, 10/10 (100%) with titer of 10, 21/25 (84%) with titer of 50, 25/29 (86%) with titer of 250, 16/19 (84%) with titer of 1250, and 9/9 (100%) with titer of >6250. Approximately 50% (49/109) of the subjects treated with somatrogon had ADA titers of 50 or 250. However, the incidence of AEs did not appear to be directly related to the ADA titer. • A total of 11 individuals in the clinical program had positive anti-carboxy terminal peptide (CTP) antibodies. The potential risks of anti-CTP antibodies are interference with diagnostic tests and risk of adverse outcomes of fertility and pregnancy.	contraindicated in patients with active malignancies. • No severe hypersensitivity reactions were noted. • No impact of ADA on IGF levels was observed in clinical program to date and no potential IGF-related AEs were observed in clinical program. IGF-1-related AEs and levels of IGF-1 that are associated with these AEs is a monitorable risk. The risk can be mitigated by the monitoring for AEs, recommendations to obtain IGF-1 levels and dose adjustments if the levels are increased above normal range. • Overall, the risk of anti-CTP antibodies on incorrect on pregnancy tests is low. • Drug labeling may be adequate to mitigate the risks of the potential impact of anti-CTP antibodies on performance of hCG-based tests.

2.2. Conclusions Regarding Benefit-Risk

There are multiple available formulations of hGH to treat pediatric GHD. Although most are injected daily, a weekly formulation was recently approved. A weekly formulation may be a more convenient and comfortable option for patients, particularly for children. All approved products effectively increase annual growth velocity and ultimately final adult height in children with PGD. The products have a well-characterized safety profile and low rates of immunogenicity.

Somatrogon increased annualized growth velocity (AGV) at the end of a 12-month treatment period and was shown to be non-inferior to Genotropin, although not superior to Genotropin. Generally, this efficacy finding in a new hGH formulation could support the benefit of the product for the proposed indication. However, reliance on one-year data presupposes the absence of factors, such as immunogenicity, that may offset growth and affect final adult height. The immunogenicity of somatrogon is unusually high; the data included in BLA demonstrated that treatment with somatrogon was associated with a high and persistent incidence of antidrug antibodies (ADA) compared to Genotropin. Furthermore, nearly all (76%) ADA-positive subjects had persistent antibodies in the somatrogon group versus 5% of ADA-positive subjects in Genotropin group. Concerningly, five subjects developed neutralizing antibodies; one of these had unexplained growth attenuation. There is also concern for patients who are treated with somatrogon and later prescribed alternative hGH treatment. If these patients develop persistent neutralizing antibodies while being treated with somatrogon, other hGH products may be rendered ineffective when they are treated later.

The 12-month safety profile of somatrogon was generally consistent with the drug class. The presence of antibodies was not associated with higher rates of adverse events, including hypersensitivity, compared to Genotropin during the one-year randomized period.

Unfortunately, there is no clear understanding why the drug is associated with unusually high immunogenicity. Immunogenicity may be device-dependent (the majority of subjects who were treated with the pen injector developed ADA) and potentially dose-dependent (0.66 mg/kg dose was associated with the highest immunogenicity rate). However, chemistry, manufacturing, and control data provided did not reveal any factors that may be device related.

Based upon review of all available efficacy data, including data submitted in a major amendment, the benefits of somatrogon do not outweigh the risks. There are other hGH products with low immunogenicity and well-characterized efficacy in the US market, including a once-weekly formulation. The unusually high immunogenicity raises uncertainty about efficacy that is not a concern with the approved hGH products.

Lastly, Office of Pharmaceutical Quality (OPQ) identified multiple deficiencies associated with quality of the product (refer to Section 9 for details and to OPQ review from 1/20/2022 in DARRTS). Satisfactory resolution of these deficiencies is required before this application may be approved.

Comments for the Applicant:

In Trial CP-4-006, AHV at 12 months was noninferior to Genotropin, although not superior. However, there was a high rate of anti-drug antibody formation (ADA) due to somatrogon exposure in clinical studies versus the active comparator (Genotropin): In trial CP-4-006, 77% of

Somatrogon-treated subjects were ADA-positive compared to 16% of Genotropin-treated subjects. 76% of ADA-positive subjects had persistent (> 6 months) antibodies in somatrogon group versus 5% of ADA-positive subjects in the Genotropin group. Five subjects in Trial CP-4-006 developed neutralizing antibodies, and one of those subjects had a concerning reduction in AHV from 11.8 cm/year (at Month 12 to 3.0 cm/year (at Month 18). There are insufficient follow up data to determine whether or not the reduction in AHV in this patient was caused by immunogenicity, and we consider attenuation of effectiveness due to immunogenicity to be a potential risk at this time. Because of the homology in amino acid sequence among somatrogon, native growth hormone, and other recombinant hGH products, there is concern that antibodies that are cross reactive to other growth hormone products could develop. If persistent these could potentially result in non-responsiveness to other hGH replacement therapy. Given the availability of other hGH replacement therapies that have similar efficacy and that do not carry this risk, somatrogon does not appear to address any identifiable unmet need that would justify its approval in light of this uncertainty, and we have concluded that the benefit – risk profile for somatrogon is unfavorable at this time.

Information Needed to Address These Deficiencies:

Provide reassurance that the anti-drug antibody (ADA) formation caused by somatrogon is not expected to have an impact on long-term growth achieved with both somatrogon and does not interfere with other hGH formulations. At a minimum, provide data to show that ADA (including neutralizing antibodies) meaningfully decrease or resolve with somatrogon discontinuation and/or changing patients to other approved hGH formulations. If neutralizing antibodies do not resolve, provide data that long-term growth is not impacted. Provide mitigation strategies to address the potential impact of neutralizing antibodies.

II. Interdisciplinary Assessment

3. Introduction

On November 30, 2020, Pfizer submitted a Biologics License Application (BLA) for somatrogon (also known as MOD-4023), a long-acting human growth hormone (hGH) derivative, under Section 351(a) of the Public Health Service Act with the following proposed indication: Treatment of pediatric subjects who have growth failure due to growth hormone deficiency.

Somatrogon is a drug-device combination product intended to be marketed as disposable prefilled pen injector. Somatrogon drug product is hGH modified by the fusion of one copy of carboxy-terminal peptide (CTP) of human chorionic gonadotropin at the amino terminus of hGH and two CTP copies in tandem at its carboxy terminus. Fusion of the CTP peptides to hGH and a high level of glycosylation extend the half-life of this fusion protein to allow for weekly injection administration.

Pediatric growth hormone deficiency (GHD) is a well-characterized condition that results from insufficient production of growth hormone (GH) by the somatotroph cells of the anterior pituitary gland. Pediatric GHD can be idiopathic or secondary to congenital causes (e.g., pituitary hypoplasia, empty cells, various genetic disorders) or acquired causes (e.g., trauma,

infection, tumors). Pediatric GHD is characterized by inadequate circulating GH and insulin-like growth factor-1 (IGF-1) levels and results in delayed growth and short stature in children with open epiphyses.

Treatment with hGH (somatropin) therapy is the standard of care for the treatment of short stature due to pediatric GHD. Exogenous hGH treatment aims at mimicking the function of GH secretion (i.e., a replacement therapy), leading to normalization of IGF-1 levels and improvement in linear growth and final adult height. Guidelines on the treatment of pediatric subjects with GHD issued by professional societies (Growth Hormone Research 2000; Grimberg et al. 2016) recommend treating pediatric subjects with confirmed GHD to normalize height during childhood and to attain normal adult height. Treatment of pediatric GHD with hGH should be discontinued once the epiphyses are closed, and subjects should be re-evaluated for GHD at that time. Depending on the etiology, GHD may or may not persist into adult life and the objectives of GH treatment in adults are different from those in children.

Currently, multiple hGH therapies are approved by the Food and Drug Administration (FDA) for the treatment of pediatric GHD, most of which require daily subcutaneous injections. A long-acting formulation (lonapegsomatropin) that allows for weekly injections was more recently approved on August 25, 2021.[1] These hGH formulations have a native GH sequence and have been approved based on the improvement in height velocity and/or change in height SDS, since long-term studies with the earlier formulations of hGH also demonstrated that improvement in AHV translates into the improvement in final adult height (e.g., Humatrope up to 8 years). Therefore, the Agency accepted AHV as an objective primary efficacy endpoint in short-term studies (1 year) evaluating efficacy of hGH formulations with native GH sequence in pediatric patients with delayed proportional growth in the specific settings of hormone deficiency, i.e., GHD.

The safety profile of hGH is generally well-characterized and adverse reactions include hypothyroidism, glucose intolerance, slipped capital femoral epiphysis, scoliosis, fluid retention, arthralgia, carpal tunnel syndrome, myalgia, risk of neoplasm, intracranial hypertension, and immunogenicity.

Currently approved hGH products include short-acting (daily or every-other-day subcutaneous injections) and a long-acting (weekly subcutaneous injections) formulation. A long-acting formulation of hGH can potentially reduce discomfort and increase compliance by requiring less-frequent injections, an advantage particularly in the pediatric population.

The Applicant included data from two clinical studies in the submitted BLA. Trial CP-4-006, a phase 3, 52-week, randomized, open-label, noninferiority study comparing the efficacy and safety of somatrogon to Genotropin in pediatric subjects with short stature due to GHD was submitted to support the efficacy and safety of somatrogon. Trial CP-4-004 was a phase 2 open-label, safety and dose-finding study comparing three doses of somatrogon with Genotropin in pediatric subjects with short stature due to GHD and was submitted as supportive data. The Applicant also included supportive long-term data from Trial CP-4-006 (second-year data) and from Trial CP-4-004 (up to 5 years).

[1] https://dailymed.nlm.nih.gov/dailymed/: FDA approved drug products

Following the original submission in 2020, on September 15, 2021, the Applicant submitted a Major Amendment that included additional immunogenicity data and additional 11-month data from the ongoing extension phases of phase 2 (Trial CP-4-004) and phase 3 (Trial CP-4-006) studies for a total of 238 subjects (spanning the period from the original data cut-off date of November 1, 2019 to December 21, 2020).

3.1. Review Issue List

The review team identified seven key review issues that had a significant impact on the overall benefit-risk determination of somatrogon. Some of these issues were identified prior to submission of the BLA, whereas others emerged during the BLA review.

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

- High Incidence and Persistence of Antidrug Antibodies in Somatrogon-Treated Subjects Observed in Clinical Program and Potential Effect on Efficacy
- Intended Population: children of All Ages With Epiphysis With GHD

3.1.2. Key Review Issues Relevant to Evaluation of Risk

- Higher Incidence of Adverse Events of Injection Site Reactions in Somatrogon Group Compared to Genotropin Group in Trial CP-4-006
- Elevated IGF-1 Level and Potential Risk of IGF-1-Related Adverse Reactions
- Potential Safety Issues Associated With High Incidence of ADA in the Clinical Program
- Risks Associated With the Presence of Anti-CTP Antibodies

3.2. Approach to the Review

Table 3 provides an overview of the clinical trials reviewed to evaluate the benefit and risk of somatrogon. Trial CP-4-006, was a Phase 3, randomized, active-controlled, open-label, 52-week study comparing the efficacy and safety of somatrogon to Genotropin. This trial was the primary source of the evidence for efficacy. FDA has accepted a single adequate and well-controlled study plus confirmatory evidence to support the approval of hGH products with a native GH sequence proposed indication consisting of data providing strong mechanistic support for the approval of hGH products with a native GH sequence to support the pediatric GHD indication. Given that pediatric GHD is a rare disease and there have been multiple hGH products approved on the basis, in pediatric GHD, somatrogon is intended to replace a deficient native hormone—human growth hormone (hGH). The Applicant has provided data demonstrating that the active moiety of somatrogon has the same primary amino acid sequence as native hGH and thus is expected to have the same action at the target receptor as native hGH. The structure-function relationship of endogenous GH is well-understood; the wide variety of GH biological effects is mediated by one mechanism of action, i.e., GH binding to and activation of GHR with subsequent transcription of genes encoding a variety of proteins, including IGF-1. No alternative receptors mediating GH activity have been identified. GH and IGF-1 stimulate epiphyseal growth plates and formation of new bone, resulting in linear growth until fusion of growth plates.

Therefore, there is a strong mechanistic understanding of how hGH exerts its effect in patients with growth hormone deficiency.

FDA has accepted short-term changes in AHV that are noninferior to the active comparator (approved hGH with a known effect on AHV) as a surrogate endpoint to evaluate the efficacy of products with a native GH sequence for the treatment of short stature in pediatric patients with GHD. Similar to other hGH clinical programs in pediatric GHD, improvement in AHV at 12 months was agreed upon during the development program of somatrogon as an acceptable surrogate endpoint to establish clinical benefit of somatrogon therapy in patients with short stature due to GHD. Agreement about long term data required at the time of BLA submission included open-label extension studies of both trial CP-4-006 and trial CP-4-004. No concerns about high immunogenicity with somatrogon were discussed during or prior the pre-BLA meeting.

Additional growth data were provided by a phase 2, 12-month dose finding study (Trial CP-4-004) in children with GHD in the same age group as CP-4-006. Trial CP-4-004 provided confirmatory evidence of effectiveness and safety of somatrogon compared to Genotropin.

Both studies (CP-4-006 and CP-4-004) had a long-term extension phase. However, long-term extension studies were open-label, single-arm studies, and lacked a control group. There was no prespecified testing for efficacy endpoints and the studies were purely descriptive. Thus, the information was considered supportive.

The review of clinical safety considered all data from both Trial CP-4-006 and Trial CP-4-004 using somatrogon.

Given the uncertainty regarding the immunogenicity data contained in the original BLA, the review team requested that the Applicant clarify whether additional immunogenicity data were available that were not part of the original submission. The Applicant submitted new immunogenicity information, which was coded as a major amendment, extending the review clock by 3 months.

Table 3. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations for Somatrogon

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration (Quantity and Units)	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-006 (main)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: Active concurrent noninferiority Randomization: Stratified randomization Blinding: Open-label	Somatrogon 0.66 mg/kg/wk[2] Number treated:109 SC Injection Q1W × 12 months Genotropin 0.034 mg/kg/day Number treated: 115 SC injection QD × 12 months	Primary: Annual HV in cm/year after 12 months of treatment Secondary: Annualized HV after 6 months of treatment Change in height SDS at 6 and 12 months, compared to baseline Change in bone maturation at the end of 12 months, compared to screening bone age (calculated as bone age/chronological age)	Planned: 220 Actual: 228	Centers: 157 Countries: 24
CP-4-006 (OLE)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: No treatment concurrent (single-arm) Randomization: No randomization (single-arm) Blinding: Open-label	Somatrogon 0.66 mg/kg/wk Number treated: 109 SC Injection Q1W (on-going)	Primary: Annual HV in cm/year after 12 months of treatment Secondary: Annualized HV after 6 months of treatment	Actual: 212	Centers: 157 Countries: 24

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration (Quantity and Units)	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-004 (main)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: Active concurrent noninferiority Randomization: Stratified randomization Blinding: Open-label	Somatrogon 0.25 mg/kg/wk Number treated: 13 SC Injection Q1W × 12 months Somatrogon 0.48 mg/kg/wk Number treated: 15 SC injection Q1W × 12 months Somatrogon 0.66 mg/kg/wk Number treated: 14 SC Injection Q1W x 12 months Genotropin 0.034 mg/kg/day Number treated: 11 SC injection QD × 12 months	Primary: Annual HV in cm/year after 12 months of treatment Secondary: HV after 6 months, change in HT SDS at 6 months, change in HT SDS at 12 months	Actual: 53	Centers: 14 Countries: 7

Trial Identifier	Trial Population	Trial Design	Drug, Dose, Number Treated, Duration (Quantity and Units)	Primary and Key Secondary Endpoints	Number of Subjects Randomized	Number of Trial Sites
CP-4-004 (OLE)	Prepubertal, growth hormone treatment-naïve children with a verified diagnosis of GHD	Control type: No-treatment concurrent (single-arm) Randomization: Genotropin population randomized to 0.25, 0.48, or 0.66 mg/kg/wk somatrogon; subjects already on somatrogon continued dose from main study Blinding: Open-label	Period III Somatrogon 0.25 mg/kg/wk Number treated: 16 SC Injection Q1W × 12 months Somatrogon 0.48 mg/kg/wk Number treated: 17 SC Injection Q1W × 12 months Somatrogon 0.66 mg/kg/wk Number treated: 15 SC injection Q1W × 12 months Period IV Somatrogon 0.66 mg/kg/wk Number treated: 44 SC Injection Q1W × 12 months Period V (PEN Year 1) Somatrogon 0.66 mg/kg/wk Number treated: 40 SC Injection Q1W × 12 months Period V (PEN Year 2) Somatrogon 0.66 mg/kg/wk Number treated: 35 SC injection Q1W × 12 months (ongoing)	Primary: Annual HV in cm/year after 12 months of treatment Secondary: HV after 6 months, Change in HTSDS at 6 months, change in HTSDS at 12 months	Period III Actual: 48 Period IV Actual: 44 Period V Actual: 40	Centers: 13 Countries: 7

Source: Clinical Study Report and adsl.xpt. and information provided in the Major Amendment (isi-supplement.pdf

[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2]This starting dose was to be reduced by 15% in subjects with two consecutive measurements of insulin growth factor-1 (IGF-1) levels above 2 standard deviation score (SDS), and IGF-1 was to continue being monitored for further dose reductions.
Abbreviations: GHD, growth hormone deficiency; HT SDS, height standard deviation score; HV, height velocity; LTE, long-term extension study; N, number of subjects; Q1W, once weekly; QD, once daily; SC, subcutaneous

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	Section 19
☒	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
	Other: (please specify): User Manual for clinical outcome assessments (Quality of Life in Short Stature Youth)	
☐	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

This BLA is acceptable from a clinical pharmacology perspective.

Table 5. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Human growth hormone (hGH) analog
Mechanism of action	Binds to growth hormone (GH) receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Some of these pharmacodynamic effects are primarily mediated by insulin-like growth factor I (IGF-I) produced in the liver.
Active moieties	Somatrogon
QT prolongation	Neither thorough QT prolongation study nor concentration-QT analyses was conducted. Electrocardiogram at predose and approximate time to maximum concentration (T_{max}) were assessed in the phase 2 dose-finding (Trial CP-4-004) and phase 3 (Trial CP-4-006) studies. In Trial CP-4-004, no QTc abnormalities were reported in either main or open-label extension periods. In Trial CP-4-006, there were four subjects with a QTcF interval >450 ms (2 in each treatment arm). None was clinically significant, and no changes in ECG were reported during the open-label extension (OLE) period of Trial CP-4-006.
	General Information
Bioanalysis	Over the duration of the somatrogon clinical development program, three pharmacokinetic (PK) assays were used (an enzyme-linked immunosorbent assay (ELISA) and an electrochemiluminescent (ECL) assay developed and validated at (b) (4) plus an ECL assay established and validated at (b) (4) The PK ECL assay at (b) (4) is identical to the PK ECL assay at (b) (4). The ELISA has a sandwich format using anti-hGH monoclonal antibody as capture and biotinylated rabbit anti-carboxy-terminal peptide (CTP) polyclonal antibody followed by streptavidin-horseradish peroxidase as detection. Both ECL assays have a sandwich format using anti-hGH monoclonal antibody as capture and Sulfo-Tag anti-CTP polyclonal antibody as detection. Validation of the PK assays and performance of these assays during sample runs were acceptable.
Healthy subjects versus patients	• In adult healthy subjects, following a single subcutaneous injection of 21 mg (0.3 mg/kg for a 70 kg adult), somatrogon concentrations reached maximum of 268.6±111.9 (mean±standard deviation [SD]) ng/mL around 12 [6-12] (median [range]) hours and decreased with an elimination half-life of 23.6±4.8 (mean±SD) hours. • In pediatric patients with growth hormone deficiency (GHD) weighing 8 to 46 kg, following subcutaneous injection of 0.66 mg/kg/week, the population PK predicted steady-state maximum concentration of 500±89 (mean±SD) ng/mL, T_{max} of 11 (6-25) (median [range]) hours and an effective half-life of 30.1±1.5 (mean±SD) hours.

Characteristic	Drug Information
Range of effective dosage(s) or exposure	The only somatrogon dose level tested in the phase 3 study was 0.66 mg/kg/week.
Maximally tolerated dosage or exposure	The highest dose tested in pediatric patients with GHD was 0.66 mg/kg/week.
Dosage proportionality	In pediatric patients with GHD, somatrogon exposure increases in a dose proportional manner for doses of 0.25, 0.48, and 0.66 mg/kg/week.
Accumulation	There is no accumulation of somatrogon after once weekly administration.
Time to achieve steady-state	Steady state is achieved with the first dose because there is no drug accumulation with once weekly dosing
Bridge between to-be-marketed and clinical trial formulations	Not applicable; to-be-marketed formulation was used in the phase 3 study
	Absorption
Bioavailability	Absolute bioavailability after subcutaneous administration of somatrogon was not determined.
T_{max}	Median (minimum, maximum): 11 (6, 25) hours.
Food effect (fed/fasted); geometric least-square mean and 90% confidence interval	Not applicable
	Distribution
Volume of distribution	In pediatric patients with GHD weighing 8 to 46 kg, the mean±SD of individual predicted apparent central volume of distribution was 5.83±4.72 L and apparent peripheral volume of distribution was 10.89±6.59 L.
Plasma protein binding	Not assessed
Drug as substrate of transporters	No studies were conducted. Somatrogon consists of 275 amino acids and the theoretical molecular mass (average) of the predominant O-linked glycoforms is ~40 kDa. Somatrogon is not expected to be a substrate for transporters due to its size.
	Elimination
Mass balance results	Not assessed.
Clearance	In pediatric patients with GHD weighing 8 to 46 kg, the mean±SD of individual predicted apparent clearance was 0.67±0.30 L/hour.
Half-life	With a mean population PK estimated effective half-life of 30.1 hours, somatrogon will be present in the circulation for about 6 days after the last dose.
Metabolic pathway(s)	Protease-mediated catabolism
Primary excretion pathways (% dosage)	Not evaluated; however, expected to be primarily into urine after catabolism

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Based on population PK, body weight had a significant effect on clearance after oral administration. Based on simulation, the dose of 0.66 mg/kg/week should provide comparable exposures over the anticipated weight range of potential patients (8-52 kg).
Age	Age was not a clinically relevant covariate for somatrogon PK based on population PK analysis.
Renal impairment	Subjects with renal impairment were excluded from enrolling in either of the pediatric clinical studies and so no information about the requirement for alteration in dosing for children with both GHD and renal impairment can be made.
Hepatic impairment	As a therapeutic protein, somatrogon is expected to be degraded by non-specific proteases and therefore hepatic impairment study was not conducted.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	Not applicable.
Inhibition/induction of transporter systems	Not applicable.
	Immunogenicity (if Applicable)
Bioanalysis	Per the Office of Biotechnology Products reviewers, immunogenicity assays were validated for semiquantitative measurement of antidrug antibodies (ADA), including assays for anti-somatrogon binding antibodies, anti-somatrogon neutralizing antibodies, anti-hGH binding antibodies, and anti-hGH neutralizing antibodies.
Incidence	In the phase 3 safety and efficacy study, among 109 patients treated with somatrogon, 84 (77.1%) tested positive for ADA.
Impact on PK/PD	The mean clearance of somatrogon decreases ~26% after patients developed ADA. The increase in exposure in ADA-positive subjects did not appear to affect the IGF-1 response.

Source: created by reviewer

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology of Somatrogon (MOD-4023)

Somatrogon is a human growth hormone analog comprised of the amino acid sequence of human growth hormone fused with one copy of the carboxy-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP (in tandem) at the C-terminus. Fusion of CTP to hGH extends the half-life and activity of the peptide in vivo and allows for once weekly subcutaneous administration. Somatrogon showed comparable binding affinity and receptor activation when tested with GHRs from humans, rats, and rhesus monkeys (see Table 6), which underscores the pharmacological relevance of the species used in nonclinical evaluations. However, potentially owing to the fused CTP domains, somatrogon bound more weakly than recombinant human growth hormone and higher levels of somatrogon were required to generate a half-maximal response in those assays.

GH regulates changes in growth and metabolism by initiating a signaling cascade that leads to increases in plasma levels of insulin-like growth factor-1 (IGF-1). Evidence suggests that STAT5b phosphorylation may be part of the signaling cascade involved in IGF-1 production (Rosenfeld and Hwa 2009). When human embryonic kidney (HEK) 293 cells expressing the hGH receptor were exposed to either somatrogon or recombinant human growth hormone, an increase in phosphorylation of STAT5b was observed. In general, these findings support the hypothesis that somatrogon has the same mode of action as GH but binds to the GH receptor with reduced affinity compared to that of recombinant human growth hormone.

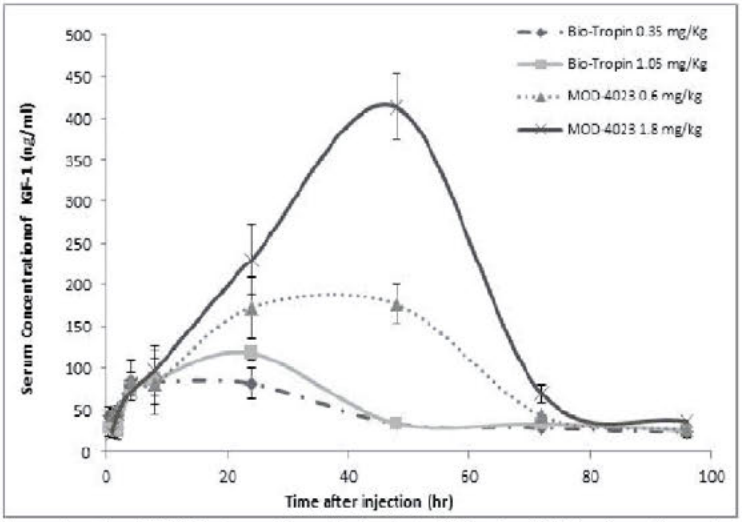
Table 6. In Vitro Pharmacology of Somatrogon Versus Recombinant Human Growth Hormone

Pharmacological Endpoint	Somatrogon (Protein content)[c]	Bio-Tropin®
Binding to hGHR[a]	K_d = 18.46 ± 11.55 nM	K_d = 0.55 ± 0.24 nM
Binding to rat GHR	K_d = 6.57 ± 0.64 nM	K_d = 0.54 ± 0.19 nM
Binding to hGHR[b]	K_d = 7.39 ± 5.23 nM	K_d = 0.91 ± 0.79 nM
Binding to rhesus monkey GHR	K_d = 13.15 ± 7.92 nM	K_d = 2.09 ± 1.33 nM
Proliferation of BAFB2B2 cells[d]	EC_{50} = 15.8 ± 2.0 ng/mL	EC_{50} = 0.36 ± 0.06 ng/mL
Inhibition of proliferation by rhGHR	IC_{50}= 29.9 ± 7.2 ng/mL	NT
Inhibition of proliferation by recombinant rat GHR	IC_{50} = 26.5 ± 4.7 ng/mL	NT
Proliferation of BAFB2B2 cells[d]	EC_{50}= 12.2 ± 2.4 ng/mL	EC_{50} = 0.37 ± 0.06 ng/mL
Inhibition of proliferation by rhGHR	IC_{50} = 67.3 ± 13.2 ng/mL	IC_{50} = 3.74 ± 1.68 ng/mL
Inhibition of proliferation by recombinant rhesus monkey GHR	IC_{50} = 212.6 ± 25.4 ng/mL	IC_{50} = 13.62 ± 5.97 ng/mL
STAT5b Phosphorylation in HEK293 cells	Somatrogon-mediated phosphorylation required higher concentrations than Bio-Tropin®-meditated phosphorylation to produce similar effect	
GH-mediated gene regulation	Somatrogon dose-dependent luciferase response. Somatrogon exhibits lower luciferase activity relative to Bio-Tropin® at similar doses, using the same mechanism of action (MOA).	

Source: Modified from the Nonclinical Overview (Table 2.4.2-1).
Bio-Tropin: Recombinant Human Growth Hormone
[a] Assay was repeated in 3 independent runs;
[b] Assay was repeated in 9 or 11 independent runs for Bio-Tropin® and Somatrogon respectively;
[c] Somatrogon concentrations refer to protein concentrations, excluding mass contr bution of O-linked glycans;
[d] BAFB2B is a murine cell line made up of Baf-3 cells stably transfected and highly expressing the hGHR
Abbreviations: EC_{50}, 50% effective concentration; K_d, dissociation constant; GH, growth hormone; hGHR, human growth hormone receptor; HEK293, human embryonic kidney 293 cells; NT, not tested; rhGHR, recombinant human growth hormone receptor; IC_{50}, 50% inh bitory concentration.

Somatrogon was evaluated in hypophysectomized rats. Following subcutaneous administration of a single dose or repeated doses of somatrogon every 4 days for 12 days, or every 7 days for 14 days, a dose-dependent increase in body weight gain was observed. Body weight gain in rats administered 0.48 mg/kg somatrogon every 4 days was similar to that seen with daily administration of 0.1 mg/kg recombinant human growth hormone. A single subcutaneous injection of somatrogon (0.6 or 1.8 mg/kg) produced higher levels of circulating human growth hormone (somatrogon) and IGF-1 levels when compared to a single subcutaneous administration of recombinant human growth hormone (0.35 or 1.05 mg/kg), consistent with its significantly longer half-life.

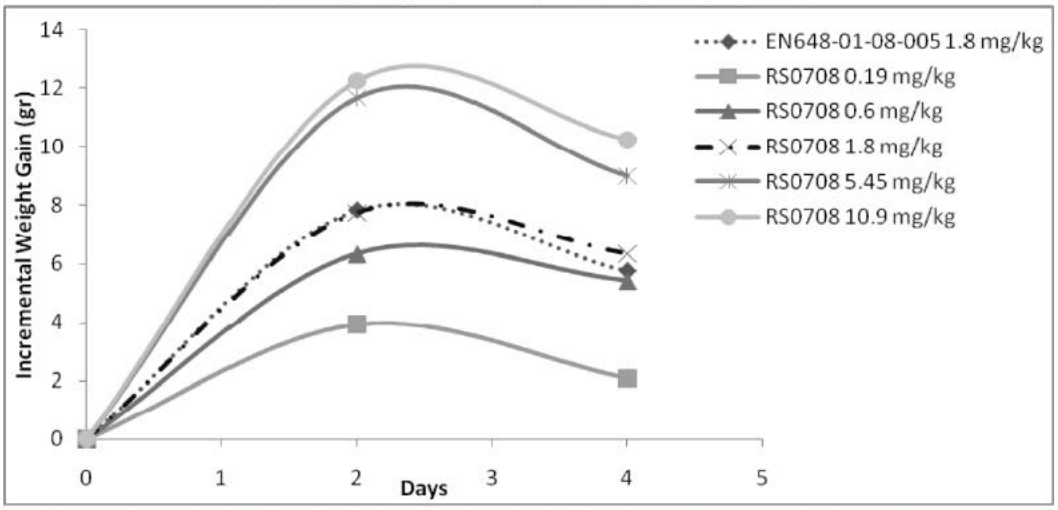
Figure 1. IGF-1 Serum Concentrations in Hypophysectomized Sprague-Dawley Rats After a Single Subcutaneous Administration of Somatrogon (MOD-4023) or Recombinant Human Growth Hormone



Serum levels of IGF-1 in hypophysectimized rats following SC injection of somatrogon and Bio-Tropin®. Data presented as average ± standard deviation, each point an average of n = 9/dose Bio-Tropin® or n = 12/dose MOD-4023 (somatrogon). Somatrogon concentrations listed are for the protein content of the test article. IGF-1 = Insulin-like growth factor-1; n = Number of subjects (rats); SC = Subcutaneous. Study PF-06836922_02Oct15_161823, CD-04-0035.

Source: Copied from Applicant's submission (Study Reference Number: CD-04-0035, Figure 3).
Bio-Tropin: Recombinant Human Growth Hormone
Abbreviation: MOD-4023, somatrogon

Figure 2. Weight Gain in Hypophysectomized Sprague-Dawley Rats After a Single Subcutaneous Administration of Somatrogon (MOD-4023)



Source: Copied from Applicant's submission (Study Reference Number: CD-04-0035, Figure 1). EN648-01-08-005:MOD-4023 Lot #EN648-01-08-005 (Batch 1). RS0708: RS0708 (Batch 2).
Abbreviation: MOD-4023, somatrogon

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Dose Selection

The somatrogon weekly dose selection of 0.66 mg/kg in the registrational Trial CP-4-006 was based on dose-response and exposure-response analyses for efficacy, biomarker, and safety data from the phase 2 study (Trial CP-4-004) in pediatric subjects with GHD aged 3 to 11 years.

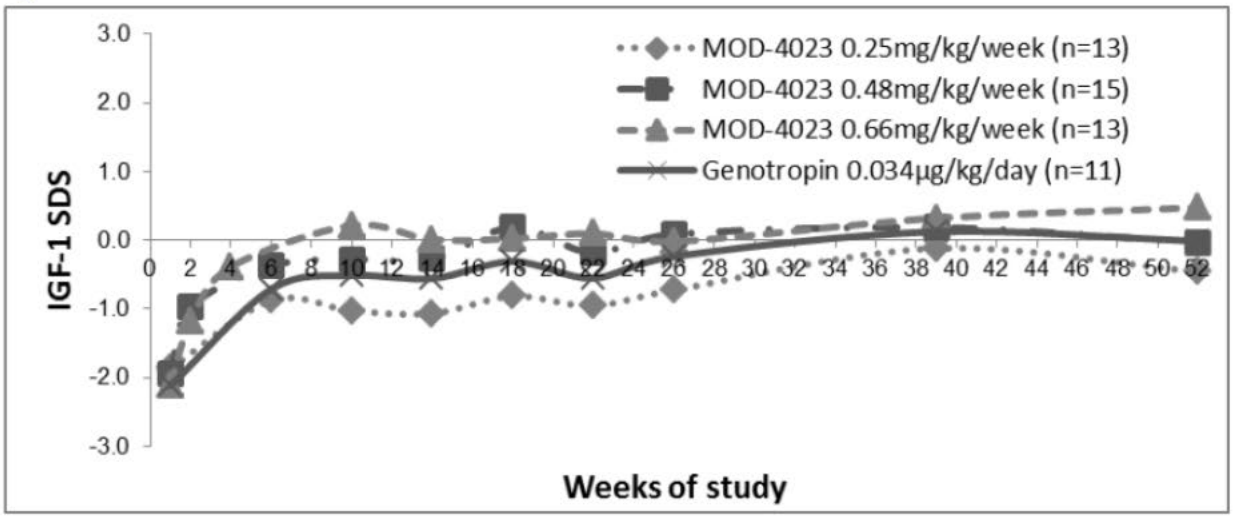
In Trial CP-4-004, somatrogon was administered weekly at 0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week (one dose per cohort) and compared to a cohort receiving daily 0.034 mg/kg dose of Genotropin. All somatrogon cohorts started at a 0.25 mg/kg/week dose and the dose was titrated up in the 0.48 mg/kg/week and 0.66 mg/kg/week cohorts during the first 6 months. At the end of the first 6-month period, an interim analysis was conducted to evaluate pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety of three doses compared to Genotropin. All dose levels were within the safety margin established in nonclinical toxicology studies. Efficacy was measured by height velocity at 12 months of treatment. As will be discussed in Section 6.2.1.4, the increase in AHV with somatrogon treatment was dose-dependent. The mean changes in AHV at 12-months were slightly higher in the high-dose cohorts (0.48 and 0.66 mg/kg/week) compared to the low-dose cohort (0.24 mg/kg/week). However, the differences in AHV between dose cohorts were small and it is unknown whether these small differences will result in differences in final adult height.

IGF-1 and IGF-1 standard deviation score (SDS) were monitored during the treatment for safety reasons, i.e., to safeguard against the risks associated with elevated IGF-1 levels, which include worsening of pre-existing tumors or development of new tumors.

In cohort 2 (0.48 mg/kg/week) and 3 (0.66 mg/kg/week), serum IGF-1 SDS peaked around 48 hours to a level beyond 0 and were within 2 SDS over 1 week. IGF-1 SDS for Cohort 1 (0.25 mg/kg/week) did not increase above 0 and dropped during the second part of the week and reached a suboptimal mean value (around -2 SDS) by Day 5.

Over 12 months, somatrogon provided an IGF-1 response within the normal range, reaching an optimal average value of 0 SDS in Cohorts 2 and 3 and not exceeding +2 SDS when testing on Day 3 or 4 postdosing (Figure 3). Somatrogon 0.48 and 0.66 mg/kg/week resulted in comparable IGF-1 SDS to that of Genotropin 0.034 mg/kg/day. Thus, somatrogon 0.66 mg/kg/week was selected for the phase 3 study (Trial CP-4-006) because, in terms of height increase (primary efficacy endpoint), 0.66 mg/kg/week was better than 0.25 and 0.48 mg/kg/week, and the closest to Genotropin 0.034 mg/kg/day (Table 7).

Figure 3. Mean IGF-1 SDS - 12-Month Trend



Source: Figure 8 of cp-4-004-report-body.pdf.
Abbreviations: IFG-1, insulin-like growth factor 1; MOD-4023, somatrogon; SDS, standard deviation score

Table 7. Height Velocity at 12-Month Visit by Cohort (cm/Year) (FAS Population; Periods I and II)

	MOD-4023			Genotropin
	Cohort 1 0.25 mg/kg/week N = 13	Cohort 2 0.48 mg/kg/week N = 15	Cohort 3 0.66 mg/kg/week N = 14*	Cohort 4 0.034 mg/kg/day N = 11
N	13	15	14	11
Mean (cm/year)	10.4	11.0	11.4	12.5
95% CI of Mean	(8.9, 12.0)	(9.7, 12.2)	(9.2, 13.7)	(11.0, 13.9)
SD	2.6	2.3	3.9	2.1
Range (cm/year)	(6.2, 14.4)	(6.5, 14.5)	(5.0, 18.3)	(9.2, 16.0)
Source Table 14.2.1.1				

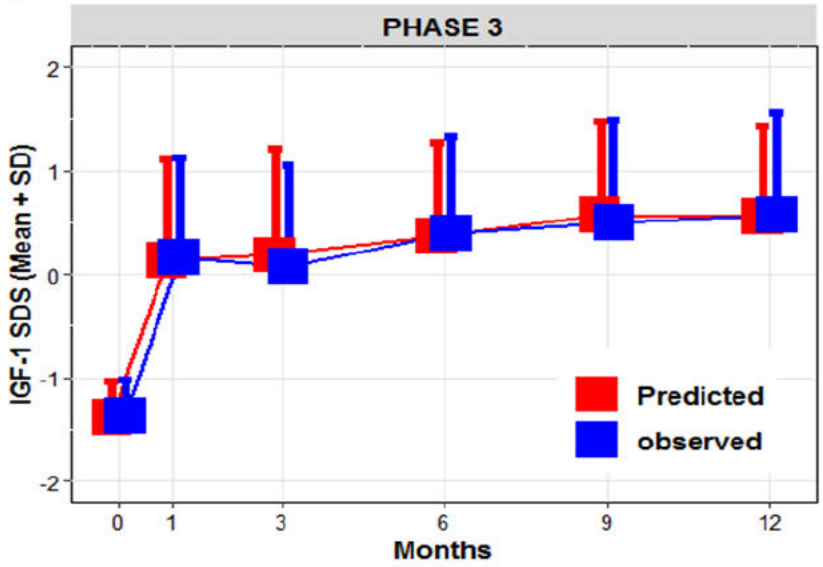
Source: Table 16 of cp-4-004-report-body.pdf.
* Cohort 3 lower level of height range attributable to Patient 08003, who was wrongly included in the study. The patient was diagnosed with psychosocial dwarfism (exclusionary condition) following study completion.
Abbreviations: CI, confidence interval; FAS, full analysis set; MOD-4023, somatrogon; SD, standard deviation

Exposure-Response Analysis From Trials CP-4-004 and CP-4-006

Based on Clinical Pharmacology team's analyses, body weight and ADA titer were identified as significant covariates for PK of somatrogon. Bodyweight based dosing strategy for somatrogon ensures comparable somatrogon exposure across all pediatric body weights. In addition to body weight, ADA titer was also a significant covariate on clearance. Prediction based on reviewer's PK/PD model indicated that ADA positive patients had higher probability of IGF-1 SDS ≥ 2 than ADA negative patients. However, there was no association between the probability of IGF-1 SDS ≥ 2 and ADA titer levels. The protocol allowed dose reduction for all subjects based on IGF-1 SDS > 2 values. Any increase in somatrogon exposure leading to increased IGF-1 levels will be addressed by monitoring IGF-1 SDS. No dose adjustment is needed based on ADA status.

Figure 4 compares observed versus predicted IGF-1 SDS at over 12 months in the phase 3 study and shows that the model adequately predicts IGF-1 SDS scores over time. It can be seen from the figure that IGF-1 SDS increases rapidly within 1 month of treatment and then continues to increase gradually to Month 6 and remains stable for the rest of the treatment.

Figure 4. Observed and Predicted IGF-1 SDS Overtime in the Phase 3 Study



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

IGF-1 SDS at 96 Hours is Representative of the Mean IGF-1 Response Over Weekly Dosing

The predicted data were used to determine the sampling time point at which IGF-1 concentration would be most correlated with the average weekly exposure. Predicted data showed that collection of samples 96 hours after dosing provided a good estimate of the mean IGF-1 SDS over the entire weekly dosing interval. Details of the simulation can be found in pharmacometrics review (appended).

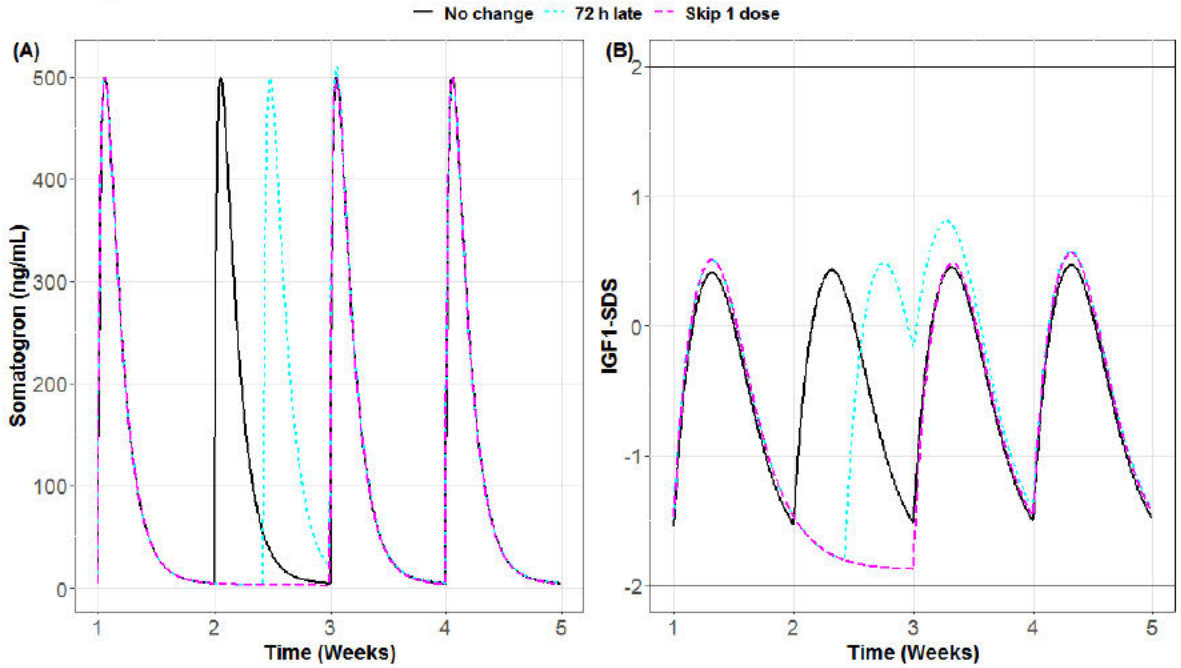
Impact of Dosing Delay or Dosing Advance on Somatrogon Exposures

Simulations were run to evaluate the impact of a missed or delayed dose on somatrogon exposures and IGF-1 in pharmacometrics review (appended)

If one dose is missed at the start of Week 2, the concentration of somatrogon will decrease, but is expected to be completely restored 1 week after the missed dose once the dose is given at the start of Week 3. The IGF-1 levels are also expected to decrease, but regular steady state profiles are expected to be restored 2 weeks after the missed dose (Figure 5).

If a dose is delayed by 3 days, slightly decreased peak concentrations are expected, whereas trough concentrations will be higher at the next scheduled dose compared to regular steady-state dosing. Two weeks after the delayed dose (during Week 4) the concentrations will be completely restored. The IGF-1 level is also expected to decrease to a lower trough value compared to steady-state dosing and the two subsequent peak values will be slightly lower and higher, respectively, compared to regular steady-state values. IGF-1 levels are restored following the dose in Week 4 (Figure 5).

Figure 5. Somatrogon and IGF-1 SDS Profiles Showing the Impact of Dose-Time Change at Week 2 on Steady State Maximum and Minimum Concentrations.



Source: Reviewer's independent analysis.
(A) Somatrogon (B) IGF-1 SDS
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

The simulation results support the following proposed labeling language regarding missing dose, which was also followed in the phase 3 protocol:

- If a dose is missed, administer TRADENAME as soon as possible within 3 days (b) (4) after the missed dose. If more than 3 days (b) (4) have passed, skip the missed dose and administer the next dose on the regularly scheduled day. (b) (4) (b) (4)

6.2. Clinical Trials Intended to Demonstrate Efficacy

6.2.1. Trial CP-4-006

The Applicant conducted one randomized, open-label, active-controlled phase 3 study for registrational purposes. Refer to Section 3.2 for the discussion on the acceptance of single adequate and well-controlled trial (plus confirmatory evidence) for the proposed indication. Trial CP-4-006 was a 12-month open-label, active-controlled study to compare the efficacy and safety of weekly somatrogon to daily Genotropin in prepubertal children with GHD, naïve-to-treatment with hGH. The trial design (randomized, active-controlled, noninferiority trial) and the duration (12 months) have been used to support approval of other hGH formulations for the same indication.

6.2.1.1. Design

The trial included a 12-week screening period followed by a 12-month main period. All subjects who completed the main period were eligible to continue treatment with somatrogon weekly

injections in the open label extension (OLE) period of the trial; no washout period was required between main and OLE periods. Refer to Section 15.1.1 for a schematic of the study design.

Eligible subjects were randomized in a 1:1 ratio to receive weekly injections of somatrogon or daily injections of Genotropin. Randomization was stratified according to peak GH levels in stimulation tests (≤3 ng/mL, >3 to 7 ng/mL, and >7 ng/mL to ≤10 ng/mL), age (>3 to ≤7 years and >7 years), and geographic region. In general, the growth rate varies with age (children <6 years old have higher AHV).[2] Very low peak GH levels on provocative testing (typically <5 ng/mL) are consistent with severe pediatric GHD, and subjects with such results are expected to benefit greatly from hGH treatment and may achieve higher AHV during the first year of treatment compared to subjects with less severe GHD and/or residual secretion of GH (Grimberg et al. 2016). Thus, FDA has accepted a stratification approach by age and peak GH levels for the studies evaluating hGH products with native GH sequence for treatment indication of short stature due to pediatric GHD.

Somatrogon and Genotropin were used in fixed doses throughout the treatment period: 0.66 mg/kg/week and 0.034 mg/kg/day, respectively. As per protocol, subjects with IGF-1 SDS above 2 in two consecutive measurements (including unscheduled visits) were to have dose reduced by 15% and further dose reduction was allowed if the subject met these criteria again prior to the two last visits (Month 9 and Month 12). The Genotropin dose used during the trial is the US-approved Genotropin dose for the treatment of short stature in pediatric patients with GHD. Somatrogon was delivered by a multi-dose disposable pre-filled pen (referred to as pen-injector throughout this review) and Genotropin was delivered by Genotropin Pen. It was not pre-specified in the protocol who would administer the study drug (caretaker or self).

The proposed-for-marketing pen injector was used in this study to administer somatrogon.

Primary Efficacy Endpoint

The primary efficacy endpoint was mean annualized height velocity (AHV) at 12 months of treatment. As discussed in Section 3.2 AHV is an acceptable validated surrogate endpoint to demonstrate efficacy and establish clinical benefit of the drugs with native GH sequence for the treatment of short stature due to pediatric GHD indication.

Secondary Efficacy Endpoints

- Secondary endpoints included growth parameters and biochemical marker measurements (as listed below). These secondary endpoints are standard in growth-promoting drugs program involving children. No hierarchical testing was pre-defined for the secondary endpoints.
- Growth-related endpoints
  - AHV at 6 months of treatment
  - Change in height standard deviation score (HT-SDS) at 6 and 12 months compared to baseline
  - Change in bone maturation at 12 months compared to screening bone age (calculated as bone age/chronological age).

[2] https://www.cdc.gov/growthcharts/index.htm

- Biochemical marker endpoints
  - Absolute IGF-1 and IGF-1 SDS levels across study visits
  - Insulin growth factor binding protein-3 (IGFBP-3) levels and IGFBP-3 SDS across study visits.

Other exploratory endpoints included evaluation of quality of life by various questionnaires. None of patient reported outcome measures used in the clinical program have been validated in this patient population. See Section 15.1.2 for a full list of endpoints.

6.2.1.2. Eligibility Criteria

The inclusion and exclusion criteria were consistent with the indication sought in this application (treatment of growth failure due to pediatric GHD).

The trial enrolled prepubertal children (3 to 11 years) with a confirmed diagnosis of GHD by two GH provocation tests, who were naïve-to-treatment with hGH, and had impaired growth defined as annualized height velocity (AHV) below the 25th percentile for chronological age (HV <-0.7 standard deviation score) and sex. Overall, these inclusion criteria are consistent with current scientific society guidelines on the diagnosis of pediatric GHD (Growth Hormone Research 2000; Grimberg et al. 2016).

The Applicant adequately excluded children with non-GHD causes of short stature (e.g., psychological dwarfism, born small for gestational age, chromosomal abnormalities, and uncontrolled diabetes). The Applicant also appropriately excluded subjects on various medical therapies that might influence growth and hence the efficacy assessment (e.g., anabolic steroids or chronic glucocorticoid therapies). Lastly, the Applicant also appropriately excluded subjects who would be at increased risk of adverse events associated with hGH treatment, including known active malignancy and intracranial tumors. Refer to Section 15.1.3 for a detailed list of the inclusion and exclusion criteria.

6.2.1.3. Statistical Analysis Plan

The primary and secondary efficacy analyses were performed using the full analysis set (FAS) which was defined as all randomized subjects who have received at least one dose of study drug. No primary estimand was stated by the Applicant.

Primary Efficacy Endpoint Analysis

The primary efficacy endpoint was AHV in cm/year at 12 months of treatment, which was calculated as follows:

$$AHV\ (cm/year) = \frac{(Ht\ at\ Visit\ 8 - Ht\ at\ Visit2)\ in\ cm}{interval\ length\ of\ (Visit\ 8 - Visit\ 2)\ in\ days} x\ 365.25$$

Where Visit 8 = 12 months, Visit 2 = baseline, and Ht = standing height

The Applicant's prespecified analysis of the primary endpoint was performed using an analysis of covariance (ANCOVA) model. The model included treatment, age group (>3 years to ≤7 years and 0 days, >7 years and 0 days), gender (male, female), peak growth hormone (GH) levels at screening (≤3 ng/mL, >3 ng/mL to ≤7 ng/mL, >7 ng/mL to ≤10 ng/mL), and region as factors and baseline height SDS as a covariate.

The primary objective of this study was to demonstrate that the effect of somatrogon is noninferior to the Genotropin effect on AHV at Month 12 of treatment. Noninferiority (NI) was

established if the lower limit of the two-sided 95% confidence interval (CI) for the mean difference "somatrogon – Genotropin" in the primary analysis was ≥-1.8 cm/year. Based on the Applicant's justification of the NI margin, the Division finds an NI of -1.8 acceptable. Refer to Section 15.1.4 for the NI justification.

If NI was confirmed, then a test for superiority of somatrogon over Genotropin would be conducted. Superiority would be claimed if the lower limit of the two-sided CI of the treatment difference is greater than or equal to 0 cm/year.

Method for Handling Missing Data for the Primary Endpoint

The Applicant used a multiple imputation method assuming missing not at random (MNAR) using SAS PROC MI with multiple imputation by fully conditional specification (FCS MI) (MNAR/FCS) method by treatment group to impute missing data at Month 12. The imputed values for the somatrogon group were reduced by 1.8 cm/year as a penalty. A total of 100 imputed datasets were created. Using the ANCOVA model described above, the least square means and 95% confidence interval of the treatment difference for each imputed set was calculated. The results were then combined for evaluation with SAS PROC MIANALYZE. The amount of missing data were low for the primary endpoint at Month 12, about 1.3% (one in the somatrogon group and two in the Genotropin group), therefore, FDA was not concerned about the approach to handling of missing data.

Subgroup Analysis

An ANCOVA model was used to determine the treatment difference between somatrogon and Genotropin at 12 months for the following categories: age group, gender, region, race, and peak GH levels in pretrial stimulations tests.

Secondary Efficacy Analyses

The secondary efficacy endpoints, AHV after 6 months of treatment, change from baseline in height SDS at 6 months and 12 months, respectively, were analyzed using an ANCOVA model with its corresponding baseline for each endpoint as a covariate.

Descriptive statistics was used to analyze the secondary endpoint, change from baseline in bone maturation at the end of 12 months, compared to screening bone age (calculated as bone age/chronological age).

Method for Handling Missing Data for the Secondary Endpoints

Missing data were imputed using a multiple imputation MNAR/FCS method, similar to the primary endpoint, however, but no penalty was added to the imputed values in the somatrogon group. Missing data were not imputed for change from baseline in bone maturation.

6.2.1.4. Results of Analyses

This section summarizes patient disposition, demographics, baseline disease characteristics, and primary and secondary efficacy results based on data submitted by the Applicant and verified by FDA.

Subject Disposition

A total of 536 subjects were screened and 308 were not randomized (Table 8). Of the 308 not randomized subjects, 263 were screen failures (most failed inclusion and/or exclusion criteria and 9 were not willing to sign informed consent) and 45 (not screen failures) were not randomized because when they were in screening when the enrollment target was met.

A total of 228 subjects with pediatric GHD were enrolled and randomized (1:1) to one of two treatment arms: somatrogon (113 subjects) and Genotropin (115 subjects). Of these, 4 subjects in the somatrogon arm did not receive any study drug (3 were withdrawn by parent/guardian and 1 was lost to follow-up). Thus, 224 subjects received at least one dose of either somatrogon (N=109) or Genotropin (N=115) and were included in the FAS. The discontinuation rate of the study was low, and a total of 99% of subjects in both arms completed the main period. Two subjects discontinued the study prematurely: one in somatrogon group (due to AE of injection site reactions) and one in Genotropin group (withdrawn by parent/guardian).

Table 8. Patient Disposition, Trial CP-4-006 (Main Period)

Disposition Outcome	Somatrogon N=109 n (%)	Genotropin N=115 n (%)
Subjects randomized and treated	109	115
Full analysis population	109	115
Per-protocol population	103	110
Safety population	109	115
Discontinued study	1 (0.9)	1 (0.9)
Adverse event	1 (0.9)	0
Withdrawal by parent/guardian	0	1 (0.9)
Completed the main study (12 months)	108 (99)	114 (99)
Completed, rolled over to open-label extension (OLE)	104 (95.4)	108 (93.9)
Completed, not rolled over to OLE	4 (3.7)	6 (5.2)
Withdrawal by subject	1 (0.9)	1 (0.9)
Withdrawal by parent/guardian	2 (1.8)	3 (2.6)
Other	1 (0.9)	2 (1.8)

Source: Analysis performed by FDA Clinical Data Scientist using ds.xpt; software, R. Figure 1 of CP-4-006 Study Report, page 46.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in specified population or group

A total of 212 subjects (104 in the somatrogon arm and 108 in the Genotropin arm) continued in the OLE period. By the cutoff date December 21, 2020, of the 104 subjects who were originally randomized to somatrogon and continued treatment on somatrogon in the OLE (soma/soma arm), 2 subjects discontinued study treatment (withdrawal by parent/guardian or subject), and of the 108 subjects in the Genotropin/somatrogon arm (Geno/soma arm) 11 subjects discontinued study treatment: 6 due to adverse events (see Section 7.6.5 for details), 3 due to withdrawal, and 2 for other reasons (not specified by the Applicant).

Review of protocol violators did not identify any significant deviations in the way the inclusion/exclusion criteria were applied in the clinical trial. The number of subjects with major violations was balanced between arms. Refer to Section 15.1.5.

Baseline Demographic and Disease Characteristics

The treatment groups were well-balanced with respect to baseline demographics (Table 9) and clinical characteristics (Table 10). Approximately 80% of the subjects in each group were male, consistent with the male predominance in other hGH pivotal trials (e.g., 85.5% males in Nutropin

pivotal trial, 73% males in Zomacton pivotal trial) and in clinical practice. The mean age at baseline was 7.8 years (range 3 to 12 years) in each group. Approximately 18% of all subjects enrolled in the study were from the United States; other subjects were from the Europe, Middle East, Asia, Oceania, Mexico, and South America regions. The predominance of non-U.S. subjects is acceptable. First, diagnostic criteria for pediatric GHD in and outside the U.S. are the same and patients generally have similar disease etiology. Manifestations of the disease are the same regardless of the region of enrollment, and comorbidities are also similar in these patients and are due to GH deficiency as well as to other pituitary hormonal deficiencies (i.e., hypothyroidism, hypocortisolism, hypogonadism). Consequently, common medications in patients worldwide include hormonal replacement therapies (e.g., levothyroxine, hydrocortisone). Thus, the efficacy and safety data on somatrogon use obtained in subjects from other countries are applicable to U.S. subjects.

In addition, age, sex, and region were taken into consideration in the subgroup analysis.

Table 9. Baseline Demographic Characteristics, Safety Population*, Trial CP-4-006

Characteristic	Somatrogon N=109	Genotropin N=115
Sex, (n%)		
Female	27 (25)	36 (31)
Male	82 (75)	79 (69)
Age, years		
Mean (SD)	7.8 (3)	7.6 (2)
Median (min, max)	7.9 (3, 12)	7.8 (3, 12)
Age group, years, (n%)		
>3 to ≤7 years	43 (39)	47 (41)
>7 years	66 (61)	68 (59)
Ethnicity, (n%)		
Hispanic or Latino	11 (10)	13 (11)
Not Hispanic or Latino	98 (90)	102 (89)
Race, (n%)		
American Indian or Alaska Native	1 (1)	0 (0)
Asian	24 (22)	21 (18)
Black or African American	0 (0)	2 (2)
Native Hawaiian or Other Pacific Islander	0 (0)	1 (1)
White	81 (74)	86 (75)
Missing	3 (3)	5 (4)

Characteristic	Somatrogon N=109	Genotropin N=115
Country of participation, (n%)		
Argentina	1 (0.9)	2 (1.7)
Australia	2 (1.8)	2 (1.7)
Bulgaria	2 (1.8)	2 (1.7)
Belarus	1 (0.9)	1 (0.9)
Canada	3 (2.8)	2 (1.7)
Colombia	4 (3.7)	4 (3.5)
Spain	10 (9.2)	9 (7.8)
Great Britain	0 (0)	3 (2.6)
Georgia	5 (4.6)	1 (0.9)
Greece	3 (2.8)	0 (0)
India	12 (11.0)	14 (12.2)
Israel	7 (6.4)	8 (7.0)
Mexico	2 (1.8)	0 (0)
New Zealand	3 (2.8)	1 (0.9)
Poland	7 (6.4)	12 (10.4)
South Korea	8 (7.3)	4 (3.5)
Russia	8 (7.3)	12 (10.4)
Turkey	1 (0.9)	0 (0)
Taiwan	0 (0)	2 (1.7)
Ukraine	13 (11.9)	11 (9.6)
United States	17 (15.6)	25 (21.7)

Source: Analysis performed by FDA Clinical Data Scientist using adsl.xpt; software, R.
* The Safety Analysis Set and Full Analysis Set populations were identical.
Abbreviations: GH, growth hormone; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; SDS, standard deviation score

Mean height SDS was approximately -3 SDS in each group. The mean peak GH level following stimulation test(s) was similar in the two groups: 5.4 and 5.8 ng/dL, consistent with the GH threshold(s) for the diagnosis of GHD (Table 10).

Table 10. Baseline Clinical Characteristics, Safety Population*, Trial CP-4-006

Characteristic	Somatrogon N=109	Genotropin N=115
Height, cm		
Mean (SD)	110 (15.3)	109.9 (13.9)
Median (min, max)	109.8 (75.1, 139.6)	110.5 (77.1, 144.3)
Peak GH, ng/dL		
Mean (SD)	5.4 (2.8)	5.8 (2.6)
Median (min, max)	5.9 (0.1, 9.9)	6.2 (0.1, 9.9)
Peak GH level group, (n%)		
≤3 ng/mL	22 (20.2)	21 (18.3)
>7 to <10 ng/mL	34 (31.2)	38 (33.0)
>3 to ≤7 ng/mL	53 (48.6)	56 (48.7)
Height SDS (Z)		
Mean (SD)	-2.9 (1.3)	-2.8 (1.3)
Median (min, max)	-2.5 (-7.5, -1.1)	-2.6 (-10, -0.5)

Source: Analysis performed by FDA Clinical Data Scientist using adsl.xpt; software, R.
* The Safety Analysis Set and Full Analysis Set populations were identical.
Abbreviations: GH, growth hormone; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; SDS, standard deviation score

There was no imbalance between treatment groups with respect to concomitant medications and other baseline comorbidities. A similar proportion of subjects in the somatrogon group and the Genotropin group used concomitant medications: 79.8% and 76.5%, respectively. The most frequent (≥10% in any treatment group) medication used was analgesics. The most frequent

comorbidities were hypothyroidism (7.1% and 8.5% in somatrogon and Genotropin groups, respectively) and pituitary hypoplasia (6.3% and 5.4% in somatrogon and Genotropin groups, respectively). These comorbidities are commonly seen in patients with GHD.

Primary and Secondary Efficacy Analyses Results

Primary Analysis

The results of the primary analysis demonstrated noninferiority of somatrogon administered once weekly to Genotropin administered once daily of increase in AHV after 12 months of treatment. The Applicant's primary efficacy results were confirmed by the statistical review team, with negligible differences. The results shown in Table 11 (FDA analysis) include imputed data for missing AHV values using multiple imputation with MNAR/FCS method. The lower bound of the 95% CI was -0.23 cm/year, which is greater than the noninferiority margin of -1.8 cm/year.

However, the difference between somatrogon and Genotropin was not statistically significant because the lower limit of the 95% CI for the mean difference between the two treatment groups was less than zero. Thus, superiority is not claimed.

Table 11. Primary Analysis: Annual Height Velocity at Month 12 in the Full Analysis Set, Trial CP-4-006

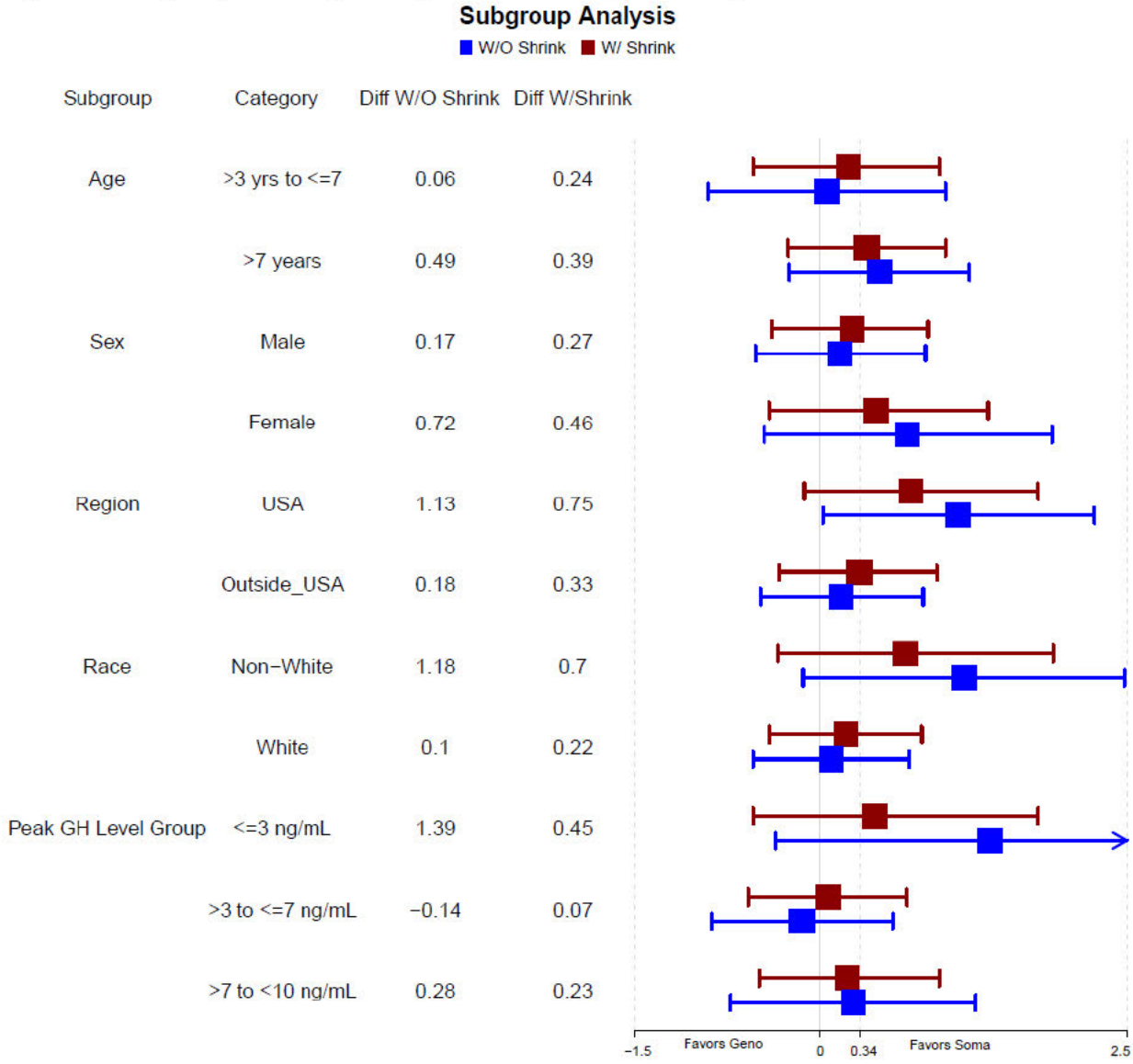
Annual Height Velocity at 12 Months	Somatrogon N=109	Genotropin N=115
Least-square mean	10.07	9.73
Treatment difference, somatrogon-Genotropin	0.34	
95% Confidence interval	-0.23, 0.91	

Source: Statistical Reviewer's analysis; adsl.xpt, advs.xpt.
Multiple imputation using the SAS PROC MI with the MNAR/FCS method.
Least-square means are from the analysis of covariance model with treatment, age group, gender, peak growth hormone levels, and region as fixed factors and baseline height SDS as a covariate.
Treatment mean difference is calculated as somatrogon−Genotropin.
Abbreviations: FCS, fully conditional method; MNAR, missing not at random; SDS, standard deviation score

Subgroup Analyses of the Primary Endpoint

Overall, the treatment effects of the subgroups supported the conclusion of non-inferiority of somatrogon to Genotropin regardless of age, sex, region, race, or baseline peak GH level. There were some variabilities in treatment differences between subgroups. Refer to Section 16.1 for the detailed subgroup analyses. However, the team concluded that these variabilities were most likely due to small sample size and large variability in the sample estimates for some subgroups. To estimate the treatment effect among subgroups with more precision, the statistical reviewer conducted an additional analysis that entailed deriving shrinkage estimates for subgroup treatment effects using a Bayesian hierarchal model (Section 16.2 for Bayesian shrinkage analysis details). Results from this shrinkage analysis also supports the noninferiority of somatrogon to Genotropin in terms of AHV regardless of age, sex, region, race or baseline peak GH level (Figure 6).

Figure 6. Subgroup Shrinkage Analysis: Annual Height Velocity at Month 12



Source: Statistical Reviewer's Analysis.

Secondary Analyses

AHV at 6 Months and Changes in Height SDS at 6 and 12 Months

Overall, the results of these analyses support the result of primary analysis. As expected, with improvement in AHV and adequate GH replacement, other growth parameters improved in both treatment groups. However, it should be noted that AHV at 6-months is less informative because the growth rate is usually greater during the first 6 months and decreases during the subsequent months and years of treatment due to well-known catch-up growth phenomenon seen in children when the cause of growth deficit is removed (Wit and Boersma 2002). This phenomenon was also observed in pivotal trials for other hGH formulations. Therefore, AHV at 12 months is more predictive of the subsequent growth if not offset by unexpected adverse reactions and/or immunogenicity.

Table 12 and Table 13 summarize the results of analyses for the secondary endpoints.

Table 12. Secondary Analysis: Annual Height Velocity at Month 6 in Full Analysis Set, Trial CP-4-006

Annual Height Velocity at 6 Months	Somatrogon N=109	Genotropin N=115
Least-square means	10.76	10.19
Treatment difference somatrogon−Genotropin	0.57	
95% Confidence interval	-0.11, 1.25	

Source: Statistical Reviewer's analysis; adsl.xpt, advs.xpt.
Multiple imputation using SAS PROC MI with the FCS method.
Least-square means are from the analysis of covariance model with treatment, age group, gender, peak growth hormone levels, and region as fixed factors and baseline height SDS as a covariate.
Treatment mean difference was calculated as somatrogon−Genotropin.
Abbreviations: FCS, fully conditional method; SDS, standard deviation score

Table 13. Secondary Analysis: Change in Height SDS at Months 6 and 12 in the Full Analysis Set, Trial CP-4-006

Parameter	Somatrogon N=109	Genotropin N=115
Mean height SDS at baseline	-2.94	-2.78
Height SDS at 6 months		
LS Means	0.54	0.48
Treatment difference somatrogon−Genotropin	0.06	
95% CI	-0.01, 0.13	
Height SDS at 12 months		
LS Means	0.91	0.86
Treatment difference somatrogon−Genotropin	0.05	
95% Confidence interval	-0.06, 0.16	

Source: Statistical Reviewer's analysis; adsl.xpt, advs.xpt.
Multiple imputation using SAS PROC MI with the FCS method.
Least-square means are from the analysis of covariance model with treatment, age group, gender, peak growth hormone levels, and region as fixed factors and baseline height SDS as a covariate.
Treatment mean difference calculated as somatrogon−Genotropin.
Abbreviations: CI, confidence interval; FCS, fully conditional method; LS, least-square; SDS, standard deviation score

Secondary endpoints were not controlled for type 1 error. If included in labeling results should be descriptive only.

Change in Bone Age

Subjects with GHD have a delay in bone age relative to chronological age and the bone age is expected to increase with growth promoting therapies. Consequently, there is a potential risk of undue acceleration in bone age with GH replacement therapy.

In study CP-4-006 as expected, there was a trend toward increased bone age at Month 12 and similar to the change observed with Genotropin treatment. However, the change from baseline was small, most likely reflecting the short duration of treatment. The small change also suggests that somatrogon treatment will not adversely advance bone age relative to chronological age.

Table 14. Secondary Analysis: Change in Bone Maturation at 12 Months in the Full Analysis Set, Trial CP-4-006

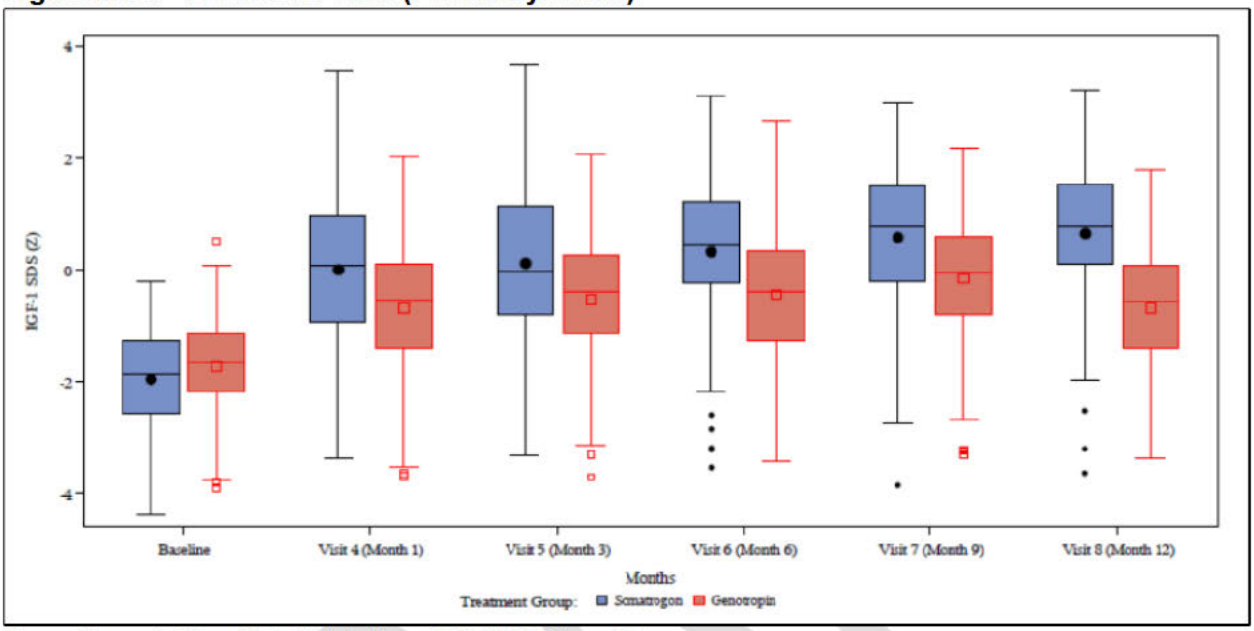
Parameter	Somatrogon N=109	Genotropin N=115
n	107	107
Baseline	0.67	0.66
Change at 12 months in bone maturation from baseline		
n	104	102
Mean (standard deviation)	0.05 (0.09)	0.06 (0.10)
Median (minimum, maximum)	0.03 (-0.18, 0.35)	0.04 (-0.18, 0.36)

Source: Statistical Reviewer's analysis; advs.xpt, adpc.xpt.
Missing data not imputed.

Change in Mean IGF-1 SDS and IGFBP-3 Across Study Visits

The mean IGF-1 SDS was low at baseline in both groups: -1.95 in the somatrogon group and -1.72 in the Genotropin group. At the end of the 12-month treatment, mean IGF-1 SDS normalized in both groups (0.65 in the somatrogon group and -0.69 in the Genotropin group) (Figure 7).

Figure 7. IGF-1 SDS Over Time (Full Analysis Set)



Source: Excerpted from Clinical Study Report CP-4-006, Figure 12.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

A total of 69 (64%) of subjects in the somatrogon group and 32 (29%) of subjects in the Genotropin group achieved IGF-1 SDS levels in the range of 0 and +2 SDS at Month 12. Levels of IGFBP-3, a major IGF-1 binding protein, also increased for both treatments with increase of IGF-1. No decrease in AHV was noted in subjects who had drug dose reduction due to elevated levels of IGF-1 SDS above 2.

It should be noted that there is no correlation between levels of IGF-1 and final height, and the target IGF-1 levels to optimize the balance between height gain and potential risks have not been established (Grimberg et al. 2016). Thus, the clinical assessment of treatment efficacy should not be based on IGF-1 levels, but rather on AHV and height SDS.

However, chronically elevated IGF-1 levels above the normal range are a safety concern due to the potential risk of effects associated with AEs including headache, intracranial hypertension, edema, and tumors. Refer to Section 7.7.2 for discussion on safety of IGF-1 elevated levels.

OLE Period

The OLEOLE period of Trial CP-4-006 was primarily designed to evaluate the long-term safety and tolerability of the drug; efficacy endpoints (AHV, height-SDS) were also collected every 12 months.

A total of 212 subjects (104 originally randomized to somatrogon and 108 originally randomized to Genotropin) enrolled in the OLE period. Of these, 102 subjects completed 2 years of somatrogon treatment (soma/soma group), and 102 subjects originally randomized to Genotropin

arm in main period completed 1 year of treatment with somatrogon by the cut-off date December 21, 2020. The longest exposure to somatrogon during OLE was 3 years, with 13 subjects from the soma/soma group. A total of 15 subjects from the Geno/soma group completed 2 years in the OLE period. Growth parameters were evaluated at each visit. Data from the OLE period demonstrated the sustained effect on average of drug on AHV during the second year of treatment with somatrogon: mean AHV was 9.1 cm/year (range 5.55, 14.32 cm/year) in soma/soma group and 8.98 cm/year (range 5.51, 13.98 cm/year) in Geno/soma group, respectively. The efficacy data also demonstrated that improvement in height SDS was also maintained during the second year of treatment (refer to Section 16.3, Table 92). However, individual data on AHV at the end of the 1-year OLE period (by subject ID, age, and sex) were not provided in the amendment which precluded analysis of whether there were outliers treated with somatrogon that did not follow the expected growth trajectory.

6.2.2. Trial CP-4-004

6.2.2.1. Design

Trial CP-4-004 was a phase 2 open-label safety and dose-finding study of different somatrogon dose levels compared to daily Genotropin in prepubertal subjects with PGHD. The trial also evaluated the efficacy of the various doses including 0.66 mg/kg/week on growth parameters and provided additional efficacy and safety data for up to 7 years of somatrogon use.

The study included a main period (12 months) and an OLE:

- The main period (open label, randomized, active control, 1-year duration) included Periods I and II (refer to Section 15.2.1, Figure 61). The OLE (refer to Section 15.2.1, Figure 62) included Periods III to V. Subjects who completed the main period of the study were eligible to continue in the OLE.
- The pre-defined criteria for dose reduction included occurrence of AEs (based on severity) and IGF-1 SDS >2 in two consecutive measurements (with dose reduced by 15%) in all periods (Period I through V).

Period I (6-Month Duration)

In Period I, subjects were randomized (1:1:1:1) to one of the three doses of somatrogon (0.25 mg/kg/week, 0.48 mg/kg/week, or 0.66 mg/kg/week) or to Genotropin (0.034 mg/kg/day). All somatrogon cohorts started at 0.25 mg/kg/week dose for 2 weeks, then the dose was increased to 0.48 mg/kg in two cohorts for another 2 weeks, and finally the dose was increased to 0.66 mg/kg/week in the third cohort.

Period II (6-Month Duration)

In Period II, each subject continued on the same somatrogon or Genotropin doses as in Period I.

Period III, Year 1 of OLE (12-Month Duration; Open Label, Three Somatrogon Dose Groups)

In Period III, subjects who received somatrogon in the main period continued on the same somatrogon dose. Subjects who were treated with Genotropin during the main period were randomized into one of the three ongoing somatrogon cohorts (0.25 mg/kg/week, 0.48 mg/kg/week, 0.66 mg/kg/week).

Period IV, Years 2 to 4 of OLE (12 to 36-Month Duration, Until Transition to Period V (PEN); Single Arm, Open Label)

In Period IV, all subjects were switched to or continued treatment with somatrogon dose of 0.66 mg/kg/week.

Period V (PEN) (Duration to Marketing Approval; Single Arm, Open Label)

Somatrogon was administered using vial/syringe from the main period (Periods I to II) through the Period IV in OLE study. All subjects had an option to switch from somatrogon administration using vial/syringe to the administration using pen injector in PEN Period during or after completing Year 2, Year 3, or Year 4 of Period IV. Subjects who completed PEN Period Year 1 could proceed to PEN Period Year 2.

Endpoints (Refer to Section 15.2.2 for the Full List of Endpoints)

- PK/PD endpoints
- Safety endpoints
- Efficacy endpoints
  - AHV (cm/year) at 12 months
  - Height at 6 months
  - Change in HT SDS at 6 months from baseline
  - Change in bone maturation at 12 months from baseline
  - Absolute IGF-1 and IGF-1 SDS levels across the study

6.2.2.2. Eligibility Criteria

The key inclusion criteria were similar to those of Trial CP-4-006: prepubertal children (3 to 10 years for girls and 3 to 11 years for boys), with confirmed diagnosis of GHD by provocative tests, and naïve to treatment. Impaired growth was defined as height SDS $\leq$2 as compared to the mean height for chronological age and gender, and AHV below the 25th percentile for the chronological age and gender.

The key exclusion criteria were also similar to those of Trial CP-4-006. The Applicant adequately excluded children with non-GHD causes of short stature (e.g., psychological dwarfism, born small for gestational age, and chromosomal abnormalities), with positive anti-hGH antibodies at screening, and on medications that may affect growth and efficacy assessment (e.g., anabolic steroids, glucocorticoids). For full inclusion and exclusion criteria, see Section 15.2.3.

6.2.2.3. Statistical Analysis Plan

The study was designed primarily as safety and dose-finding study. No formal statistical inference was prespecified or performed for this study. No primary estimand was stated by the Applicant. All efficacy endpoints, annual HV at 12 months, HV (cm/year) at 6 months, and changes in height SDS at 6 and 12 months from baseline were presented using descriptive statistics. The 95% confidence interval (CI) was provided for mean annual HV for each treatment group. All efficacy endpoints are summarized based on data from full analysis set (FAS), defined as all enrolled subjects who have follow-up data for the efficacy endpoint of AHV. There were no missing data in the study.

6.2.2.4. Results of Analyses – Trial CP-4-004

Disposition

A total of 181 subjects were screened, of which 121 subjects were screen failures, and 4 subjects were not randomized due to withdrawing consent prior to randomization (no explanation was given for consent withdrawal).

Fifty-six subjects were enrolled in this study and randomized to one of 4 treatment cohorts (1:1:1:1) in the main study. Three of the 56 subjects withdrew consent prior to receiving any study medication (one patient assigned to somatrogon and 2 subjects assigned to Genotropin). A total of 53 subjects received at least one dose of the study drug and were included in the full analysis set (FAS): 42 subjects were randomized to one of the three somatrogon dose groups (14 subjects to 0.25 mg/kg/week, 15 subjects to 0.48 mg/kg/week, and 14 subjects to 0.66 mg/kg/week) and 11 subjects to Genotropin group (Table 15). One subject (ID# (b) (6)) randomized to the 0.66 mg/kg/week cohort was later noticed to have psychosocial dwarfism. Of 53 subjects, 51 subjects completed 12-month of treatment and 2 subjects discontinued trial preliminary. No subjects discontinued Trial CP-4-004 due to AEs during the main period.

Table 15. Patient Disposition, Trial CP-4-004 (Main Period)

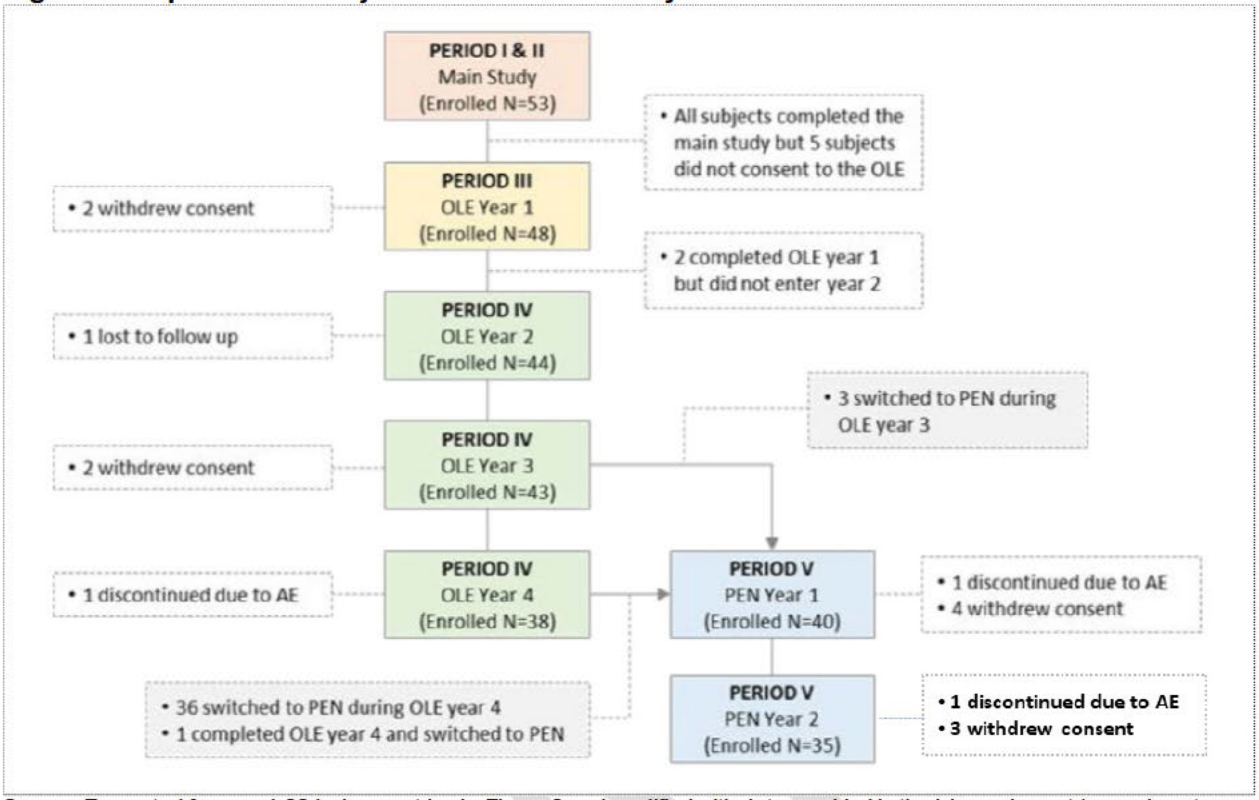
Disposition Outcome	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Subjects randomized	14	15	14	43	13
Full analysis subset	13	15	14	42	11
Per-protocol population	13	15	13	41	11
Safety population	13	15	14	42	11
Discontinued study drug	0	0	0	0	0
Adverse event	0	0	0	0	0
Discontinued study	1 (7.7)	0	1 (7.1)	2 (4.8)	0
Withdrawal by subject	0	0	1 (7.1)	1 (2.4)	0
Other	1 (7.7)	0	0	1 (2.4)	0

Source: Analysis performed by the FDA Clinical Data Scientist using ds.xpt; software, R.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects in specified population or group

Following completion of the main period, a total of 48/53 subjects entered Year 1 of the OLE (Period III), and 5/53 subjects did not consent to the OLE. Of the 48 subjects who entered OLE-Year 1, 38 subjects continued treatment with somatrogon at the doses they were randomized to in the main period of the study, and 10 subjects treated with Genotropin in the main period of the study were randomized to one of three somatrogon dose groups. Overall, in OLE-Year 1, 16 subjects were treated in dose cohort 0.25 mg/kg/week, 17 subjects in dose cohort 0.48 mg/kg/week, and 15 subjects in dose cohort 0.66 mg/kg/week.

Subject disposition in the OLE period was updated with additional data provided in the amendment supplement and is shown in the flowchart below in Figure 8.

Figure 8. Disposition of subjects flow chart for Study CP-4-004 OLE



Source: Excerpted from cp-4-004-ole-report-body, Figure 2 and modified with data provided in the isi,supplement (amendment submitted on September 15, 2021)

Review of protocol violations identified one major violation (ID # (b) (6)). The patient was randomized to somatrogon 0.66 mg/kg/week and received 52 doses. Due to continuous low IGF-1 levels during the treatment, poor compliance was investigated and confirmed. Following completion of the 12-month study, the patient was discontinued due to diagnosis of psychosocial dwarfism. No additional deviation met the criteria for major protocol deviation. Other protocol deviations were balanced among arms.

Demographics

Overall, no significant imbalances were noted between treatment arms in baseline demographic (Table 16) and clinical characteristics (Table 17) of the population in the main period. The demographic and disease characteristics were also similar to that of Trial CP-4-006 population. More males than females were enrolled in the study. Children enrolled were slightly younger than those enrolled in Trial CP-4-006 (mean age 6 years versus 7.6 years, respectively).

Table 16. Baseline Demographic Characteristics, Safety Population, Trial CP-4-004 (Main Period)

Characteristic	Somatrogon 0.25 mg/kg/wk N=13	Somatrogon 0.48 mg/kg/wk N=15	Somatrogon 0.66 mg/kg/wk N=14	Total Somatrogon 0.66 mg/kg/wk N=42	Genotropin N=11
Sex, (n%)					
Female	3 (23)	6 (40)	5 (36)	14 (33)	3 (27)
Male	10 (77)	9 (60)	9 (64)	28 (67)	8 (73)
Age, years					
Mean (SD)	6 (2)	6 (2)	6 (2)	6 (2)	6 (2)
Median (min, max)	6 (4, 11)	5 (3, 10)	6 (3, 10)	6 (3, 11)	5 (4, 9)
Race, (n%)					
Black or African American	0 (0)	1 (7)	0 (0)	1 (2)	0 (0)
Other	1 (8)	0 (0)	0 (0)	1 (2)	1 (9)
White	12 (92)	14 (93)	14 (100)	40 (95)	10 (91)
Country of participation, (n%)					
Bulgaria	1 (8)	0 (0)	2 (14)	3 (7)	1 (9)
Belarus	2 (15)	5 (33)	3 (21)	10 (24)	3 (27)
Greece	0 (0)	1 (7)	1 (7)	2 (5)	0 (0)
Hungary	0 (0)	1 (7)	1 (7)	2 (5)	0 (0)
Russia	6 (46)	3 (20)	4 (29)	13 (31)	3 (27)
Ukraine	3 (23)	4 (27)	3 (21)	10 (24)	4 (36)
United States	1 (8)	1 (7)	0 (0)	2 (5)	0 (0)

Source: Analysis performed by the FDA Clinical Data Scientist using adsl.xpt; software, R.
Abbreviations: GH, growth hormone; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; SDS, standard deviation score

Mean height SDS was approximately -4 SDS in each group. Mean peak GH level following stimulation test(s) was similar in all groups: varying from 3.8 to 4.1 ng/dL and is consistent with the GH threshold(s) for the diagnosis of GHD (Table 17).

Table 17. Baseline Clinical Characteristics, Safety Population, Trial CP-4-004 (Main Period)

Characteristic	Somatrogon 0.25 mg/kg/wk N=13	Somatrogon 0.48 mg/kg/wk N=15	Somatrogon 0.66 mg/kg/wk N=14	Total Somatrogon 0.66 mg/kg/wk N=42	Genotropin N=11
Height, cm					
Mean (SD)	103 (12.5)	100.8 (12.1)	100.1 (14.7)	101.3 (12.9)	97.8 (12)
Median (min, max)	99.6 (83.6, 127.1)	97 (80.3, 126.2)	98.2 (82.2, 124)	97.1 (80.3, 127.1)	95.9 (79.9, 117.4)
Peak GH, ng/dL					
Mean (SD)	3.9 (3.1)	4.1 (2.6)	4 (2.9)	4 (2.8)	3.8 (2.8)
Median (min, max)	3.5 (0.4, 9.9)	4.4 (0.7, 9.3)	3.9 (0.3, 9.8)	3.9 (0.3, 9.9)	3.9 (0.1, 10)
Peak GH level group, (n%)					
≤2 ng/mL	5 (38.5)	4 (26.7)	4 (28.6)	13 (31.0)	3 (27.3)
>2 and ≤7 ng/mL	6 (46.2)	9 (60.0)	8 (57.1)	23 (54.8)	7 (63.6)
>7 and ≤10 ng/mL	2 (15.4)	2 (13.3)	2 (14.3)	6 (14.3)	1 (9.1)
Height SDS, (Z)					
Mean (SD)	-3.6 (1)	-3.7 (0.9)	-4.2 (1.4)	-3.9 (1.1)	-4.2 (1.6)
Median (min, max)	-3.6 (-5.6, -2.2)	-3.6 (-5.1, -2.4)	-3.7 (-7.5, -2.5)	-3.7 (-7.5, -2.2)	-3.4 (-6.9, -2.7)

Source: Analysis performed by FDA Clinical Data Scientist using adsl.xpt; software, R.
Abbreviations: GH, growth hormone; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation; SDS, standard deviation score

No imbalance was noted between treatment groups with respect to other baseline comorbidities and concomitant medications. Pituitary hypoplasia was the most frequently reported comorbidity in all treatment groups (9/13 subjects, 4/15 subjects, 3/14 subjects, and 5/11 subjects in somatrogon groups 0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week, and Genotropin group, respectively) and is a condition commonly seen in GHD population. Other comorbidities were reported in ≤2 subjects in each group. The most frequent concomitant medications were balanced among treatment groups and included thyroid hormone replacement, mucolytics, and penicillin, which are commonly used in this age population of GHD.

Efficacy Results

Main Period (12 Months)

The analyses of data demonstrated improvement in all mean (SD) growth parameters and biomarkers at Week 52.

AHV

The mean AHV increased in all somatrogon dose groups and in Genotropin group at 6 and 12 months of treatment (Table 18). The increase in AHV with somatrogon treatment was dose-dependent. All somatrogon groups had numerically smaller AHV compared to the Genotropin group.

Table 18. Annual Height Velocity at Months 6 and 12 by Cohort in All Treated Subjects, Trial CP-4-004

	Somatrogon			Genotropin
Parameter	Cohort 1 0.25 mg/kg/Week N=13	Cohort 2 0.48 mg/kg/Week N=15	Cohort 3 0.66 mg/kg/Week N=14*	Cohort 4 0.034 mg/kg/Week N=11
N	13	15	14	11
Month 6				
Mean (cm/year)	11.8	12.5	13.0	15.0
95% CI of mean	9.6, 13.9	11.1, 13.8	9.9, 16.0	13.1, 16.9
SD	3.6	2.4	5.3	2.9
Range (cm/year)	5.7, 17.5	7.9, 16.5	5.3, 25.1	10.2, 18.5
Month 12				
Mean (cm/year)	10.4	11.0	11.4	12.5
95% CI of mean	8.9, 12.0	9.7, 12.2	9.2, 13.7	11.0, 13.9
SD	2.6	2.3	3.9	2.1
Range (cm/year)	6.2, 14.4	6.5, 14.5	5.0, 18.3	9.2, 16.0

Source: Statistical Reviewer's analysis; adhtvel.xpt.
* Cohort 3 lower level of height range attributable to Patient 08003, who was wrongly included in the study. The patient was diagnosed with psychosocial dwarfism (exclusionary condition) following study completion.
Abbreviations: CI, confidence interval; SD, standard deviation

Change from Baseline in Height SDS at 6 and 12 Months

An improvement in height SDS was observed during treatment with somatrogon at Month 6 and at Month 12 (Table 19). Similar to the improvement in AHV, the improvement in height SDS was dose dependent with greatest improvement in height observed with dose 0.66 mg/kg/week.

Table 19. Change in Height SDS at Months 6 and 12 in All Treated Subjects, Trial CP-4-004

	Somatrogon			Genotropin
Parameter	Cohort 1 0.25 mg/kg/Week N=13	Cohort 2 0.48 mg/kg/Week N=15	Cohort 3 0.66 mg/kg/Week N=14*	Cohort 4 0.034 mg/kg/Week N=11
Month 6				
Mean	0.65	0.75	0.84	1.00
SD	0.36	0.25	0.44	0.35
Range	0.12, 1.31	0.30, 1.28	0.06, 1.64	0.48, 1.74
Month 12				
Mean	1.09	1.19	1.35	1.51
SD	0.53	0.49	0.69	0.47
Range	0.32, 2.15	0.28, 2.05	0.06, 2.47	0.82, 2.38

Source: Statistical Reviewer's analysis; adhtsds.xpt
* Cohort 3 narrower height range attributable to Patient 08003, who was wrongly included in the study. The patient was diagnosed with psychosocial dwarfism (exclusionary condition) following study completion.
Abbreviations: CI, confidence interval; SD, standard deviation; SDS, standard deviation score

Change in Mean IGF-1 SDS and IGFBP-3 at 12 Months

The IGF-1 values in the somatrogon group improved overtime in a dose-dependent manner in the 12-month main period of Trial CP-4-004. The mean (range) of IGF-1 SDS values observed at 12 months were -0.46 (-2.9, 1.4), -0.03 (-2.6, 1.5), and 0.36 (-1.2, 1.3) for somatrogon dose cohorts 0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week, respectively. IGF-1 SDS value in Genotropin group at 12-month time point was -0.015 (-3.6, 1.5). During the 12-month study, 1 patient (ID 20004) in the dose group 0.66 mg/kg/week had IGF-1 levels above 2 SDS at 5 visits (Visits 5, 6, 7, 10, and 11). Somatrogon dose was reduced to 0.48 mg/kg/week prior to Visit 6 and at Month 12 the IGF-1 was normalized (SDS 1.09). No AEs related or unrelated with IGF-1 increase were reported for this subject. No subjects were reported with IGF-1 SDS >2 in the other dose cohorts. The proportion of subjects who achieved IGF-1 SDS between 0 and +2 at Month 12 of the main period increased with higher somatrogon dose: 5 (38%) subjects in cohort dose 0.25 mg/kg/week, 9 (60%) in cohort dose 0.48 mg/kg/week, and 10 (71%) in cohort dose 0.66 mg/kg/week. The proportions of patients with IGF-1 SDS 0-+2 in the two highest somatrogon dose cohorts were similar to that of Genotropin group [7 (64%) subjects], demonstrating that similar number of patients achieved IGF-1 normal SDS. Levels of IGFBP-3, a major IGF binding protein, also increased as expected with increase of IGF-1 in somatrogon and Genotropin groups.

Overall, the changes in growth parameters and biomarkers from baseline in the 0.66 mg/kg/week cohort at the end of the first year of treatment are consistent with these parameter changes seen in Trial CP-4-006.

OLE Period

The Applicant presented the results of efficacy analyses using data from the OLE up to 6 years (a total of 7 years treatment). Analysis of individual values showed that growth rate decreased through the years in OLE as subjects aged and approached pubertal age. AHV values below 5 cm/year were observed intermittently in one female and one male who entered the study at 5 years of age, and in two subjects approaching puberty (a female of approximately 12 years of age and a male of approximately 15 years of age) at Month 12 of the PEN Year 1 period (individual listing of AHV values was not provided for PEN Year 2). The transition of subjects through different dose cohorts from one year to another during the OLE phase (refer to study design in Section 6.2.2.1) led to variable dose exposure withing the same cohort, which confounded the

interpretation of the efficacy results. No dose reduction due to IGF-1 SDS level above 2 were required in any during the OLE phase.

Therefore, changes in AHV were analyzed in the group of subjects who were exposed to 0.66 mg/kg/week dose only throughout the trial (up to the cut-off date of December 21, 2020), which are summarized below. The changes in growth parameters in other groups are discussed in Section 16.4, Table 93 and Table 94.

Of the 12 subjects who were originally randomized to somatrogon 0.66 mg/kg/week at the main period and continued at this dose in OLE Year 1, 11 subjects were treated with somatrogon up to 3 years of OLE (total of 4 years from entry), and 1 subject completed OLE Year 4 treatment (total of 5 years from entry). Mean AHV was: 10.74 cm/year at the end of OLE Year 1, 9.55 cm/year at OLE Year 2, 9.03 cm/year at OLE Year 3. The subject who completed OLE Year 4 achieved AHV of 7.59 cm/year. All 11 subjects switched to pen injector (in PEN period) and of those, 9 subjects completed PEN Year 1 with a mean AHV of 8.3 cm/year and 7 subjects completed PEN Year 2 with a mean AHV of 8.1 cm/year. The total duration (starting in main period to PEN Year 2) of somatrogon treatment at 0.66 mg/kg/week was approximately 7 years (See Table 94 in Section 16.5 for full data).

Overall, these subjects on average appeared to continue growth up to a total of 7 years of treatment with somatrogon including when switching to a pen product presentation. No outliers who stopped growing were identified among subjects treated with the to-be-marketed dose (i.e., 0.66 mg/kg/week) and to-be-marketed formulation (i.e., pen-injector) (7 subjects who were treated for a total of 2 years in the PEN period).

6.3. Key Review Issues Relevant to Evaluation of Benefit

6.3.1. High Incidence and Persistence of Antidrug Antibody in Somatrogon-Treated Subjects Observed in Clinical Program and Potential Effect on Efficacy

Issue

Somatrogon treatment induced a high and persistent rate of antidrug antibodies (ADA) compared to Genotropin in Trials CP-4-004 and CP-4-006, with the presence of cross-reactive and neutralizing antibodies.

Background

Pharmacotherapy with biological agents can induce the development of antidrug antibodies (ADAs). Several factors may contribute to the immunogenicity of GH produced by recombinant DNA technology, such as cellular and chemical contaminants, as well as changes in the intrinsic primary and secondary structure of recombinant hGH that may occur during the production processes (Ahangari et al. 2004). The main concern with anti-GH antibodies is their potential to interfere with GH by changing GH PK or by directly blocking binding of GH to the GH receptor, thereby impacting drug effectiveness on growth. Apart from efficacy concerns, there are also ADAADA-related safety concerns, including immunogenicity-related adverse reactions (e.g.,

injection site reactions, hypersensitivity reactions, and autoimmune syndromes) and ADA-related decrease in drug clearance which increases exposure to drug (refer to Section 6.1) and that may affect the safety profile of the drug (e.g., increase in frequency or severity of drug class adverse reactions, such as hyperglycemia, tumors, intracranial hypertension, etc.) (Binder et al. 2019). This section will focus on the effect of high incidence and persistence of ADAs on efficacy. Refer to section 7.7.3 for potential immunogenicity-related safety issues.

While direct comparison of the incidence of ADA positivity between products may be misleading due to variations in the sensitivity and specificity of the assays as well as several other factors (e.g., assay methodology, sample handling, timing of sampling, concomitant medication, and underlying disease), the incidence of ADA in GHD children reported in product labels of currently marketed somatropin is generally low, varying from zero to 6.3%.[3]

Assessment

- **High incidence of ADA antibodies in subjects treated with somatrogon**

In this development program, in both Trials CP-4-006 and CP-4-004, the incidence of somatrogon-induced ADA was higher compared to the Genotropin comparator.

In the main period of Trial CP-4-006, 84 (77%) subjects in the somatrogon group developed ADA compared to 18 (16%) subjects in Genotropin group. In the OLE period, a total of 114/212 subjects (54%) were ADA-positive: 78/104 subjects (75%) from the original somatrogon group and 36/108 subjects (33%) from the original Genotropin group (Table 20). This observation is consistent with a conclusion that the majority of the seroconverted subjects in the somatrogon arm of the main period continued to be ADA-positive during the subsequent year in OLE. The incidence of positive ADA in the somatrogon group originally treated with Genotropin also increased in the OLE, but it is unclear why subjects treated with Genotropin during the main period had a lower incidence of seroconversion in OLE compared to somatrogon-treated subjects. Somatrogon is nearly identical to the native hGH. Cross-reactivity of the ADA was demonstrated with the endogenous protein. Samples positive in the ADA screening were further tested in the confirmatory assay for anti-somatrogon antibody and if confirmed positive were subsequently tested for CTP and hGH specificity (refer to Section 7.7.4 for discussion on anti-CTP safety). In addition, confirmed anti-somatrogon Ab samples were tested for neutralizing activity. Thus, ADA-positive subjects include those who also tested positive for NAb and/or anti-CTP.

ADA that blocks somatrogon activity by directly blocking the binding of somatrogon to the hGH receptor are called neutralizing antibodies (Nabs). NAb are a concern for long-term treatment because anti-somatrogon NAbs may reduce both drug efficacy and endogenous hGH activity. Five subjects were reported to have NAbs in Trial CP-4-006 (2 subjects were reported in the original NDA and three additional subjects in the Major Amendment submitted on September 15, 2021). Of these 5 subjects, 2 subjects (ID# (b) (6) and ID# (b) (6)) tested positive for NAb after 6 months of treatment and one of these subjects (ID# (b) (6)) tested positive again after 12 and 27 months of treatment. One subject (ID# (b) (6)) tested positive for NAbs at the baseline of OLE period, i.e., after 12 months of treatment in the main period, and 2 subjects (ID# (b) (6)) tested NAb-positive after 24 months of treatment (for more details on

[3] https://dailymed.nlm.nih.gov/

subjects with NAbs refer to Table 28). The earliest time point in which a subject tested positive for NAb was at 6 months of treatment with somatrogon.

Table 20. Incidence of ADA in Trials CP-4-006 and CP-4-004 (Main and Extension Phases)

Trial	N	ADA+	NAb	Anti-CTP
CP-4-006 Main				
Somatrogon	109	84 (77%)	2 (2%)	3 (3%)
Genotropin	115	18 (16%)	0	N/A
CP-4-006 OLE (at month 12 OLE)				
Previously randomized to somatrogon	104	78 (75%)	3 (3%)[1]	3 (3%)
Previously randomized to Genotropin	108	36 (33%)	0	1 (1%)
CP-4-004 Main				
Somatrogon 0.25 mg/kg dose group	13	0	0	0
Somatrogon 0.48 mg/kg dose group	15	5 (33%)	0	0
Somatrogon 0.66 mg/kg dose group	14	5 (36%)	0	0
Genotropin	11	2 (18%)	0	0
CP-4-004 OLE				
Year 1 (3 dose groups together)	48	12 (25%)	0	0
Year 2 (0.66 mg/kg dose group)	44	11 (25%)	0	0
Year 3 (0.66 mg/kg dose group)	43	11 (26%)	0	0
Year 4 (0.66 mg/kg dose group)	38	2 (5%)	0	0
PEN period[2] Year 1	40	15 (38%)	0	3 (8%)
PEN period[2] Year 2	35	13 (37%)	0	2 (6%)[3]

Source: Generated by Clinical Reviewer with information provided in the BLA original submission (isi.pdf), Major Amendment submission (isi.supplement.pdf), and responses to Information Requests.
[1] Of these three subjects, one subject (# (b) (6)) is also included among those NAb positive in the main period.
[2] PEN period used prefilled pen injector; other OLE periods and the main study of Trial CP-4-004 used vial presentation for injection. Trial CP-4-006 (Main and OLE studies) also used prefilled pen injector.
[3] One of the three subjects positive for anti-CTP in PEN Year 1 tested positive again in PEN Year 2 and was included in the two subjects counted for PEN Year 2.
Abbreviations: ADA, antidrug antibodies; NAb, neutralizing antibody; CTP, carboxy-terminal peptide; OLE, open-label extension

Although the incidence of ADA in Trial CP-4-004 was lower than in Trial CP-4-006, the rate of ADA-positive subjects in Trial CP-4-004 was higher in the somatrogon group compared to the Genotropin group. In the main period of the trial, 36% (5/14) of subjects treated with somatrogon 0.66 mg/kg/week and 18% of subjects treated with Genotropin developed ADA. The incidence of ADA in the lower somatrogon dose cohort (0.48 mg/kg/week) was also higher (33%) compared to the Genotropin group (Table 20). In the CP-4-004 OLE, the incidence of ADA-positive subjects in Year 4 was lower (5%) compared to the incidence in Years 1 to 3 (approximately 25%). However, it should be noted that most of the subjects in Year 4 (36) switched to PEN Year 1 at various points during the Year 4, i.e., they did not complete Year 4. No NAbs were reported in CPCP-4-004 (main and OLE periods).

Differences in ADA incidence among studies were not attributed to the testing strategy since equivalent validated immunogenicity assays were used in CP-4-004 and CP-4-006. Although the testing was performed at different sites, cross-testing of samples showed consistency in the results. Notably the ADA incidence in the Genotropin arms was consistent across studies.

Confirmed samples with anti-somatrogon antibodies were evaluated for their specificity to the hGH and CTP portions of somatrogon. The majority of anti-somatrogon-antibodies cross-reacted with hGH. In study CP-4-006, 85 of 92 (92.3%) of somatrogon-treated patients with ADA-positive showed cross-reactivity to hGH at some or all timepoints tested. Lastly, a total of 11 somatrogon subjects (7 in the CP-4-006, main and OLE periods and 4 in CP-4-004, PEN period) were reported with antibodies against the carboxy-terminus peptide (CTP) of the human chorionic gonadotropin (hCG) fused to hGH in somatrogon (anti-CTP antibodies). These

antibodies do not affect hGH part of the molecule and, thus, are unlikely to affect efficacy of the drug. The safety concerns with anti-CTP antibodies are addressed in Section 7.7.4.

Among all the subjects who tested positive for ADA in either arm during the clinical program, the ADA titers in the somatrogon arm were higher than those in the Genotropin arm. High titers of antibody and sustained antibody response can lead to the formation of immune complexes that can alter the pharmacokinetics of the drug, induce immune responses, and form immune complex deposits (refer to FDA Guidance for Industry, Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection). Moreover, sustained and high levels of ADA could lead to development of NAb with the potential to reduce drug efficacy and endogenous hGH activity as described above.

In Trial CP-4-006, main period, the ADA titer median for somatrogon arm was 250 (range 10 to 6250) at Month 6 and 50 (10 to 6250) at Month 12, respectively, while for Genotropin arm the titer median (range) was 10 (10 to 1250) at Month 6 and 10 (10 to 250) at Month 12. In the OLE period, ADA titers continued to be high in both groups, originally randomized to somatrogon and originally randomized to Genotropin: median (range) was 250 (10 to 6250) and 50 (10 to 6250), respectively. See Section 16.5, Table 95 and Table 96.

In Trial CP-4-004, main period, the median ADA titer at Month 6 was 50 (range 50 to 1250) and 250 (50 to 1250) in dose cohorts 0.48 mg/kg/week and 0.66 mg/kg/week, respectively. At Month 12 of the main period, the median ADA titer (range) was 250 (50 to 1250) and 250 (25 to 250) in dose cohorts 0.48 mg/kg/week and 0.66 mg/kg/week, respectively (See Table 97 in Appendix, Section 16.5). Median ADA titer (range) during the subsequent years of treatment were 50 (10 to 1250) in OLE Year 1; 250 (50 to 1250) in OLE Year 2; 250 (50-6250) in OLE Year 3; 130 (10 to 250) in OLE Year 4. Median ADA titer (range) in PEN period, was 250 (10 to 6250) and 50 (10 to 1250) in PEN Year 1 and Year 2, respectively. See Table 98 in Section 16.5.

Persistence of ADA Positivity

In addition to the high incidence of ADA, there was also persistence of positive ADA noted in the clinical program.

The Applicant used published criteria to assess persistence (Shankar et al. 2014), as presented in Section 16.5 and summarized as: ≥ 2 ADA-positive samples at time points separated by a period of ≥ 16 weeks (irrespective of any ADA-negative samples in between), or ADA-positive sample only at the last time point of the study treatment period, or at a time point < 16 weeks before an ADA-negative last sample. Most subjects treated with somatrogon who developed ADA had persistent antibodies through the OLE period of both trials. In Trial CP-4-006, ADA-positive subjects were first reported at the 6-month time point (main period) and nearly all subjects (83/84) met the criteria for persistent antibodies. ADA in subjects treated with Genotropin were predominantly transient (Table 21).

Table 21. Proportions of Subjects With Persistent ADA in Trials CP-4-006 and CP-4-004 (Main Period)

	CP-4-006		CP-4-004	
ADA-Positive Subjects	Somatrogon (N=109)	Genotropin (N=115)	Somatrogon (N=42)	Genotropin (N=11)
Total number of subjects per group	84 (77%)	18 (16%)	10 (24%)	2 (18%)
Subjects with persistent ADAs	83 (76%)	6 (5%)	7 (17%)	1 (9%)

Source: Prepared by the Medical Officer with data excerpted from Integrated Summary of Immunogenicity-appendix-tables-figures, Table 14.3.6.2.11, Table 16.2.8.5.3.1, CP-4-004-lab-measurements, Listing 16.2.9.6.1, CP-4-004-ole-lab-measurements, Listing 16.2.9.6, and data submitted in response to FDA Information Requests dated February 19, 2021 and October 14, 2021.
Abbreviation: ADA, antidrug antibodies

In Trial CP-4-006, OLE period (1 year), 114 of the 212 subjects (54%) tested ADA-positive and of those 112 (98%) met the pre-defined criteria for persistent ADAs.

In Trial CP-4-004, OLE, the incidence of ADA-positive by year was similar throughout the period: 13/48 (27%) in Year 1, 13/43 (30%) in Year 2, 12/38 (32%) in Year 3, 15/40 (38%) in PEN Year 1, and 14/34 (41%) in PEN Year 2. With exception of 2 subjects in Year 1, all subjects had persistent antibodies and several subjects tested positive for at least 4 years.

The presence of NAbs did not meet the persistence criteria. Samples positive for NAbs were observed in a single occasion in 4 of 5 subjects. In one subject (ID# (b) (6)) NAbs were positive at 3 time points (Month 6, Month 12 and Month 27). Although no clinically significant reduction in AHV was observed in this subject, no data are available after the Month 27 time point because this subject reached the end-of-study time point at Month 27 (the subject was from a site in India, where the OLE study was limited to one year). The Applicant did not provide data confirming that the Nabs resolved after drug discontinuation in this subject.

Lastly, the rate of ADA in adult patients with GHD observed in phase 3 clinical trial evaluating efficacy and safety of somatrogon compared to placebo in adult patients with GHD (CP-4-005) was 8%. Of note, the trial did not demonstrate a statistically significant difference between somatrogon group (n=133) and placebo group (n=65) in the improvement of truncal fat mass (primary endpoint) from baseline to 26 weeks: -0.3 kg versus 0.1 kg, p=0.08.

Factors That May Explain the High Immunogenicity of the Product

The clinical and Office of Biotechnology Products (OBP) review teams conducted further analyses to identify factors that led to high immunogenicity. The results of these analyses are discussed here.

Somatrogon immunogenicity has been assessed in patients from studies CP-4-006 (registrational, main and OLE periods) and CP-4-004 (phase 2, main, and OLE periods) using equivalent validated assays. The immunogenicity testing paradigm was found to be adequate for the assessment of ADA in clinical samples. It is notable that the rate of ADA formation was similar for Genotropin between studies CP-4-006 and CP-4-004 confirming that assay/methodology was not the cause for differences between trials in ADA rate.

Based on the data from clinical program, the following factors were investigated further as potential candidates that may at least partially explain the high ADA rate and persistence of ADAs. It was noted that higher ADA rates were observed in patients who 1) were treated with the same drug dose (i.e., 0.66 mg/kg/week) delivered by the pen injector in trial CP-4-006 (77%) compared delivered by the pen injector in trial CP-4-006 (77%) compared to the vial for

injection in trial CP-4-004 (36%) and 2) received higher doses in trial CP-4-004 (36%, 33% and zero for 0.66 mg/kg/week, 0.48 mg/kg/week, and 0.25 mg/kg/week, respectively (refer to Table 22). These factors are discussed here.

- Device (PEN)-dependency

The drug product formulation of somatrogon underwent changes with the development of a prefilled pen injector delivery system, that replaced the vial for injection configuration used in Trial CP-4-004. The pen injector was implemented in Trial CP-4-006 and in CP-4-004, PEN-OLE phase. Development of antibodies to the CTP portion of the molecule were only observed with somatrogon treatment using the pen injector (3% in trial CP-4-006 and up to 8% in PEN Period of trial CP-4-004). No anti-CTP antibodies were identified in Trials that used the vial-stored frozen formulation (CP-4-004 or CP-4-005) and only 1 adult patient tested positive for NAbs in CP-4-005. However, the absence of anti-CTP antibodies in trial CP-4-004 with vial use might be related to the small sample size of the trial and overall rarity of these antibodies observed in the clinical program.

There are a number of factors associated with the chemistry, manufacturing, and controls (CMC) changes adopted during the transition to the pen injector presentation (used in Trial CP-4-006 and OLE PEN period of Trial CP-4-004) that could potentially lead to high ADA development: [redacted] (b) (4) are also risk factors for ADA formation (refer to CMC review). Thus, FDA asked the Applicant to further investigate these issues and to provide product characterization information that could help to understand the high incidence of ADA in subjects using the pen injector (refer to the IR from March 29, 2021). The Applicant's response included data investigating potential immunogenicity risk factors for somatrogon, manufacturing process control comparability between the frozen and liquid configurations of the DP, and a list of DP lots used in the clinical program. The Applicant was unable to conclude whether any of these factors were responsible for the induction of ADA formation. The Applicant also reported that [redacted] (b) (4) an immunogenicity risk factor highlighted by FDA in a previous communication, were not identified in [redacted] (b) (4) the pen injector. Overall, the FDA assessment of the overall Applicant's information did not reveal a causative factor for the increased ADA incidence and the nature of ADA observed in somatrogon-treated patients, especially when using a pen injector device.

- Dose-dependency

Development of ADA was absent in the somatrogon low dose (0.25 mg/kg/week) group and was similar in the middle (0.48 mg/kg/week) and high (0.66 mg/kg/week dose groups in the main period of phase 2 Trial CP-4-004. At Month 6, a higher proportion of subjects treated with somatrogon 0.66 mg/kg/week and 0.48 mg/kg/doses had developed ADA than those treated with 0.25 mg/kg/week or Genotropin Table 22. A similar trend was noted at Month 12, however, the incidence of ADA in 0.66 mg/kg/week group was slightly lower compared to 0.48 mg/kg/week group, which might be due to the overall small number of subjects per group.

Table 22. Incidence of ADA in the Somatrogon Dose Groups and Genotropin Group at 6 and 12 Months, Trial CP-4-004 (Main Period)

	Somatrogon			Genotropin
Parameter	0.25 mg/kg/wk N=13	0.48 mg/kg/wk N=15	0.66 mg/kg/wk N=14	0.034 mg/kg/wk N=11
ADA+ subjects, n (%)				
Month 6	0/13 (0)	5/15 (33.3)	5/14 (35.7)	2/11 (18.2)
Month 12	0/13 (0)	3/15 (20.0)	2/14 (14.3)	1/11 (9.1)

Source: Prepared by the Medical Officer based on data excerpted from the Integrated Summary of Immunogenicity, Table 12.
Abbreviation: ADA, antidrug antibody

Overall, a broad range of ADA risk was observed among the clinical trials (if trial 005 conducted in adults but not submitted in this NDA is considered) despite use of the same assays, with a particularly high and unexpected ADA response in Trial CP-4-006. In this trial, subjects were initiated on somatrogon using the pen device, while Trial CP-4-004 dosed subjects using a vial and syringe for the first 44 years before switching to the pen, potentially priming them to lower antibody response. However, review of CMC data did not reveal any factors that may be device-related. At this time the cause of the immunogenicity findings remains unknown, and hence non-remediable.

Effect of ADA on Somatrogon PK: Decreased Clearance of Somatrogon from Circulation in ADA-Positive Subjects

Although limited PK data were obtained from Trial CP-4-004 and CP-4-006 from sparse PK sampling design, higher somatrogon concentrations were seen in ADA-positive subjects compared to ADA-negative subjects (Figure 27, Figure 30, Table 62, Table 63, Table 68, and Table 69).

To better understand this finding, the impact of immunogenicity on PK was further assessed using a population PK approach, in which ADA status was a time-varying covariate for clearance. Based on model predicted PK parameters, the mean clearance of somatrogon decreases ~26% after patients developed antidrug antibodies (Table 83 and Table 84 of the Pharmacometrics Review).

The increase in exposure in ADA-positive subjects did not appear to impact IGF-1 response. When plotting IGF-1 SDS from Trial CP-4-004 and CP-4-006 by ADA status, the range of IGF-1 SDS values among those who tested ADA positive to somatrogon overlap with those who tested ADA negative at different time points (Figure 28, Figure 29, and Figure 31) One of the concerns with the decreased somatrogon clearance is that it may be due to the formation of antibody-drug complexes, although this has not been evaluated in the somatrogon clinical program. High titers of ADA and sustained antibody response can potentially lead to the formation of immune complexes that can alter the pharmacokinetics of the drug, induce immune responses and immune complex deposition (Guidance 2014).

Potential Effect of ADA on Somatrogon-Induced Growth

The high incidence of ADA raises concerns regarding growth attenuation affecting final adult height.

To better understand the relationship between ADA and growth, the reviewers analyzed growth parameter values among both ADA-positive and -negative subjects at Month 12 in Trials CP-4-006 and CP-4-004.

In Trial CP-4-006, main period, no meaningful difference in mean AHV (Table 23) and height SDS (Table 24) were noted between ADA-positive subjects and ADA-negative subjects during the 12-month treatment period. The growth observed in ADA-positive subjects was also comparable to the growth parameters observed in the Genotropin group. Further information is provided in Table 99 and Table 100 in Section 16.5.

Table 23. Mean AHV by ADA Status in Trial CP-4-006 (Main Period)

	Mean AHV (cm/Year)					
	Somatrogon			Genotropin		
Timepoint	ADA+ (N=84)	ADA- (N=25)	Mean Difference[1] Between ADA+ and ADA-	ADA+ (N=18)	ADA- (N=97)	Mean Difference[1] Between ADA+ and ADA-
Month 3	11.90	10.44	1.18 (-0.63, 2.99)	13.65	9.99	3.19 (1.21, 5.18)
Month 6	10.96	10.48	0.13 (-1.03, 1.29)	11.37	9.88	0.90 (-0.51, 2.30)
Month 9	10.34	10.35	-0.37 (-1.41, 0.68)	10.87	9.73	0.64 (-0.63, 1.91)
Month 12	10.21	10.07	-0.24 (-1.22, 0.74)	10.54	9.52	0.51 (-0.65, 1.68)

Source: Prepared by the Medical Officer with data excerpted from the Integrated Summary of Immunogenicity, Tables 22 and 23.
[1] Mean difference (95% confidence interval) based on the analysis of covariance model.
Abbreviations: AHV, annualized height velocity; ADA, antidrug antibody

Table 24. Changes in HT SDS From Baseline by ADA Status, Trial CP-4-006 (Main Period)

	Mean HT SDS (cm)					
	Somatrogon			Genotropin		
Timepoint	ADA+ (N=84)	ADA- (N=25)	Mean Difference[1] Between ADA+ and ADA-	ADA+ (N=18)	ADA- (N=97)	Mean Difference[1] Between ADA+ and ADA-
Month 3	0.33	0.25	0.062 (-0.03, 0.15)	0.42	0.23	0.145 (0.04, 0.25)
Month 6	0.58	0.47	0.057 (-0.07, 0.19)	0.64	0.44	0.107 (-0.03, 0.25)
Month 9	0.75	0.67	0.012 (-0.16, 0.18)	0.88	0.63	0.121 (-0.07, 0.32)
Month 12	0.95	0.86	0.005 (-0.20, 0.21)	1.10	0.79	0.139 (-0.10, 0.38)

Source: Prepared by the Medical Officer with data excerpted from the Integrated Summary of Immunogenicity, Tables 24 and 25.
[1] Mean difference (95% confidence interval) based on the analysis of covariance model.
Abbreviations: HT SDS, height standard deviation; ADA, antidrug antibody

Findings in AHV and HT SDS at 12 months of OLE period were similar to those of the main period. No significant differences were noted between subjects by their original randomization in the main period and by ADA status (Table 25).

Table 25. Mean AHV and mean HT SDS by original randomization and ADA status at 12 month OLE, Trial CP-4-006

	Originally randomized to somatrogon		Originally randomized to Genotropin	
	ADA + (N=91)	ADA - (N=18)	ADA + (N=38)	ADA - (N=69)
n	69	14	28	46
AHV (cm/year)				
Mean (SD)	8.10 (1.86)	7.47 (1.38)	8.44 (1.94)	8.14 (1.83)
Median	7.91	7.37	8.20	7.98
Min, max	1.48, 13.14	4.89, 9.88	4.74, 13.65	5.19, 12.94
HT SDS				
Mean (SD)	-1.37 (0.80)	-1.42 (0.96)	-1.15 (0.63)	-1.23 (0.73)
Median	-1.23	-1.60	-1.17	-1.24
Min, max	-3.94, 0.76	-3.45, 0.13	-2.43, 0.15	-3.00, 0.37

Source: Excerpted from isi.supplement, Table 14 and Table 15.
Abbreviations: ADA, antidrug antibody, AHV, annualized growth velocity, HT SDS, height standard deviation

In Trial CP-4-004, the AHV at 12 months was similar between ADA-positive and ADA-negative subjects within all dose groups, with no apparent trend related to somatrogon dose assignment or

treatment group (somatrogon versus Genotropin). Overall, the magnitude of differences between ADA-positive and ADA-negative subjects is small. See Table 100, Section 16.5.

Table 26. Mean AHV and Mean Change in HT SDS by ADA Status in the Somatrogon and Genotropin Groups, Trial CP-4-004 (Main Study)

	Somatrogon 0.25 mg/kg/wk N=13		Somatrogon 0.48 mg/kg/wk N=15		Somatrogon 0.66 mg/kg/wk N=14		Genotropin N=11	
Parameter	ADA+ n=0	ADA- n=13 (100%)	ADA+ n=5 (33%)	ADA- n=10 (67%)	ADA+ n=5 (36%)	ADA- n=9 (64%)	ADA+ n=2 (18%)	ADA- n=9 (82%)
Mean AHV (cm/year)	N/A	10.4	12.5	10.2	10.9	11.7	14.5	12.0
Mean HT SD (cm)	N/A	-2.55	-2.42	-2.58	-3.30	-2.66	-3.18	-2.64

Source: Table 7 provided in response to the Information Request dated October 14, 2021.
Abbreviations: ADA, antidrug antibodies; AHV, annualized height velocity; HT SDS, height standard deviation score; SD, standard deviation

In the OLE period, which had new ADA-positive subjects and no comparator arm, there was a trend of decreasing growth parameters over the subsequent years of treatment in both ADA-positive and ADA-negative subjects. However, no meaningful differences were noted (Table 27) (complete data in Table 102). A small decline in growth rate was observed during the second year of treatment and is consistent with what is observed with all hGH products: the largest increase in AHV is usually observed during the first 6 to 12 months of treatment (due to the catch-up phenomenon) and decreases during subsequent years of treatment. Growth velocity also decreases due to other natural factors, including age.

Table 27. Mean AHV and Mean HT SDS by ADA Status in the Somatrogon Group in Trial CP-4-004 OLE (Years 1 to 4 and PEN)

Mean AHV (cm/Year)/HT SDS (cm)	AHV/HT SDS (cm) at End of Years 1-4 and PEN (Years 1 and 2)					
	0.25 mg/kg/Week		0.48 mg/kg/Week		0.66 mg/kg/Week	
	ADA+	ADA-	ADA+	ADA-	ADA+	ADA-
Year 1 (N)	0	13	5	10	5	9
	7.59/-1.33	7.75/-2.17	7.85/-1.74	7.48/-1.96	9.01/-2.91	8.67/-1.72
Year 2 (N)	-	-	-	-	14	29
AHV/HT SDS	-	-	-	-	7.26/-1.71	7.56/-1.54
Year 3 (N)	-	-	-	-	14	24
AHV/HT SDS	-	-	-	-	6.71/-1.47	7.36/-1.15
Year 4	-	-	-	-	1	0
AHV/HT SDS	-	-	-	-	4.63/-2.53[1]	
PEN/Year 1 (N)	-	-	-	-	15	20
AHV/HT SDS	-	-	-	-	6.31/-1.04	7.48/-0.43
PEN/Year 2	-	-	-	-	15	15
AHV/HT SDS	-	-	-	-	6.47/-0.72	6.48/-0.14

Source: Table prepared by Medical Officer with data excerpted from the Integrated Summary of Immunogenicity, Table 19; Clinical Study Report CP-4-004 OLE, Table 22 and Table 23; and isi-supplement, Table 10 (Major Amendment).
[1] In Year 4 there was only one subject.
Abbreviations: AHV, annualized height velocity; ADA, antidrug antibody; N, number of subjects (for ADA+, N is the largest number of subjects ADA+ at any time)

No neutralizing antibodies developed in Study 004, and no differences in 12-month growth between ADA-positive and ADA-negative subjects and subjects treated with Genotropin were noted.

Potential Impact of Neutralizing Antibodies on Growth

The high incidence of ADA increases the risk of developing neutralizing antibodies, which may reduce native/endogenous GH activity and promote epitope spread (Disis et al. 2004; Hintermann et al. 2011). As described above, a total of five subjects tested positive for NAbs in the somatrogon clinical program.

The growth parameters of these five subjects were further reviewed (Table 28). Four of the five subjects did not have significant changes in AHV after testing positive for NAb. However, subject # (b) (6) (6-year-old) had a significant decrease in AHV (from 11.8 to 3.0 cm/year) at Month 18, after testing positive for NAb at Month 12 (summarized in the shaded area in Table 28). See narrative for this subject below.

Table 28. ADA Titers and Growth Measurements in Subjects With NAb Over Time, Trial CP-4-006 (From Entry to the Main Period, to the OLE)

Subject ID	Gender/Age (Years) at Entry	Timepoint From Entry	ADA Titer	NAb Somatrogon	NAb hGH	AHV (cm/Year)	HT SDS (cm)	IGF-1 SDS	IGF-1 (mcg/L)
(b) (6)	Male/ 7.3	Baseline		N	N	NA	-3.745	-3.54	22
		Month 1	N	NA	NA	NA	NA	-2.44	51
		Month 3	50	N	N	17.8	-3.19	-0.80	119
		Month 6	250	N	N	15.9	-2.66	0.07	178
		Month 9	50	N	N	13.9	-2.38	0.34	208
		Month 12	250	N	N	13.7	-2.14	NA	NA
		Month 18	250	N	N	9.8	-1.62	-2.38	66
		Month 24	**250**	**N**	**Y**	**7.1**	**-1.68**	**-0.03**	**207**
		Month 30	NA	NA	NA	7.2	-1.46	-2.69	NA
		Month 33	NA	NA	NA	8.2	-1.09	NA	NA
(b) (6)	Male/ 9.5	Baseline	N	N	N	NA	-3.66	-3.50	33
		Month 1	N	NA	NA	NA	NA	-0.28	201
		Month 6	10	N	N	10.9	-3.04	1.33	362
		Month 12	50/250	N	N	10.8	-2.50	2.61	508
		Month 18	1250	N	N	10.8	-1.98	1.54	426
		Month 24	**1250**	**N**	**Y**	**9.2**	**-1.81**	**2.28**	**518**
		Month 30	NA	NA	NA	8.1	-1.71	1.46	NA
		Month 33	NA	NA	NA	7.6	-1.78	NA	NA
(b) (6)	Female/ 9.5	Baseline	N	N	N	NA	-6.86	-3.54	20
		Month 1	N	NA	NA	NA	NA	-1.35	112
		Month 6	250	N	N	15.4	-5.52	-3.21	31
		Month 12	**250**	**N**	**Y**	**15.5**	**-4.33**	**0.63**	**280**
		Month 18	10	NA	NA	8.3	-3.79	1.41	406
		Month 24/EOS	50	N	N	9.7	-3.41	1.28	408
(b) (6)	Male/ 6.3	Baseline	N	N	N	NA	-7.48	-3.70	16
		Month 1	N	NA	NA	NA	NA	-2.46	44
		Month 6	10	N	N	11.8	-6.95	-3.54	20
		Month 12	***10***	***Y***	***N***	***11.8***	***-6.40***	***-1.84***	***72***
		Month 18	*N*	*NA*	*NA*	*3.0*	*-6.75*	*-1.68*	*90*

Subject ID	Gender/Age (Years) at Entry	Timepoint From Entry	ADA Titer	NAb Somatrogon	NAb hGH	AHV (cm/Year)	HT SDS (cm)	IGF-1 SDS	IGF-1 (mcg/L)
(b) (6) *	Male/ 3.0	Baseline	N	N	N	NA	-6.18	-3.05	17
		Month 1	N	NA	NA	NA	NA	-1.56	49
		Month 6	**>6250**	**Y**	**N**	**20.1**	**-3.73**	**0.27**	**122**
		Month 12	**1250**	**Y**	**N**	**17.8**	**-2.25**	**1.19**	**178**
		Month 18	1250	N	N	9.7	-1.68	2.13	258
		Month 27	**1250**	**N**	**Y**	**9.3**	**-1.24**	**3.02**	**NA**

Source: Prepared by the Medical Officer with data excerpted from the Clinical Study Report, Trial CP-4-006 and from the Major Amendment, Appendix 1, Table 3.1.13.
Bolded rows are timepoints reported with neutralizing antibodies. The subject with a decrease in AHV is shaded in gray; italics indicate timepoints of neutralizing antibody occurrence and of subsequent reduction in AHV.
* Subject completed the study as per protocol in India, and no further data are available on this subject.
Median (range) AHV for age group (>3 to ≤7) years: 10.0 (7.9, 17.8) cm/year.
Median (range) AHV for age group >7 years: 9.5 (4.6, 17.8) cm/year.
Abbreviations: ADA, antidrug antibody; AHV, annualized height velocity; HT SDS, height standard deviation score, IGF-1, N, negative; NA, not available; NAb, neutralizing antibody; OLE, open-label extension

Subject (b) (6) was a 6-year-old male subject (study site in India) who was randomized to somatrogon 0.66 mg/kg/week in the main phase. Following completion of the main phase, the subject entered the OLE phase at the same somatrogon dose (0.66 mg/kg/week). Except for GHD, no other medical history was reported. Concomitant medications included calcium carbonate/cholecalciferol (prophylaxis of calcium deficiency) and ferric hydroxide polymaltose complex (for anemia). The thyroid stimulating hormone (TSH) was slightly elevated (6.03 mIU/mL, normal range 0.35-5.8 mIU/mL) and normal thyroxine (free T4) at baseline; however, no medical history of hypothyroidism was reported. Both TSH and free T4 levels returned to within normal range at Month 6, 9, and 12 (No values are available for Month 18). Hematology tests showed low levels of hemoglobin and hematocrit from baseline to Month 3 and one treatment-emergent adverse event of anemia was reported at Month 1. No other clinically significant laboratory abnormalities were reported throughout the study. The subject first tested positive for ADA during the main phase at Month 6 (titer 10) and was negative for NAbs; at Month 12, both ADA (titer 10) and NAbs were positive, and at Month 18 (Month 6 of OLE), ADA was negative. AHV was consistently higher at Month 3, Month 6, Month 9, and Month 12 (12.8, 11.8, 11.4, 11.8 cm/year, respectively) than at Month 18 (3.0 cm/year). Similarly, HT SDS was consistently improving (-7.2, -7.0, -6.7, -6.4 at Month 3, Month 6, Month 9, and Month 12, respectively) slightly regressed to -6.8 at Month 18. IGF-1 SDS values although showing a trend to improvement, did not reach normalization during the 18-month treatment (see Table 28). The presence of ADAs was not associated with adverse events, hypersensitivity, injection site reactions or other clinical events. No missing doses and no major protocol deviations were reported. No data are available for this subject after the 18-month time point (the Month 24 time point was likely just a few weeks beyond the data lock date of the amendment report). Given lack of other explanation for the significant decrease in AHV at Month 18, an impact of NAbs blocking the somatrogon effect on growth cannot be ruled out in this subject. Two NAb cell-based assays were developed to monitor NAbs against somatrogon and against hGH. These assays rely on the ability of somatrogon or hGH to induce cell proliferation by binding to the hGH receptor expressed on the cell surface of a murine lymphocyte cell line. Both assays were adequately validated. Although both ligands induce cell proliferation upon engaging the GH receptor of the cell, somatrogon has a much lower affinity for the receptor, leading to a 26-fold difference in the sensitivity of the somatrogon NAb assay compared to hGH NAb assay. This could explain the higher proportion of positive samples for anti-hGH NAb compared to anti-somatrogon NAb.

Overall, it is concerning that only subjects treated with somatrogon developed NAbs and that 4 of 5 subjects developed NAbs with specificity to hGH, which could potentially have an impact on native GH. Although there does not appear to be an association between neutralizing antibodies and the 12-month growth rate in 4 of 5 subjects, the data are limited and longer-term data are needed to adequately assess whether there is an association. All subjects who developed NAbs were from the registrational study (Trial CP-4-006), i.e., treated with somatrogon dose 0.66 mg/kg/week and pen injector, which are the dose and presentation intended for the to-be-marketed product. The increase in exposure in ADA-positive subjects did not appear to impact IGF-1 response. When plotting IGF-1 SDS from Trial CP-4-004 and CP-4-006 by ADA status, the range of IGF-1 SDS values among those who tested ADA positive to somatrogon overlap with those who tested ADA negative at different time points (Figure 28, Figure 29, and Figure 31).

Conclusion

We conclude that the available immunogenicity data demonstrate an unresolved risk of uncertain clinical significance, that unfavorably affects benefit-risk considerations. Unexpectedly high and persistent ADA titers, mostly cross reactive to native GH, were observed in the clinical program in somatrogon treated subjects. The available data suggest that for most subjects ADA did not have an impact on growth. However, a concern remains for the development of NAbs, which developed in a small subset of subjects with ADA (2-3%). One of the 5 subjects who developed NAbs had an unexpected significant decline in growth rate that, to date, has gone unexplained because of insufficient follow up time. Therefore, there is uncertainty about the clinical relevance of NAbs at this time including the potential for somatrogon non-responsiveness resulting in lack of growth, as well as the potential concern of non-responsiveness to other hGH products if cross reactive antibodies persist. The concern about immunogenicity cannot be resolved during this review cycle by requesting further information, as follow up data on the patient of concern will need to be collected over time. Furthermore, without an identified cause of the immunogenicity, we are unable provide advice to the sponsor on suggested remediation strategies to reduce immunogenicity risk.

Dissent

No dissent.

6.3.2. Intended Population: Children of All Ages With Open Epiphysis With GHD

Issue

Whether the overall data included in BLA support the efficacy of the drug in patients <3 years with pediatric GHD

Background

The Applicant proposes an indication for children with pediatric GHD of all ages whose epiphyses are not closed.

Assessment

Children younger than 3 years were not included in the somatrogon clinical program. Therefore, the efficacy, safety, and PK of this drug are unknown in these children.

Efficacy in younger children cannot be extrapolated for a number of reasons. First, growth failure due to GHD is rarely diagnosed in children < 2 years old, and the most common causes of growth failure during the first year of life are small for gestational age or genetic causes. In addition, neonatal GHD manifests by hypoglycemia. Importantly, the PK profile of this long-acting drug is different from other approved hGH formulations. It is therefore not clear if subjects younger than 3 would have a similar, greater, or lower IGF-1 response to somatrogon compared to subjects 3 years and older. If subjects under 3 years exhibit an exaggerated IGF-1 response with somatrogon, given that somatrogon has a longer half-life than the currently available daily GH therapies, any adverse events observed may not be easily reversible upon discontinuation of the drug. Lastly, binding of estimated IGF to insulin receptors may exaggerate hypoglycemia in neonates with GHD.

Conclusion

Because of lack of safety, efficacy, and PK data of somatrogon in children below the age of 3 years, somatrogon should be indicated only for the treatment of pediatric patients >3 years old with open epiphyses.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical program to support the use of somatrogon for the long-term treatment of pediatric subjects who have growth failure due to inadequate secretion of endogenous growth hormone included a series of in vitro and in vivo pharmacology studies, pharmacokinetic studies in rats and monkeys, toxicity studies in rats (up to 4-week duration) and monkeys (up to 26-week duration), and reproductive toxicity studies in rats. Nonclinical findings were consistent with the pharmacologic activity of growth hormone. ADAs against the hGH component and, to a lesser extent, the CTP component of somatrogon, were observed in rats and monkeys. However, there was no evidence that ADAs affected somatrogon exposure or pharmacodynamic activity. ADA formation and impact in animals is not generally considered to be predictive of a similar response in humans. However, ADA evaluations may inform study interpretation. Overall, no unexpected safety signals were identified with somatrogon in the completed nonclinical studies. All adverse effects observed in animals were associated with exaggerated pharmacology of excess growth hormone in healthy animals. Therefore, PharmTox recommends approval of this BLA.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The following AEs are labeled in the hGH drug class. These are discussed in Sections 7.6.7 and 7.7.1:

- Neoplasms
- Impaired glucose intolerance
- Hypothyroidism
- Adrenal insufficiency
- Intracranial hypertension
- Pancreatitis
- Edema (and edema-induced AEs such as arthralgia, headache, hypertension, carpal tunnel syndrome)
- Slipped femoral capital epiphyses and scoliosis
- Injection site reactions and lipodystrophy
- Immunogenicity
  - All therapeutic proteins have the potential for immunogenicity. Treatment of patients with therapeutic proteins, such as hGH, may result in immune responses of varying clinical significance based on product- and patient-specific factors. Overall, the immunogenicity of approved hGH products is low and incidence of ADA in GHD children reported in product labels of currently marketed somatropin varies from zero to 6.3%.[4]
  - A high and persistent rate of ADAs was observed in the somatrogon clinical program (Section 6.3.1). In addition, treatment with somatrogon was associated with development of anti-CTP antibodies that may be interfere with pregnancy tests (Section 6.3.1) and affect fertility and pregnancy outcomes (Section 7.7.4). The safety issues associated with immunogenicity are further explored in Section 7.7.3 and 7.7.4.

Additional safety concerns with hGH replacement therapy in pediatric GHD and that are not labeled in the drug class include chronically elevated levels of IGF-1 and accelerated bone aging.

- Elevated IGF-1 Levels

There is a concern with all hGH formulations that chronically elevated IGF-1 levels above the normal range may be associated with various AEs characteristic of acromegaly, including headache, intracranial hypertension, edema, and tumors. Thus, the team analyzed the incidence of elevated IGF-1 SDS above +2 SDS (threshold established by the Applicant) and association of elevated IGF-1 levels with AEs. The levels of IGF-1 that are clearly associated with adverse reactions are not established to date.

- Accelerated Bone Aging

Treatment with all growth-promoting therapies may potentially accelerate bone age, leading to premature closure of the growth plate and shorter-than-expected final adult height. However, patients with GHD have a delay in bone age relative to chronological age and the bone age is expected to improve on treatment. Thus, bone age was an efficacy endpoint in the somatrogon clinical program and is discussed in Section 6.2.2.4.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

Somatrogon has not been approved in any country; therefore, there has been no postmarketing experience with somatrogon.

[4] https://dailymed.nlm.nih.gov/

7.4. FDA Approach to the Safety Review

7.4.1. Source of Data for Clinical Assessment

The safety data are derived from two trials in pediatric subjects, age 3 to 11 years with GHD: a phase 3 study, Trial CP-4-006 (completed main period and ongoing OLE period) and a phase 2, dose-finding study, Trial CP-4-004 (completed main period and ongoing OLE period).

The cut-off data lock date for the ongoing open-label studies was November 1, 2019. Review of safety data also included data provided in the 4-month safety update (4-MSU) with cutoff date of December 21, 2020.

7.4.2. Safety Analysis Plan and Definitions

The prespecified safety analysis plan and definitions were reviewed during the clinical development program and were acceptable.

The Safety Population was defined as all subjects with GHD who were enrolled in the studies and treated with at least one dose of study drug. Use of descriptive statistics was predefined in the study protocols for summarizing the safety outcomes. The review team agreed with the proposed approach.

Treatment-emergent AEs (TEAEs) were protocol-defined as any AE with onset or worsening after the initiation of study drug and up to 30 days after study drug discontinuation.

For Trial CP-4-004, AEs were classified in four severity grades: Mild or Grade I (event does not affect the patient's usual daily activities); Moderate or Grade II (event interrupts the patient's usual daily activities); Severe or Grade III (event causes considerable interference with the usual daily activities); and Life threatening or Grade IV (the event is incapacitating). For Trial CP-4-006, the classification was similar, but Grade IV (life-threatening) was not included.

No major issues were identified with respect to recoding, coding, and categorizing AEs. The Applicant translated verbatim terms to Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) for the events reported in the trials. The translations were reviewed and found overall acceptable, unless specifically noted in this review.

Lastly, the review team conducted a separate analysis of adverse reactions (ARs) occurring during main period of Trial CP-4-006 and CP-4-004 using FDA Medical Queries (FMQ). FMQs were developed by FDA to improve the capture of synonymous adverse event terms and to improve overall safety signal detection. PTs that were not captured by FMQ were added to the AR analysis.

7.4.3. Reviewer's Approach to Safety Evaluation

The clinical reviewer used the safety data originating from the main phase of Trial CP-4-006 as the primary source for safety assessment. This study provides the most informative data on common product-related safety issues because it allows side-by-side comparison of somatrogon to Genotropin (with established safety profile in the proposed indication), were obtained in randomized groups with frequent assessment and had an approximately 12-month duration of controlled observation. Supportive safety data are provided from the ongoing OLE period of Trial CP-4-006 and from Trial CP-4-004 (main period and ongoing OLE period). Safety data from the supportive pediatric study (Trial CP-4-004) are complicated due to the different

exposure to the proposed dose (0.66 mg/kg/week), use of lower doses for 12 months, absence of control group, potential confounding effect of previously used Genotropin, and the use of a different product presentation (vial versus pen injector used in the registrational trial). Thus, the supportive safety data (i.e., from CP-4-006 OLE, CP-4-004 main and OLE studies) are used to look for conspicuous clinically important events only rather than comparative analyses.

Considering the significant differences in trial designs, including randomization, use of control arms, duration, doses studied, previous exposure to Genotropin in number of subjects, the clinical reviewer also analyzed and presented the safety data separately for each individual trial.

Clinical trial data were independently analyzed by clinical review team using Python software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

7.5. Adequacy of Clinical Safety Database

Overall, while the level of exposure to the study drug during the clinical development program does not satisfy the International Conference on Harmonisation (ICH) E1 guidelines for safety assessment of chronically administered medications, the level of exposure of somatrogon is adequate for a chronically administered drug in the rare disease of pediatric GHD. Similar level of exposure was used for the approval of other hGH products (e.g., Zomacton - 164 subjects, Omnitrope - 86 patients) for pediatric GHD indication. Thus, the safety database from two pediatric trials was considered as adequate for a comprehensive safety assessment of somatrogon for the proposed indication, patient population, and dosage regimen at the time of BLA submission.

The high rate of ADA identified during the review of BLA raises potential safety concerns with long-term use of the drug, i.e., ADA-induced new safety signals or increase in frequency/severity of known safety signals. The12-month controlled safety data from trial CP-4-006 were considered to be adequate to evaluate and to conclude whether there is any impact of ADA on frequency/severity of AEs is observed during the 12-month treatment. In addition, the safety data from OLE periods of trials CP-4-006 and CP-4-004 evaluated the long-term effect of ADA on safety profile of somatrogon and provided additional supportive long-term safety data for somatrogon in the intended population (up to 5 years). However, it should be noted that long-term data are derived from an overall small, uncontrolled sample, with different doses of somatrogon (trial CP-4-004), previous exposure to Genotropin, and use of different delivery systems, pen injector versus vial/syringe.

In the somatrogon development program, a total of 269 subjects received at least one dose of somatrogon with a mean exposure duration of 21 months. Of these, 264 (217 in Trial CP-4-006 and 40 in Trial CP-4-004) subjects received at least one dose of 0.66 mg/kg/week administered by pen injector. A total of 123 subjects received only somatrogon 0.66 mg/kg/week from the onset of treatment; all other subjects initially received either lower doses of somatrogon or Genotropin and were later switched to somatrogon. Of the 123 subjects, 116 (99%) subjects were exposed to somatrogon for ≥1 year, 110 (89%) subjects for ≥2 years, 24 (20%) subjects for ≥3 years, 11 (9%) subjects for ≥4 years, and 11 (9%) subjects for ≥5 years.

In Trial CP-4-006, a total 217 subjects received at least one dose of 0.66 mg/kg/wk of somatrogon during the main and/or OLE periods up to the cut-off date of December 21, 2020. In

the main period of the study, the mean exposure to somatrogon was 363 days (Table 29). Approximately 99% of subjects in both groups completed the 12-month main study.

Table 29. Duration of Exposure, Safety Population, Trial CP-4-006 (Main Study)

Variable	Somatrogon N=109 n (%)	Genotropin N=115 n (%)
Duration of treatment (days)		
Mean (SD)	362.5 (31.8)	354.5 (27.8)
Median (minimum, maximum)	364.0 (63.0, 413.0)	358.0 (78.0, 382.0)
Subjects treated, by duration, n (%)		
Completed 1 year	108 (99.1)	114 (99.1)

Source: Analysis performed by the FDA Clinical Data Scientist using adex.xpt; software, Python.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

In the OLE period of the study, of the 212 subjects (104 originally randomized to somatrogon and 108 originally randomized to Genotropin) 102 subjects in each group (98% and 94%, respectively) completed 1 year of treatment with somatrogon 0.66 mg/kg/week (Table 103, Section 17.1).

In the phase 2 study (Trial CP-4-004), main period, a total of 14 subjects were exposed to somatrogon 0.66 mg/kg/week using vial formulation for ≥6 months and <12 months (Table 104). One subject (ID# (b) (6)) was discontinued due to wrongly included in the study and one subject withdrew from the study. Thus, of the 14 subjects originally randomized to somatrogon 0.66 mg/kg/week, 12 subjects continued on this dose through the OLE period using the vial presentation (for up to 4 years) and 11 subjects switched to the pen-injector after completing 2-4 years with vial presentation. Seven of the 11 subjects in the PEN group completed >24 months but less <36 months. The longest exposure to somatrogon dose 0.66 mg/kg/week during the OLE (vial and pen presentation) was ≥ 6 years and < 7 years (in 4 subjects) with a total exposure (main + OLE period) of up to 7 years (Table 105).

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns, Trials CP-4-006 and CP-4-004

Overall, the type and frequencies of AEs seen with the somatrogon treatment in the clinical program (Trials CP-4-006 and CP-4-004) were generally consistent with the known safety profile of the hGH drug class.

No death was reported. The incidence of serious adverse events (SAEs) was low in trials and all but one (scoliosis) SAEs did not appear to be drug-related. A total of 10 subjects discontinued the studies prematurely due to an AE up to the cut-off date of December 21, 2020, and 1 subject was reported as permanently discontinued due to AE after the cut-off date. The majority of AEs reported during the clinical program were nonserious, mild, or moderate. In Trial CP-4-006, the most frequent AEs were injection site reactions which are expected with an injectable drug. A higher incidence of injection site reactions was noted with somatrogon use compared to Genotropin use. However, most reaction were nonserious and resolved without drug discontinuation (6 subjects in the trial discontinued prematurely due to injection site reactions).

Refer to Section 7.7.1 for further discussion of injection site reactions. Overall, the safety profile of somatrogon in trial CP-4-004 was similar to that observed in Trial CP-4-006.

There was a high and persistent ADA titer in subjects treated with somatrogon in both trials (refer to Section 7.7.3 for details) to date. However, no imbalance in hypersensitivity reactions and/or in frequency or severity in drug class AEs between ADA-negative and ADA-positive subjects was identified in the clinical program. The absence of impact of ADA on severity/frequency of class adverse reactions observed in the clinical program is reassuring to conclude that the risk of hypersensitivity AEs due to somatrogon is low and not an approvability concern. In light of the ADAs, however, the necessity of postmarketing surveillance will be considered if a favorable benefit risk can be established supporting approval of the product.

7.6.2. Overall Treatment-Emergent Adverse Event Summary, Trials CP-4-006 and CP-4-004

In Trial CP-4-006, the majority of subjects in both groups developed at least one AE during the 12-month treatment period (Table 30). The incidence of SAEs was low and there was no imbalance in the frequency of SAEs between treatment arms; SAEs appeared to be unrelated to study drug. Only a few subjects discontinued the study drug due to the AE of injection site reactions.

Table 30. Overview of Treatment-Emergent Adverse Events, Controlled Trial Safety Population, Trial CP-4-006 (Main Period)

Event Category	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Any AE	95 (87.2)	97 (84.3)	2.9 (-6.2, 12.0)
Moderate or severe AE	36 (33.0)	28 (24.3)	8.7 (-3.1, 20.5)
Any SAE	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
SAE with fatal outcome	0	0	0.0 (0.0, 0.0)
AE leading to discontinuation of study drug	1 (0.9)	0	0.9 (-0.9, 2.7)
AE leading to dose modification of study drug	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
AE leading to interruption of study drug	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
AE leading to reduction of study drug	0	0	0.0 (0.0, 0.0)
AE leading to delay of study drug	0	0	0.0 (0.0, 0.0)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
Grading scale: mild, moderate, severe
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

No safety concerns emerged in Trial CP-4-004 that were not apparent in Trial CT-4-006 (Table 31). No deaths and no SAEs were reported in the trial, and none of subjects discontinued the main (12-month) period of the trial due to an AE.

Table 31. Overview of Treatment-Emergent Adverse Events, Trial CP-4-004 (Main Period)

Event Category	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Any AE	10 (76.9)	10 (66.7)	10 (71.4)	30 (71.4)	8 (72.7)
Moderate or severe AEs	2 (15.4)	3 (20.0)	3 (21.4)	8 (19.0)	4 (36.4)
Any SAE	0	0	0	0	0
SAE with fatal outcome	0	0	0	0	0
AE leading to discontinuation of study drug	0	0	0	0	0
AE leading to dose modification of study drug	0	0	1 (7.1)	1 (2.4)	1 (9.1)
AE leading to interruption of study drug	0	0	0	0	1 (9.1)
AE leading to reduction of study drug	0	0	1 (7.1)	1 (2.4)	0
AE leading to delay of study drug	0	0	0	0	0

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as any AE with onset post-treatment.
Grading scale: mild, moderate, severe.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

The AE profile reported in OLE periods of both trials were similar to those reported in main periods (refer to Table 106 and Table 107, Section 17.2).

Overall, no new adverse reactions were detected in study CP-4-006 (114 subjects completed 2 years) and study CP-4-004 (4 subjects completed up to 7 years).

7.6.3. Deaths, Trials CP-4-006 and CP-4-004

No deaths were reported in either Trial CP-4-006 or Trial CP-4-004 (including main periods and open-label extension periods).

7.6.4. Serious Adverse Events, Trials CP-4-006 and CP-4-004

Overall, the incidence of the SAEs was low in the somatrogon clinical program, and all SAEs occurred in one subject each. The majority of SAEs appeared to be unrelated to the drug.

Trial CP-4-006

In the main period, 3 (2.8%) somatrogon-treated subjects and 2 (1.7%) Genotropin-treated subjects had SAEs (Table 32). All SAEs occurred in 1 subject each. After review of the narratives, these occurrences likely represent common events in this age group.

Table 32. Serious Adverse Events, Safety Population, Trial CP-4-006 (Main Study)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Any SAE	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
Chronic tonsillitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Gastroenteritis	1 (0.9)	0	0.9 (-0.9, 2.7)
Pneumonia	1 (0.9)	0	0.9 (-0.9, 2.7)
Tonsillitis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Ureterolithiasis	0	1 (0.9)	-0.9 (-2.6, 0.8)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

During the OLE period (as of the cutoff date of December 21, 2020), 10/212 (4.7%) subjects were reported with 10 SAEs (6 subjects originally randomized to somatrogon and 4 originally randomized to Genotropin as shown in Table 33). Most subjects reported 1 SAE each and 3 subjects reported 2 SAEs each (1 subject -pharyngitis streptococcal and pneumonia, 1- noninfective sialadenitis and lymphadenitis, and 1- appendicitis and peritonitis). After reviewing the narratives of all SAEs reported, SAEs appear to be unrelated to study drug. AEs, such as appendicitis, diverticulitis, Kawasaki's disease, peritonitis (as a complication of appendicitis), pharyngitis, pneumonia, tonsillitis, adenoidal hypertrophy, abdominal pain, lymphadenitis, and sialadenitis, are not uncommon in this age group. An SAE of adrenal insufficiency was considered as unrelated to study drug based on long duration of treatment prior to the event and no treatment interruption during the event. The event was most likely related to the exacerbation of preexisting adrenal insufficiency by the acute infection (see the narrative in Section 17.3).

Table 33. Serious Adverse Events, Safety Population, Trial CP-4-006 (Open-Label Extension)

Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Any SAE	6 (5.8)	4(3.7)	10 (4.7)
Appendicitis	1 (1.0)	1 (0.9)	2 (0.9)
Adenoidal hypertrophy	1 (1.0)	0	1 (0.5)
Adrenal insufficiency	1 (1.0)	0	1 (0.5)
Diverticulitis	1 (1.0)	0	1 (0.5)
Kawasaki's disease	1 (1.0)	0	1 (0.5)
Peritonitis	1 (1.0)	0	1 (0.5)
Pharyngitis streptococcal	1 (1.0)	0	1 (0.5)
Pneumonia	1 (1.0)	0	1 (0.5)
Tonsillitis	1 (1.0)	0	1 (0.5)
Abdominal pain	0	1 (0.9)	1 (0.5)
Lymphadenitis	0	1 (0.9)	1 (0.5)
Noninfective sialadenitis	0	1 (0.9)	1 (0.5)

Source: adae.xpt; software, Python. Data based on response to the Information Request dated October 14, 2021.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

Trial CP-4-004

There were no reports of SAE during the 12-month main period.

During the OLE period, a total of 4 subjects reported 4 SAEs (gastric disorder [ID# (b) (6)] and thyroid gland abscess [ID# (b) (6)] in Year 1, scoliosis [ID# (b) (6)] in Year 4, and schwannoma [ID# (b) (6)] in PEN Year 2). After review of the narratives, it appears that 2 of 4 SAEs (thyroid gland abscess and gastric disorder) were unrelated to the study drug. The subject with SAE of gastric disorder had also an underlying medical condition of adrenal insufficiency, and it is unclear whether nausea and vomiting (gastric disorder) were due to the acute infection or they were symptoms of adrenal insufficiency precipitated by acute infection, nausea, and vomiting; without serum cortisol levels at time of the event no firm conclusion can be made. The event of nausea and vomiting was not related to the study drug (the event occurred after 1 year of treatment with somatrogon and somatrogon was not interrupted). The event resolved and the subject continued treatment with somatrogon.

The other two of 4 SAEs, schwannoma and scoliosis, were considered as possibly related or probably related, respectively. These events are briefly summarized below:

- The subject with schwannoma (ID# (b) (6)) experienced this AE after approximately 5 years of exposure to somatropin (Genotropin for 1 year and somatrogon for approximately 4 years). While long-term exposure to GH with persistent elevation of IGF-1 may induce tumor growth, IGF-1 SDS levels in this subject were below 2. Schwannoma is a tumor that develops from the Schwann cells (peripheral nervous system). Given that schwannoma may result from genetic diseases and that this subject had a history of congenital eye disease, it is conceivable that the tumor originated from genetic disorders. Although there is no clear evidence to support study drug causality in this case an effect of somatropin on tumor growth cannot be completely ruled out and this SAE is considered possibly related to the study drug (see summarized narratives in Section 17.3).
- The subject with scoliosis (ID # (b) (6)) was a 14-year-old female who experienced worsening of scoliosis during the fourth year of treatment with somatrogon. The subject completed 12 months of treatment in the main period of the study at the dose of 0.48 mg/kg somatrogon and continued with the same dose in OLE. Somatrogon dose was scaled up to 0.66 mg/kg/week (vial formulation) on Day 1569 (approximately 4 years from first dose) and approximately 9 months later she was diagnosed with scoliosis and dose was reduced to 0.56 mg/kg/week. On Day 1935 (approximately 90 days after first diagnosis), the Investigator noticed worsening of the scoliosis and the drug was discontinued permanently. The Applicant indicated that this subject had a pre-existing diagnosis of mild scoliosis. A causal relationship between the drug and the event cannot be excluded due to the well-known effect of hGH formulations on bone growth. Worsening of pre-existing scoliosis is a known AE associated with use of hGH and is included in Warning and Precaution section of all hGH labels.

7.6.5. Dropouts and/or Discontinuations Due to Adverse Events, Trials CP-4-006 and CP-4-004

The drop-out rate due to AEs was low in the clinical program. A total of 10 discontinuations due to AEs were reported during the up to the data cut-off date of December 21, 2020. In addition, 1 discontinuation due to AE was reported approximately one week after the cut-off date and was included in this safety analysis. Of the 11 subjects who discontinued treatment prematurely due to AEs, there were 8 subjects in Trial CP-4-006 (1 in the main period and 7 in the OLE period) and 3 subjects in Trial CP-4-004 (all in the OLE period. Most subjects who discontinued somatrogon prematurely did so because of nonserious AEs of injection site reactions (6 subjects

in Trial CP-4-006). The other AEs that led to the early drug discontinuation were scoliosis (SAE), Schwannoma (SAE), osteochondrosis, anxiety, and irritability (reported after cut-off date).

Trial CP-4-006

In Trial CP-4-006, main period, only one subject in the somatrogon group permanently discontinued the study prematurely due to a nonserious AE of injection site reaction of moderate intensity (erythema and indurations). This subject (ID # (b) (6)) was a 9-year-old female who experienced injection site reactions on Day 58 (last dose prior to event was on Day 57), which resolved without sequela on Day 63; and the subject was permanently discontinued on Day 81.

During the OLE period (as of the data lock date of December 21, 2020), 7 subjects discontinued study prematurely due to AEs: 5 subjects due to injection site reactions (erythema, pruritus, induration, and pain), and 1 subject (ID# (b) (6)) due to increased anxiety. No reason for the anxiety was provided in the narrative, but the only AE of PT anxiety in the trial was coded by *fear of injection*. In addition, 1 subject (ID# (b) (6)) discontinued due to nonserious AE of irritability (irritable mood) approximately one week after the cut-off date. This subject was a 3-year-old male who experienced intermittent events of irritability during the main and OLE periods (see Section 17.3 for narratives). All AEs were nonserious and except for the AE of irritability occurred in subjects originally randomized to Genotropin.

Trial CP-4-004

No premature discontinuation of the trial due to AEs was reported in the main period.

During the OLE period, 3/48 (6.3%) subjects were permanently discontinued due to AEs: 1 subject (ID # (b) (6)) due to SAE of scoliosis during the period IV of OLE, 1 subject (ID# (b) (6)) during the PEN Year 1 due to the nonserious event of osteochondrosis, and 1 subject due to an SAE of Schwannoma (ID # (b) (6)) in PEN Year 2. The event of scoliosis was considered as probably related to the study drug and is described above (refer to SAEs in Section 7.6.4). Upon review of the data, the event of osteochondrosis was considered unrelated to study drug and the event of Schwannoma was considered possibly drug-related. See full narrative in Section 17.3.

7.6.6. Treatment-Emergent Adverse Events, Trials CP-4-006 and CP-4-004

Data from the controlled main periods of Trials CP-4-006 and CP-4-004 were used to evaluate the overall safety profile of somatrogon. In addition, the Applicant included data from OLE periods of both studies to support long-term safety of the drug. However, data from the OLE periods are confounded by the previous exposure to hGH, the absence of the control group in these periods and the small number of subjects treated with somatrogon beyond 2 years further complicates the long-term safety assessment. Thus, the long-term safety data from Study CP-4-004 OLE should be interpreted with caution.

Trial CP-4-006

The majority of subjects in somatrogon (87%) and Genotropin groups (84%) developed at least 1 treatment-emergent AE (TEAE) during the 12-month treatment period. The TEAEs occurring at ≥1% frequency in somatrogon arm and with a risk difference >1% over the Genotropin arm are shown by PT in Table 34.

Table 34. AEs by Preferred Term With Higher Incidence in Somatrogon Arm (>1%) and With Risk Difference >1%, Safety Population, Trial CP-4-006 (Main Period)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Any AE	95 (87.2)	97 (84.3)	2.9 (-6.2, 12.0)
Injection site pain	43 (39.4)	29 (25.2)	14.2 (2.1, 26.3)
Injection site erythema	9 (8.3)	0	8.3 (3.1, 13.5)
Injection site pruritus	6 (5.5)	0	5.5 (1.2, 9.8)
Arthropod bite	6 (5.5)	1 (0.9)	4.6 (-0.0, 9.2)
Rhinitis	6 (5.5)	1 (0.9)	4.6 (-0.0, 9.2)
Injection site swelling	5 (4.6)	0	4.6 (0.7, 8.5)
Hypothyroidism	7 (6.4)	3 (2.6)	3.8 (-1.6, 9.2)
Free fatty acids increased	5 (4.6)	1 (0.9)	3.7 (-0.6, 8.0)
Injection site induration	4 (3.7)	1 (0.9)	2.8 (-1.1, 6.7)
Conjunctivitis allergic	3 (2.8)	0	2.8 (-0.3, 5.9)
Hypertriglyceridemia	3 (2.8)	0	2.8 (-0.3, 5.9)
Molluscum contagiosum	3 (2.8)	0	2.8 (-0.3, 5.9)
Pyrexia	18 (16.5)	16 (13.9)	2.6 (-6.8, 12.0)
Pharyngitis	7 (6.4)	5 (4.3)	2.1 (-3.8, 8.0)
Oropharyngeal pain	6 (5.5)	4 (3.5)	2.0 (-3.4, 7.4)
Influenza	5 (4.6)	3 (2.6)	2.0 (-2.9, 6.9)
Abdominal pain	4 (3.7)	2 (1.7)	2.0 (-2.3, 6.3)
Enterobiasis	4 (3.7)	2 (1.7)	2.0 (-2.3, 6.3)
Nausea	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Rhinitis allergic	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Aphthous ulcer	2 (1.8)	0	1.8 (-0.7, 4.3)
Attention deficit/hyperactivity disorder	2 (1.8)	0	1.8 (-0.7, 4.3)
Enteritis	2 (1.8)	0	1.8 (-0.7, 4.3)
Hordeolum	2 (1.8)	0	1.8 (-0.7, 4.3)
Hypoesthesia	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site hemorrhage	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site warmth	2 (1.8)	0	1.8 (-0.7, 4.3)
Muscle spasms	2 (1.8)	0	1.8 (-0.7, 4.3)
Pharyngitis streptococcal	2 (1.8)	0	1.8 (-0.7, 4.3)
Gastroenteritis	4 (3.7)	3 (2.6)	1.1 (-3.5, 5.7)
Hypoinsulinemia	4 (3.7)	3 (2.6)	1.1 (-3.5, 5.7)
Iron deficiency anemia	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
Rash generalized	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

The results of the FMQ analyses that either occurred with higher incidence in somatrogon arm and with a risk difference ≥1%, were new, or rendered different results than in Table 34 are marked in italics in Table 35.

Table 35. AEs by FDA Medical Query (Narrow) and Preferred Term With Higher Frequency (>1%) in Somatrogon and Risk Difference >1%, Safety Population, Trial CP-4-006 (Main Study)

FMQ (Narrow) Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Local administration reactions	*47 (43.1)*	*29 (25.2)*	*17.9 (5.7, 30.1)*
Injection site pain	*43 (39.4)*	*29 (25.2)*	*14.2 (2.1, 26.3)*
Injection site erythema	*9 (8.3)*	*0*	*8.3 (3.1, 13.5)*
Injection site pruritus	*6 (5.5)*	*0*	*5.5 (1.2, 9.8)*
Injection site swelling	*5 (4.6)*	*0*	*4.6 (0.7, 8.5)*
Injection site induration	*4 (3.7)*	*1 (0.9)*	*2.8 (-1.1, 6.7)*
Injection site hemorrhage	*2 (1.8)*	*0*	*1.8 (-0.7, 4.3)*
Injection site warmth	*2 (1.8)*	*0*	*1.8 (-0.7, 4.3)*
Injection site bruising	*2 (1.8)*	*1 (0.9)*	*0.9 (-2.1, 3.9)*
Injection site hypertrophy	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Injection site inflammation	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Nasopharyngitis	*36 (33.0)*	*33 (28.7)*	*4.3 (-7.8, 16.4)*
Rhinitis	*6 (5.5)*	*1 (0.9)*	*4.6 (-0.0, 9.2)*
Pharyngitis	*7 (6.4)*	*5 (4.3)*	*2.1 (-3.8, 8.0)*
Rhinitis allergic	*3 (2.8)*	*1 (0.9)*	*1.9 (-1.6, 5.4)*
Pharyngitis streptococcal	*2 (1.8)*	*0*	*1.8 (-0.7, 4.3)*
Viral pharyngitis	*2 (1.8)*	*1 (0.9)*	*0.9 (-2.1, 3.9)*
Nasopharyngitis	*25 (22.9)*	*29 (25.2)*	*-2.3 (-13.5, 8.9)*
Hemorrhage	*3 (2.7)*	*0*	*2.8 (-0.3, 5.8)*
Contusion	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Epistaxis	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Traumatic hematoma	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Nausea (narrow FMQ)	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Bronchospasm	*3 (2.8)*	*1 (0.9)*	*1.9 (-1.6, 5.4)*
Asthma	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Bronchospasm	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Bronchial hyperreactivity	*1 (0.9)*	*1 (0.9)*	*0.0 (-2.5, 2.5)*
Paresthesia	*2 (1.8)*	*0*	*1.8 (-0.7, 4.3)*
Hypoesthesia	*2 (1.8)*	*0*	*1.8 (-0.7, 4.3)*
Pyrexia	*18 (16.5)*	*17 (14.8)*	*1.7 (-7.8, 11.2)*
Pyrexia	*18 (16.5)*	*16 (13.9)*	*2.6 (-6.8, 12.0)*
Body temperature increase	*0*	*2 (1.7)*	*-1.7 (-4.1, 0.7)*
Fatigue	*3 (2.8)*	*2 (1.7)*	*1.1 (-2.8, 5.0)*
Fatigue	*2 (1.8)*	*1 (0.9)*	*0.9 (-2.1, 3.9)*
Lethargy	*1 (0.9)*	*0*	*0.9 (-0.9, 2.7)*
Malaise	*1 (0.9)*	*1 (0.9)*	*0.0 (-2.5, 2.5)*

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event

The most common AEs by FMQ analysis in somatrogon group were injection site reactions (43%), nasopharyngitis (33%), and pyrexia (16.5%). They also occurred more frequently in the somatrogon group compared to Genotropin group. The other AEs that were seen more frequently in somatrogon group compared to Genotropin group were hemorrhage, nausea, bronchospasm, paresthesia, and fatigue. Injection site reactions are discussed in detail in Section 7.7.1. All other AEs that were seen more frequently in somatrogon group are briefly summarized below. Refer to Section 17.4, Table 108, and Table 109 for details on the AEs reported in Trial CP-4-006, main period.

Nasopharyngitis and Pyrexia

The proportion of patients with all types of nasopharyngitis events (reported as PTs of rhinitis, pharyngitis, rhinitis allergic, pharyngitis streptococcal, viral nasopharyngitis and nasopharyngitis) during somatrogon treatment was higher (33%) compared to Genotropin (29%). The proportion of subjects with pyrexia (reported as pyrexia and body temperature increased) was also slightly higher in the somatrogon group compared to Genotropin group (17% versus 15%) but unlikely to be a clinically meaningful difference. However, no imbalance in absolute number of subjects per group with AEs of nasopharyngitis or pyrexia was noted: nasopharyngitis: 36 subjects (somatrogon) versus 33 subjects (Genotropin) and pyrexia: 18 subjects (somatrogon) versus 17 subjects (Genotropin). All events were nonserious, of short duration and resolved without treatment interruption. In addition, nasopharyngitis and pyrexia are common events in the pediatric population.

Nausea, Bronchospasm, Hemorrhage, Paresthesia,

The overall incidence of these AEs was low in the trial; these AEs occurred in ≤3 subjects each.

- The events of nausea occurred in 3 subjects treated with somatrogon and 1 subject treated with Genotropin. All events were of short duration and resolved without drug discontinuation.
- The FMQ 'bronchospasm' (3 subjects in somatrogon group versus 1 subject in Genotropin group) included the PTs of 'asthma', 'bronchospasm' and bronchial hyperreactivity'. There was no imbalance in frequency of these AEs when they were analyzed by each PT reported. Only event of 'bronchial hyperreactivity' occurred in 2 subjects (1 in somatrogon group and 1 in Genotropin group). All other AEs occurred in somatrogon group only and in 1 subject each. All events were of short duration and resolved without treatment interruption. All events of bronchospasms in somatrogon group and in Genotropin group were in subjects negative for ADA.
- The FMQ of 'hemorrhage' included PT of 'contusion', 'epistaxis' and traumatic hematoma'. The incidence of hemorrhagic AEs was low, all AE by PT occurred in 1 (0.9%) subject, each. All hemorrhagic events were due to trauma and/or infection and unrelated to the study drug. These AEs are not unusual in the pediatric population and the imbalance was observed only when the PTs were combined. Thus, I do not recommend including the FMQ of 'hemorrhage" in the labeling.
- Paresthesia was reported in 2 subjects in somatrogon group only. The etiology of the event is unclear but may be due to edema and compression of nerves. The events were of short duration and resolved without treatment.

Trial CP-4-004

The incidence and type of AEs observed in Trial CP-4-004 was similar to those observed in Trial CP-4-006, except for the AEs of headache and anemia. In Trial CP-4-006, the incidence of headache was lower in somatrogon group (17%) and in Genotropin group (22%) and anemia was reported at the same rate (6%) in both treatment groups. In the main period of Trial CP-4-004 these AEs were the most frequently AEs reported in the somatrogon (all doses) group compared to the Genotropin group [anemia (including the PTs of anemia, hemoglobin decreased, and iron deficiency anemia) 19% versus 9%, respectively and headache 12% versus 9%, respectively]. See Table 110 and Table 111 in Section 17.4.

None of the subjects with AEs of headache were reported in the high-dose somatrogon group (0.66 mg/kg/week); 4 subjects were in the lowest dose group (0.25 mg/kg/week) and 1 subject in 0.48 mg/kg/week. One subject treated with Genotropin had AE of headache.

Anemia was reported in 3 subjects treated with 0.25 mg/kg/week, 2 subjects treated with 0.48 mg/kg/week and 3 subjects treated with 0.66 mg/kg/week, versus 1 subject in Genotropin group. The reviewer team analyzed individual reports of anemia and concluded that the increased proportion of subjects with anemia might be poor diet-related (most cases were from Eastern Europe countries) or due to uneven randomization at some sites. For example, one of the sites (Site #11) reporting 4 cases of anemia in somatrogon group had a total of 7 subjects randomized to somatrogon and no subjects randomized to Genotropin (See Table 112 in Section 17.4).

The observed imbalances in frequency of AEs of headache and anemia between somatrogon and Genotropin groups is unclear but may be due to the factors described above or simply by chance. The difference in the somatrogon exposure and small size of safety database complicate the assessment of causality of these events. The observed events were nonserious, of short duration and resolved without treatment interruption. In addition, headache is not an uncommon event in this age group, and anemia is also frequently seen in children with poor nutrition.

AEs of cough, hemorrhage, and injection site reactions occurred in 2 subjects each only in the somatrogon group. All other AEs occurred only in the somatrogon group, in 1 subject each: back pain, peripheral edema, hypoglycemia and urticaria.

OLE Periods of Trials CP-4-006 and CP-4-004

During the OLE periods, no new safety signals were detected. In the OLE period of Trial CP-4-006, of 212 subjects, 159 (75%) experienced at least one treatment-emergent AE, with a higher proportion of subjects reporting AEs among those who were originally randomized to Genotropin (87 subjects, 81%) as compared to subjects originally randomized to somatrogon (72 subjects, 69%), most likely due to the differences in the exposure to somatrogon between the treatment arms. See full information in Section 17.4, Table 113.

The most frequent (incidence > 5%) AEs continued to be injection site reactions reported in 71 (34%) subjects (with injection site pain being the most common), nasopharyngitis in 46 (22%) subjects, pyrexia in 29 (14%) subjects, headache in 23 (11%) subjects, vomiting in 18 (9%), cough in 17 (8%) subjects, and Influenza in 12 (6%). All other AEs occurred in ≤5% in any of the originally randomized group. Most events were nonserious and resolved without drug discontinuation.

In the CP-4-004 OLE period, the AEs were reported in the original submission (data lock date November 1, 2019) by dose groups in Period III, year 1 of OLE, (0.25 mg/kg/week, 0.48 mg/kg/week, and 0.66 mg/kg/week), Period IV (0.66 mg/kg/week, cumulative years 2-4), and Period V (ongoing PEN Year 1). The most frequent AEs across groups were in the SOC of Infections and Infestations, with the most frequent reported PTs of upper respiratory tract infection (12/44 subjects) and bronchitis (7/44 subjects), which are common events in this age group; all other AEs were reported in < 3 subjects (Section 17.4, Table 114).

Additional information provided in the amendment (data cut-off December 21, 2020) contained safety data for subjects who completed PEN Year 1 and Pen Year 2. Of all subjects who completed up to PEN Year 2 period, 40/48 (83%) subjects had at least one AE. The incidence of treatment-emergent AEs by OLE year was 25/48 (52%) subjects in Year 1, 22/44 (50%) in Year

2, 18/43 (42%) in Year 3, 17/38 (45%) in Year 4, 23/40 (58%) in PEN Year 1, and 15/35 (43%) in PEN Year 2.

The type of AEs in subjects who were switched to pen treatment was similar to AEs observed during other periods of the study. During PEN Year 1 (N=40), 23 (57.5%) subjects reported at least one AE and the most frequently reported AEs were: 8 (20%) subjects had nasopharyngitis, 3 (7.5%) subjects had injection site reactions, 2 (5.0%) subjects each had headache and hemorrhage; all other AEs were reported in 1 subject each (Table 115, Section 17). During PEN Year 2 (N=35), 15 (42.9%) subjects reported at least one AE and the most frequent AEs were similar to those reported in PEN Year 1 (Table 116, Section 17.4).

Overall, most AEs seen in the OLE periods were nonserious and of mild or moderate severity. However, the assessment of long-term impact of immunogenicity on safety is complicated due to the different exposure to the somatrogon (some patients were treated with lower doses during the 12-month main period and first year in OLE), previous Genotropin treatment, absence of control group, and different somatrogon presentation (vial versus pen injector).

In conclusion, given the established safety profile in this class, there were no new or unexcepted AEs identified in the clinical program. Most events were nonserious and mild, did not require drug discontinuation, and resolved without treatment. The type and frequency of AEs were in general consistent between the trials. The slight differences in the frequency of AEs noted between somatrogon and Genotropin treatment groups during the first year of treatment in Trial CP-4-006 do not appear to be clinically meaningful. The AEs of nasopharyngitis, pyrexia, bronchospasm, paresthesia, and nausea also represent common events in the pediatric population. These risks can be communicated through labeling; none of the above AEs require inclusion in Warnings and Precautions.

Except for the high immunogenicity, no other significant safety issues were identified in the clinical program. However, there was no imbalance in the frequency of the AEs by ADA status in somatrogon group during the 12 months of treatment (refer to Section 7.7.3) in trial CP-4-006 and no new or increase in frequency of already observed AEs was noted in OLE periods of both trials. The absence of imbalance in severity/frequency of known AEs by ADA status and of new safety signals with long term treatment, even though ADA persist, is reassuring.

7.6.7. Adverse Events of Special Interest

As stated in Section 7.2, tumorigenesis, intracranial hypertension, slipped capital epiphysis, glucose intolerance and diabetes mellitus, pancreatitis, adrenal insufficiency, fluid retention (manifested by arthralgia, myalgia, and nerve compression) are class-specific adverse events and are included in all approved hGH labels.

Thus, adverse events of special interest (AESI) included these adverse events. The Applicant also included injection site reactions in AESI since injections site reactions are not unexpected adverse events with all injectable drugs. In addition, the Applicant included AE of pain in extremity due to the "reported frequency" of this AE in the clinical program. Lastly, immune reactions were evaluated as AESI. See the Applicant's definition of AESI in Table 117, Section 17.5.

The AESI are briefly summarized below, except the AEs of injection site reactions, glucose abnormalities and immune reactions, which are discussed in Sections 7.7.1, 7.6.8, and 7.7.3, respectively.

Slipped Capital Femoral Epiphysis, Intracranial Hypertension

There were no reports in the clinical program with slipped capital femoral epiphysis or intracranial hypertension.

Since headache may be a symptom of intracranial hypertension, the review team also evaluated the adverse events of headache. The overall incidence of headache was low in both CP-4-006 and CP-4-04. In Trial CP-4-006 (main period), the frequency of headache in the somatrogon group was lower (17%) than in the Genotropin group (22%). In Trial CP-4-004 main study, the incidence of headache was slightly higher in all somatrogon dose groups combined (12%) versus Genotropin group (9%). In Trial CP-4-006, 4 subjects in somatrogon group and 3 subjects in the Genotropin group met the criteria for fundoscopic evaluations (i.e., signs or symptoms of benign intracranial hypertension, such as persistent headaches or headache accompanied by nausea//vomiting that is not self-limited) and none had evidence of intracranial hypertension. In Trial CP-4-004, fundoscopic evaluation was performed in 18 subjects in the somatrogon group and 5 subjects in the Genotropin group and there were no findings of intracranial hypertension. All cases of headache were mild, transient, and resolved without treatment interruption.

Adrenal Insufficiency

GH increases cortisol metabolism via the enhanced conversion of cortisol to inactive cortisone. Thus, treatment with hGH formulations may unmask adrenal insufficiency in hypopituitary patients who have decreased adrenocorticotropic hormone reserves. Patients treated with glucocorticoid replacement therapy may also require increase in doses of glucocorticoids during the treatment with somatrogon. The risk of hypoadrenalism is included in Warnings and Precautions section of all recombinant human growth hormone (hGH) labels.

The incidence of AE of adrenal insufficiency was low in the clinical program (4 subjects treated with somatrogon and 1 subject treated with Genotropin). No adrenal crisis was reported, and most were mild and resolved without drug discontinuation. One case of SAE of adrenal insufficiency was unlikely to be related to the study drug.

In Trial CP-4-006, no subject treated with somatrogon in main period had an AE of adrenal insufficiency, and 1 subject treated with Genotropin had adrenal insufficiency. In the OLE period, 2 subjects had adrenal insufficiency: 1 subject (# (b) (6)) previously randomized to somatrogon had a SAE of adrenal insufficiency (refer to Sections 7.6.1 and 17.3 for case narrative) and 1 subject (# (b) (6)) previously randomized to Genotropin had a nonserious AE of adrenal insufficiency.

In Trial CP-4-004, 2 subjects treated with low doses (0.25 mg/kg/week and 0.48 mg/kg/week, respectively) had adrenal insufficiency in main period. All events were mild, nonserious and resolved without drug discontinuation. No subjects treated with 0.66 mg/kg/week dose had adrenal insufficiency.

Fluid Retention

Growth hormone is known to cause sodium and fluid retention. Thus, the safety data of somatrogon were reviewed for clinical manifestations of fluid retention such as edema, arthralgia, myalgia, nerve compression (carpal tunnel syndrome, paresthesia).

Overall incidence of these AEs was low in the clinical program, and there was no imbalance in number of the events between the treatment groups. No AEs of carpal tunnel syndrome were

reported in subjects treated with somatrogon. There were 2 AEs of myalgia reported in the Genotropin group in Trial CP-4-006 (main period) and 1 case reported in Trial CP-4-004 (OLE period) in the somatrogon group 0.25 mg/kg/wk (Period III). Arthralgia was reported in 5 subjects in somatrogon group versus 8 in Genotropin group in main period of Trial CP-04-006 and in 3 subjects in OLE period (all subjects previously randomized to Genotropin). In Trial CP-4-004, arthralgia was reported in 1 subject (dose group 0.25 mg/kg/week) during the main period and in 3 subjects during the OLE period. Peripheral edema was reported in 1 subject treated with somatrogon 0.25 mg/kg/week in Trial CP-04-004, no subjects in Trial CP-04-006 treated with somatrogon had AE of peripheral edema. Paresthesia was reported in 2 subjects in Trial CP-04-006 treated with somatrogon. All events were nonserious, mild, intermittent, and resolved without treatment.

Pain in Extremity

Pain in the extremities is not a labeled AE in hGH products. However, the Applicant included "pain in extremity" as adverse event of special interest based on their review of frequency of reporting and relatedness to study treatment. The safety data review showed that the number of subjects with "pain in extremity" by PT was low in the clinical program. There was no imbalance in frequency of pain in extremity between treatment arms in Trial CP-4-006, main period [5 (5%) subjects in somatrogon and 5 (4%) subjects in Genotropin group]. This AE was reported in 4 (2%) subjects during the OLE period of Trial CP-04-006 (1 subject in previously randomized to somatrogon and 3 subjects previously treated with Genotropin). In Trial CP-4-004, there were 2 (5%) subjects (1 in somatrogon and 1 in Genotropin group) with AE of pain in extremity reported during the main period only. In the age group studied, this type of pain is not uncommon and may also represent "growing pain" that is the most common cause of musculoskeletal pain in children during period of growth or is secondary to frequent activity-related accidents seen in this age group. All events were nonserious, of short duration and did not require drug discontinuation.

Scoliosis

Risk of scoliosis with hGH is included in Warnings and Precautions of all hGH labels. The incidence of AE scoliosis was low in clinical program: two subjects treated with somatrogon in CP-4-006 had AE of scoliosis, one of them was considered as SAE (refer to Section 7.6.1).

Neoplasms

IGF-1 is a growth promoting factor, and chronically elevated IGF-1 levels may play a role in tumorigenesis. There is no conclusive evidence regarding increased risk of neoplasms in patients with GHD treated with rhGH. However, based on the putative biological mechanism, all hGH formulations are contraindicated in patients with active malignancies and risk of neoplasm is included in the Warnings and Precautions section of all hGH labels.

The incidence of neoplasms in subjects using somatrogon was low in the clinical program. There was no imbalance in the number of subjects with neoplasms reported in somatrogon-treated subjects versus Genotropin-treated subjects in the main period of Trial CP-4-006: 2 subjects in somatrogon group [(ID # (b) (6) - melanocytic nevus and # (b) (6) - skin papilloma) and 2 subjects in the Genotropin group (ID # (b) (6) and (b) (6) - skin papilloma)] had skin tumors. In the OLE period of CP-4-006, 2 subjects had skin papilloma; one of the two (# (b) (6) from the Genotropin group) was previously reported to have skin papilloma during main period.

In Trial CP-4-004, 1 subject in the low-dose group (# (b) (6)) was reported to have a skin papilloma and one subject (ID# (b) (6) originally randomized to Genotropin) reported a malignancy (schwannoma) during the OLE period (refer to Section 7.6.4 for further information on the SAE of schwannoma). These AEs may be drug-related due to the long exposure to somatrogon (5 years), however, other confounding factors such as underlying genetic disorder and absence of the control complicates the conclusion regarding casualty of the event.

Overall, there were no unexpected findings regarding increased risk of malignant or benign tumors with somatrogon use. Because of the high and persistent rate of ADA seen in clinical program that may potentially alter drug clearance and lead to chronically elevated IGF-1 levels above normal range, concerns regarding tumorigenesis remain the same if not higher for somatrogon compared to formulations with lower ADA production (refer to Section 7.7.2).

Pancreatitis

Pancreatitis is included in the Warnings and Precautions section of all hGH labels and should be investigated especially in pediatric patients with abdominal pain. The safety review of the somatrogon clinical program revealed no subjects with AEs of elevated pancreatic enzymes or AEs of pancreatitis.

Few subjects in either group had AEs of abdominal distension, abdominal pain, nausea, and vomiting that are suggestive of pancreatitis, which were evaluated by the Applicant as AESI. The overall number of subjects with these gastrointestinal AEs was lower in the somatrogon group in the main period of Trial CP-4-006 (12 versus 14, respectively). No increase in incidence of these AEs was observed in the OLE: a total of 11 subjects (3 originally randomized to somatrogon and 8 originally randomized to Genotropin) had these AEs. In Trial CP-4-004, 2 subjects in the somatrogon group and 1 in the Genotropin group had GI AEs.

All events were nonserious, mild, transient, and resolved without treatment discontinuation. It is unlikely that these events were related to pancreatitis. In addition, no levels of pancreatic enzymes were evaluated, and no imaging studies were performed at time of the events. In addition, these gastrointestinal symptoms are not uncommon symptoms seen in young children.

Hypothyroidism

Treatment with hGH products may unmask previously undiagnosed or subclinical central hypothyroidism. The AESI of thyroid function impairment captured AEs of blood thyroid stimulating hormone decreased, thyroid stimulating hormone increased, congenital hypothyroidism, hypothyroidism, primary hypothyroidism, thyroid disorder, and thyroxine free (free T4) decreased.

The overall incidence of thyroid-related AEs associated with somatrogon was low. No imbalance in incidence of these AEs was observed. In Trial CP-4-006, 10 (9%) subjects in somatrogon versus 11 (10%) subjects in Genotropin had thyroid-related AEs. Two subjects (originally randomized to Genotropin) had thyroid-related AEs in OLE period of Trial CP-4-006. In Trial CP-4-004, a total of 10 subjects treated with somatrogon had thyroid-related AEs: 4 subjects in main period (1 subject in dose group 0.25 mg/kg/wk, 1 in dose group 0.48 mg/kg/week, 2 in dose group 0.66 mg/kg/week) and 6 subjects in the OLE period.

All events were nonserious, mild to moderate, and resolved without treatment discontinuation. All subjects were asymptomatic.

7.6.8. Laboratory Findings, Trials CP-4-006 and CP-4-006

There is a known risk of hyperglycemia, elevated alkaline phosphatase and phosphate levels associated with use of hGH. There is also a concern with all hGH formulations that chronically elevated IGF-1 levels above the normal range may be associated with various AEs characteristic of acromegaly, including headache, intracranial hypertension, edema, and tumors.

Thus, the Medical Officer focused on the occurrence of out-of-range values and adverse events related to these biochemical changes. In addition, results of liver and renal tests by treatment group were reviewed and summarized in this section. The results of these analyses are briefly summarized below and in Section 7.7.2.

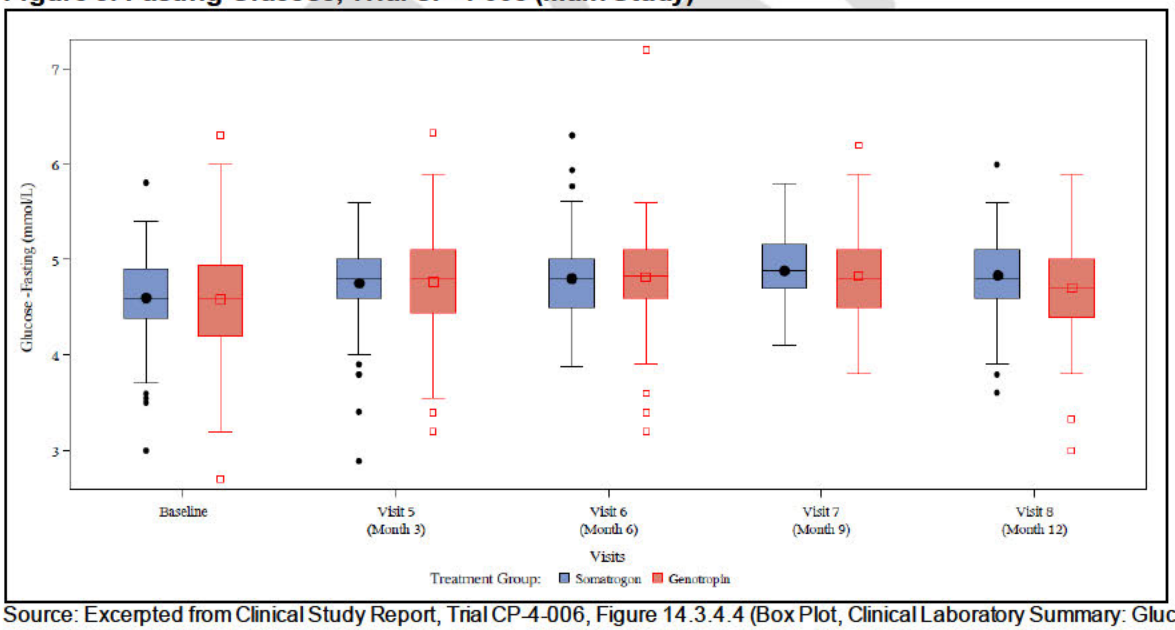
Analyses of other laboratory values did not identify any new safety signals.

Parameters of Glucose Control (Fasting Blood Glucose, HbA1C, and Insulin Levels)

The risk of hyperglycemia is due to direct insulin antagonistic effects of GH and is included in all hGH labels. Overall, no clinically meaningful changes in glucose parameters were observed in Trials CP-04-006 and CP-4-004 and in OLE periods.

In the main period of Trial CP-4-006, increases in mean fasting glucose were similar in both treatment groups during the main period and varied from 0.15 to 0.29 mmol/L (2.7 to 5.2 mg/dL) in the somatrogon groups and from 0.14 to 0.25 mmol/L (2.5 to 4.5 mg/dL) in the Genotropin groups (Figure 9).

Figure 9. Fasting Glucose, Trial CP-4-006 (Main Study)



Source: Excerpted from Clinical Study Report, Trial CP-4-006, Figure 14.3.4.4 (Box Plot, Clinical Laboratory Summary: Glucose Metabolism.

The mean fasting glucose ranged from 2.89 mmol/L (52 mg/dL) to 6.3 mmol/L (113 mg/dL) in somatrogon group; and from 3.0 mmol/L (54 mg/dL) to 7.2 mmol/L (130 mg/dL) in Genotropin group at each study visit throughout the study. Six subjects in the somatrogon group had fasting glucose values above normal range [100 mg/dl (5.6 mmol/l)] compared to 13 subjects in Genotropin group. The highest glucose values reported in 2 somatrogon-treated subjects was 6.3 mmol/L (113 mg/dL) (subjects # (b) (6) and # (b) (6)) and was 7.2 mmol/L (130 mg/dL) - in 1

Genotropin-treated subject (Subject (b) (6)). The subjects were asymptomatic and glucose levels normalized in all subjects without treatment. See details in Section 17.6.

Increases in mean HbA1c varied from 0.04% to 0.18% in the somatrogon group and 0.07% to 0.12% in the Genotropin group. The mean HbA1c ranged from 4.1% to 6.0% in somatrogon group, and from 4.2% to 9.1% in Genotropin group. No subjects in somatrogon group had AE of hyperglycemia or had a new diagnosis of diabetes mellitus.

Changes in insulin levels were small and not clinically meaningful. In Trial CP-4-004, all changes in glucose, insulin, and HbA1C levels were small and of unknown clinical significance.

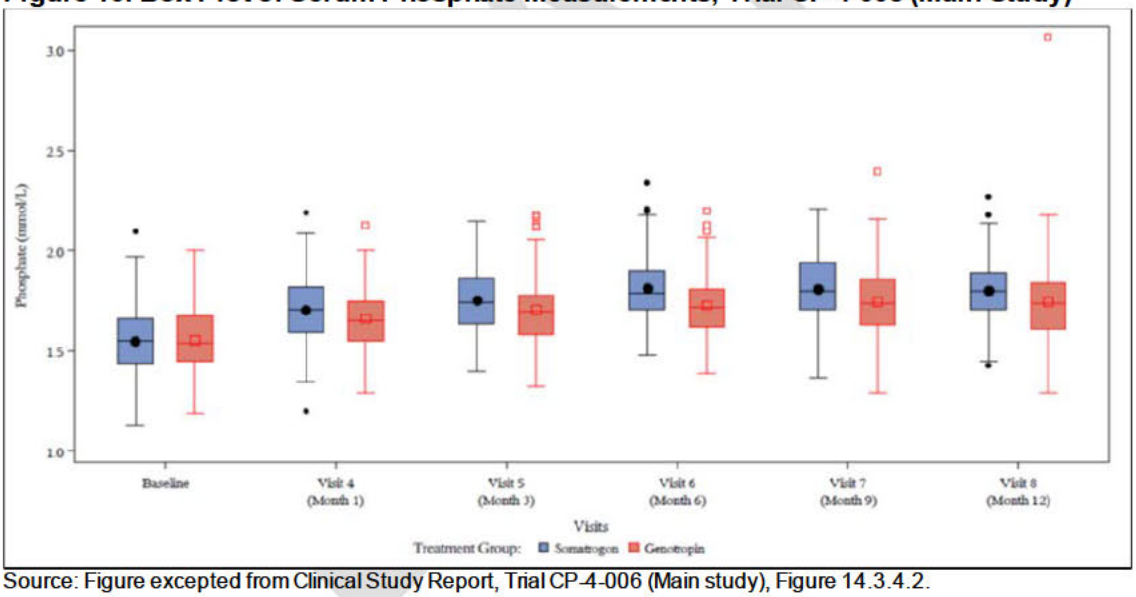
No clinically meaningful changes in glucose parameters and no AEs related to glucose metabolism impairment were reported during the OLE periods of both studies.

Elevated Serum Phosphate

Increased serum phosphate level is an expected effect with all hGH and is due to the GH action on renal tubular reabsorption of phosphate. The potential risk of elevated serum phosphate levels is included in the Warnings and Precautions section of all hGH labels.

Mean serum phosphate level at the end of 12-month treatment in Trial CP-4-006 increased in subjects treated with somatrogon or Genotropin but remained within normal reference pediatric range (Figure 10).

Figure 10. Box Plot of Serum Phosphate Measurements, Trial CP-4-006 (Main Study)



Source: Figure excepted from Clinical Study Report, Trial CP-4-006 (Main study), Figure 14.3.4.2.

The mean values of serum phosphate at (at Month 12) was 2.34 mmol/L in the somatrogon group and 3.07 mmol/L in the Genotropin group.

No elevated phosphate levels above normal reference range and no phosphate-related AEs were reported in the trial. No changes in serum phosphate levels were reported in Trial CP-4-004, main period and in OLE of both studies.

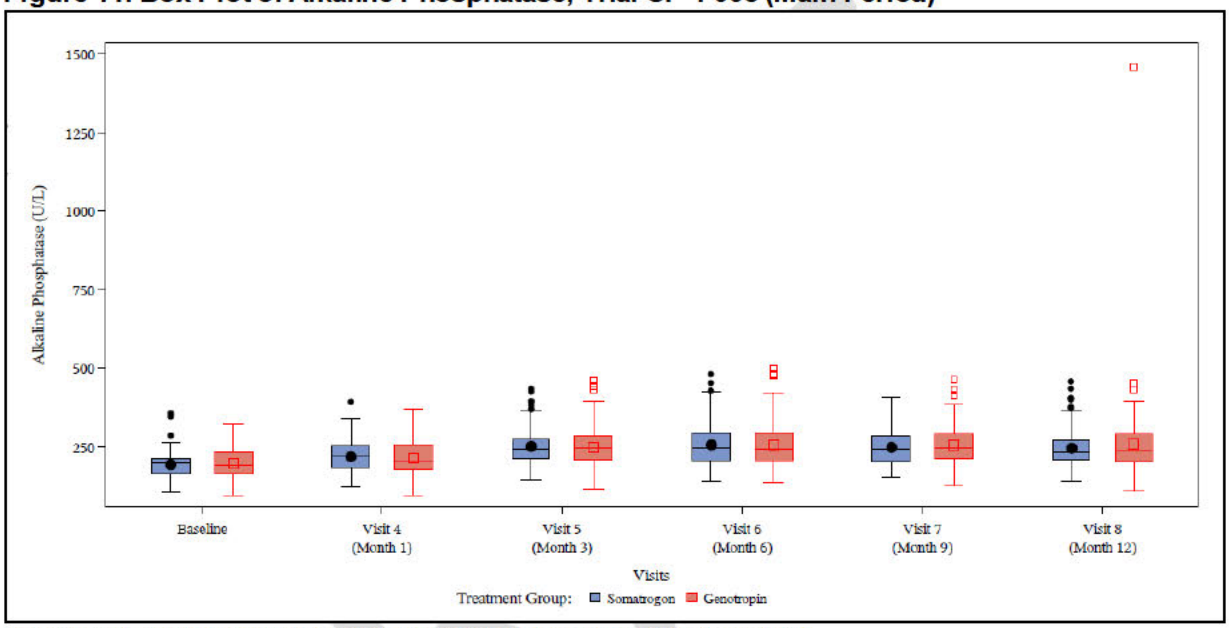
Elevated Alkaline Phosphatase

Growth hormone promotes bone growth, and elevation in alkaline phosphatase (AlkPhos; primarily in bone alkaline phosphatase isomer) is expected with hGH treatment. Thus, the risk of

elevated AlkPhos levels is included in Warnings and Precautions section of all hGH labels.

As expected in growing children, AlkPhos increased during the study in all subjects but remained within normal pediatric reference range (upper normal limit 417 U/L) in the majority of subjects. Mean AlkPhos was 193 U/L at baseline in somatrogon group and 190 U/L in Genotropin group. At the end of 12-month treatment, mean AlkPhos levels were 247 U/L in somatrogon group and 259 U/L in Genotropin group. Fifteen subjects in somatrogon arm and 26 subjects in Genotropin arm during the main period of Trial CP-4-006 had a single elevated AlkPhos value above normal reference range (Figure 11). All subjects were asymptomatic, and events resolved during the subsequent visit(s) without treatment.

Figure 11. Box Plot of Alkaline Phosphatase, Trial CP-4-006 (Main Period)



Source: Excerpted from Clinical Study Report, Trial CP-4-006, Main Period, page 351.

The highest level of AlkPhos was 1459 U/L in subject # (b) (6) at Month 12 treatment with Genotropin; the event was not reported as AE. A case report for this subject was reviewed. This subject also had slightly elevated serum albumin (48 g/L, reference range 29 to 47 g/L), bilirubin (25 micromol/L, reference range 3 to 21 micromol/L), and creatine kinase (209 U/L, reference range 18 to 158 U/L) at the 12-month time point; however, other liver enzymes were within normal range. No other clinically significant findings were noted, and subject was asymptomatic. The event of single AlkPhos increase resolved at next visit, and subsequent AlkPhos measurements during the OLE period were within normal limits.

A single AE of "elevated AlkPhos level" (335 and 320 U/L at Month1) was reported in one subject in Genotropin group (ID # (b) (6)). These levels are within normal reference range in the pediatric population.

All values were within normal range in Trial CP-4-004 OLE period (See Figure 65Appendix Section 17.6).

Liver Tests

No clinically significant elevations of liver enzymes were reported for subjects in the somatrogon group.

Two subjects in the Genotropin group had each a single event of elevated. Subject (ID# (b) (6)) was reported for an adverse event of increased of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) at Month 1. The increased levels of ALT (61 U/L) and AST (62 U/L) were mild and normalized at a subsequent unscheduled visit. There was no elevation of bilirubin levels. Subject (ID# (b) (6)) was reported for elevated ALT from Month 3 to Month 9 and elevated AST at Month 6 and Month 9. At Month 9, ALT reached a level >3 x ULN (130 U/L), and at a second unscheduled visit the AST normalized (36 U/L). Bilirubin levels remained within normal values.

No subjects had liver function test results that met the criteria for Hy's law.

Serum Creatinine and Blood Urea Nitrogen

In study CP-4-006, serum creatinine levels were within normal range at all time points, except for 4 subjects (1 subject in the somatrogon group and 3 in the Genotropin group) who had a single time point with slightly elevated values of no clinical significance. Blood urea nitrogen (BUN) was also slightly elevated in the subject from the somatrogon group and was normal in the 3 subjects from the Genotropin group. The subject from the somatrogon group (ID# (b) (6)) was a 8-year-old male who had a creatinine of 58 mmol/L (normal range for age 26.5-61.9 mmo/L) and BUN of 8.8 mmol/L (normal range for age 1.4-8.6) at Month 12 of the main period. This subject was positive for ADA from Month 6 of the main period (ADA titers 10, 10, and 50 at Month 6, 9, and 12, respectively) to Month 12 of OLE (ADA titers 50 and 1250 at Month 6 and Month 12 of OLE, respectively). There was no evidence of relationship between the presence of ADA and altered creatinine and BUN levels. Creatinine and BUN values normalized at the following time point in all 4 subjects.

7.6.9. Electrocardiogram

No dedicated QTc interval study for somatrogon was conducted. The interdisciplinary review team consultant indicated that a thorough QT study was not required based on the labeling practice for large molecules and known hGH product class safety information (no QT prolongation) (refer to review in DARRTS from March 18, 2021). According to ICH E14 Guidance on QT/QTc evaluation (Guidance 2005), large, targeted proteins (e.g., hGH) "have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or nonclinical studies." There were no QT-related safety signals in nonclinical studies (refer to Section 5.1). The interdisciplinary review team also reviewed electrocardiogram (ECG) data obtained from Trial CP-4-006 and concluded that there were no large increases in the QTc interval and none of the subjects had QT-associated adverse reactions. The reviewer concluded that "submitted ECG data do not indicate any unexpected or important effects of somatrogon on the QTc interval at clinically relevant exposures associated with the proposed dose" (see Section 17.6 for more details). No additional labeling is recommended.

7.6.10. Vital Signs and Physical Examination

No clinically meaningful changes in vital signs and in physical examination, except for height and weight, were observed in the clinical program.

7.7. Key Review Issues Relevant to Evaluation of Risk

7.7.1. Higher Incidence of Adverse Events of Injection Site Reactions in Somatrogon Group Compared to Genotropin Group in Trial CP-4-006

Issue

A higher incidence of adverse events of injection site reactions was reported in the somatrogon arm versus Genotropin arm during the 12-month treatment period in Trial CP-4-006. Also, the proportion of subjects in the somatrogon group with severe score in each injection site category (pain score, bruising, erythema/redness, induration/swelling, itching, and redness) was higher than in the Genotropin group.

Background

Somatrogon is an injectable drug and, thus, injection site reactions are expected AEs. Thus, the injection site reactions were evaluated and reported by the Applicant as AESI throughout the clinical program. Injection site reactions were the most frequent adverse reaction reported in Trial CP-4-006 in both treatment groups. However, an imbalance in AEs of injection site reactions between treatment groups was noted: 43% (somatrogon) versus 25% (Genotropin).

Assessment

The review team analyzed the potential reasons for the observed imbalance in AE of injection site reaction (ISR) between treatment groups in Trial CP-4-006.

The Applicant's strategy for ISR reporting as AE included the following algorithm (see Section 17.6 for ISR grading scores):

- Injection site reaction of moderate or severe intensity reported or observed at the time of site visit or during a telephone visit
- Injection site reaction between the last and present visit or remaining at the time of visit which require medical attention, or injection site reaction resulting from a previous injection, other than the last injection
- Any other injection site reaction deemed abnormal to the investigator's judgement
- Pain score ≥4 as reported in the patient diary, according to the Pain Rating Scale [score 0 (no hurt), 1 (hurts a little bit), 2 (hurts a little more), 3 (hurts even more), 4 (hurts a whole lot), and 5 (hurts worse)]
- This strategy for reporting ISRs as AEs is unclear and have not been used in previous hGH programs and was not agreed upon by the Agency during the development program. In addition, the algorithm used for Trial CP-4-004 was different from that used for CP-4-006 (e.g., it did not include pain level >4 as in CP-4-006).

All other ISR that were recorded in the case report form (CRF) but did not meet the above criteria were not reported as an AE. This strategy was considered as not appropriate by the review team since all reactions that occurred during the trial regardless of the severity or other Applicant's predefined criteria are considered as adverse events. Thus, the review team analyzed AEs of ISRs included in the *adae* dataset and all ISRs regardless of meeting the criteria for AE

included in the *adsr* (injection site reactions) dataset as well as all ISRs regardless of being reported as AEs. The results of these analyses are briefly summarized below.

The results of the review team's analysis of AEs of ISR (that met predefined criteria for AE and that were included in *adae* dataset) using FMQ (Table 36) confirmed the Applicant's findings: there was a higher proportion of subjects who experienced AEs of ISR in the somatrogon group compared to the Genotropin group (43% versus 25%, respectively). The most frequent ISR was pain in both treatment groups, although higher in the somatrogon group than in Genotropin group (39% versus 25%, respectively). In addition to pain, subjects in the somatrogon group experienced injection site reactions categorized by 9 different PTs (erythema, swelling, induration, hemorrhage, pruritus, warmth, bruising, hypertrophy, and inflammation), while subjects in Genotropin group had only 2 additional ISR by PT: 1 injection site induration and 1 injection site bruising. All reactions were nonserious, resolved without interventions and did not require treatment or dose adjustment. Only 1 subject discontinued the main period of Trial CP-4-006 because of ISRs of induration and erythema. Many subjects experienced more than one AE of injection site reaction.

Table 36. Incidence of AEs of Injection Site Reactions (by FMQ and PT), Trial CP-4-006 (Main Study)

Adverse Event	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Local administration reactions (FMQ, narrow)	47 (43.1)	29 (25.2)	17.9 (5.7, 30.1)
Preferred term			
Injection site pain	43 (39.4)	29 (25.2)	14.2 (2.1, 26.3)
Injection site erythema	9 (8.3)	0	8.3 (3.1, 13.5)
Injection site pruritus	6 (5.5)	0	5.5 (1.2, 9.8)
Injection site swelling	5 (4.6)	0	4.6 (0.7, 8.5)
Injection site induration	4 (3.7)	1 (0.9)	2.8 (-1.1, 6.7)
Injection site hemorrhage	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site warmth	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site bruising	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Injection site hypertrophy	1 (0.9)	0	0.9 (-0.9, 2.7)
Injection site inflammation	1 (0.9)	0	0.9 (-0.9, 2.7)

Source: adae.xpt; software, Python.
Table prepared by the Clinical Data Scientist and adapted by the Medical Reviewer to select AEs of injection site reactions.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term

In addition to the higher incidence in ISRs, the frequency of subjects in the somatrogon group with severe ISRs in each category (pain score, bruising, erythema/redness, induration/swelling, itching, and redness) was higher than the frequency in the Genotropin group. For example, in somatrogon versus Genotropin groups, there were 29 (30%) versus 14 (14%) subjects with pain score 5 (increasing from 0 to 5), 3 (3%) versus 1 (1%) in bruising score 2 (0 to 2), 10 (10%) versus 0 in erythema/redness score 2 (0 to 2), 7 (7%) versus 1 (1%) in induration/swelling score 2 (0 to 2), 6 (6%) versus 0 in itching score 2 (0 to 2), and 6 (6%) versus 4 (4%) in tenderness score 1 (0 to 1), respectively.

The overall number of events of injection site reactions, regardless of being reported as AE, was also higher in the somatrogon group (422 events) compared to the Genotropin (84 events).

When the review team analyzed all ISR regardless whether they were reported as AEs or not, there was no imbalance in frequency of ISR: 97 (89%) subjects in the somatrogon arm and 102

(89%) in the Genotropin arm. Overall, the imbalance in frequency of reported AEs of ISR may be attributable to the inappropriate reporting strategy of ISR as AE described above, which appears to label only more severe ISRs as AEs. Not all ISR recorded in CRF were reported as AEs, but only those that met the prespecified criteria (see above). The observed imbalance in AEs of ISR was most likely driven by the imbalance in severity of ISR between the groups since the less severe ISR were not recorded as AEs (See Table 118, Section 17.6 for ISR incidence by severity). For example, more subjects in the somatrogon group reported a pain score >5 (29% of subjects in somatrogon group and 14% of subjects in Genotropin group), and thus more AEs of injection site pain were recorded in the somatrogon group compared to Genotropin group. It should be also noted that the assessment of severity of pain was subjective and was based on the subject's reports recorded in CRF that is not reliable in the pediatric population (e.g., younger patients may report the anxiety of needles as severe pain). The criteria for the severity grading scale for ISR were also not defined and no grading scoring system was used (e.g., CTCAE); the severity grading of ISR was based on the Investigator's discretion. In addition, the observed imbalance may also stem from the fact that not every all ISR that occurred in the Genotropin group during a week of treatment were reported as AEs. Rather, only those that had the highest severity score were considered an AE for that week. In the somatrogon group, all AEs of ISR that met predefined criteria were reported after each weekly injection; in the Genotropin group, injection site reactions were recorded at least once weekly, and only the most severe occurrence was recorded as AE for that week.

During the OLE study (Trial CP-4-006), no increase in the frequency or severity of ISR were noted. All AEs were nonserious and resolved within short period of time. Five additional subjects discontinued trial prematurely due to ISR: (with manifestations of pain, erythema, induration, and pruritus). The incidence of injection site reactions in subjects who were originally randomized to Genotropin in main period and switched to somatrogon treatment in OLE was comparable to the incidence seen in somatrogon group during the main period: 44% versus 43%, respectively. Moreover, the incidence of injection site reactions in subjects who were originally randomized to somatrogon and continued treatment with somatrogon in OLE decreased over time: 22% subjects reported injection site reactions. The decrease in incidence might be due to the development of tolerability to the injections over the time. However, the open-label design, short duration of treatment in OLE (compared to main period), lack of control group and previous exposure to other hGH treatment (Genotropin) in OLE complicates the overall assessment.

In Trial CP-4-004, the incidence of injection site reactions during main period was considerably lower compared to Trial CP-4-006 (Table 37). The overall lower incidence rate of ISR observed in this study may be due to the small size of study or different reporting strategy for these AEs (pain score of >4 was not a criterion anymore for the reporting ISR as AE).

A total of 6/42 subjects who received any dose of somatrogon in main period developed injection site reactions: 2 in the main period and 4 in the OLE-PEN period (3 in PEN Year 1 and 1 in PEN Year 2). No subjects in the Genotropin group had injection site reactions. All events were nonserious and resolved without treatment. No subjects discontinued the study due to ISRs.

Table 37. Incidence of Injection Site Reactions, Trial CP-4-004 (Main and OLE Studies) by Treatment Arms by FMQ (Narrow)

Trial	N	n (%)
CP-4-004 – Main		
Somatrogon 0.25 mg/kg	13	1 (7.7%)
Somatrogon 0.48 mg/kg	15	0
Somatrogon 0.66 mg/kg	14	1 (7.7%)
Somatrogon – all doses	42	2 (4.8%)
Genotropin	11	0
CP-4-004 – OLE		
PEN Year 1 (pen injector)	40	3 (7.5%)
PEN Year 2 (pen injector)	35	1 (2.9%)

Source: Table prepared by the Medical Officer with data excerpted by the Clinical Data Scientist.
Abbreviations: FMQ, FDA medical query; N, number, OLE, open-label extension

Effect of ADA on ISR AEs

Because of the high rate of ADA in subjects treated with somatrogon (refer to Section 7.7.3), the question was also raised whether the somatrogon-induced ISRs are associated with immunogenicity. To explore this, the review team conducted additional analyses of the incidence of somatrogon-induced AEs of ISR by antidrug antibody status. The results of these analyses are briefly summarized below.

There was a slightly higher incidence of AEs of ISR in the ADA-positive somatrogon subgroup compared to the negative ADA subgroup during the main period of Trial CP-4-006: in 40 out of the 84 subjects (48%) who were ADA-positive and in 8 of the 25 subjects (32%) who were ADA-negative, respectively (Table 38). Similarly, in the OLE period, among subjects who were originally randomized to somatrogon, more subjects with positive ADA experienced AEs of injection site reactions compared to subjects with negative ADA. This observation does not confirm a relationship between ADA status and ISR.

All AEs of ISR were nonserious, mild or moderate, transient, and self-limiting.

Table 38. Incidence of Injection Site Reactions by ADA Status, Trial CP-4-006

Trial CP-4-006 Main Study				Trial CP-4-006 OLE Study			
Somatrogon		Genotropin		Originally Randomized to Somatrogon		Originally Randomized to Genotropin	
ADA+	ADA-	ADA+	ADA-	ADA+	ADA-	ADA+	ADA-
N=84	N=25	N=18	N=97	N=88	N=16	N=38	N=69
40 (48%)	8 (32%)	3 (17%)	26 (27%)	20 (23%)	3 (19%)	17 (45%)	30 (44%)

Source: Prepared by the Medical Reviewer from data provided by the Clinical Data Scientist.
Abbreviations: ADA, antidrug antibody; OLE, open-label extension

Conclusion

The imbalance observed in the rates of AEs of injection site reactions between somatrogon and Genotropin groups in Trial CP-4-006 (43% versus 25%) may be related to the Applicant's overall strategy of reporting ISR. Not all ISR recorded in the study were labeled as AEs- only those that met certain criteria. In addition, ISRs were reported weekly and in the Genotropin group (daily injection), only the ISR that had the highest severity during a week of reporting were reported as AEs; the less severe ISR in the same week would not be reported as an AE. In contrast, for the one, weekly somatrogon injection, any ISR that met prespecified criteria were reported. When all ISRs were analyzed regardless of whether or not met criteria for reporting as

AEs, there were no imbalances in frequency of ISRs (97 versus 102 subjects in somatrogon and Genotropin groups, respectively).

Although it appears that a higher percentage of subjects with ADA had injection site reactions, causality cannot be confirmed from the data. Small difference in the rates of ISRs between ADA-positive and -negative subjects may be due to the uneven number of subjects in each group and/or the fact that not all ISR were coded as AEs.

Although there was an increased frequency of ISRs of severe score in somatrogon group compared to Genotropin group, all ISR were nonserious, resolved without treatment or drug interruption, and were mild or moderate in severity. Only few subjects discontinued the study CP-4-006 due to ISRs.

Overall, ISRs are expected and can be mitigated through appropriate labeling in Section 6. However, this reviewer recommends including all ISRs in the label regardless whether they have been coded as AEs or not in the trial.

Dissent

No dissent.

7.7.2. Elevated IGF-1 Level and Potential Risk of IGF-1-Related Adverse Reactions

Issue

Persistent elevation of IGF-1 SDS>2, i.e., IGF-1 SDS >2 on 2 or more consecutive measurements was observed more frequently in somatrogon group versus Genotropin group in Trial CP-4-006. Chronically elevated IGF-1 levels may be associated with AEs such as tumors, hyperglycemia, intracranial hypertension, headache, and edema.

Background

Pediatric GHD is a hormone-deficient condition and is associated with low GH and IGF-1 levels. Exogenous GH treatment in pediatric GHD is a replacement therapy and the overarching goal is to mimic the function of endogenous GH secretion. Thus, it is expected that binding of hGH to the human growth hormone receptor (hGHR) will raise IGF-1 levels, which is what occurs physiologically. There is, however, a concern that hGH-induced, chronically elevated IGF-1 levels above the normal range may be associated with AEs including headache, intracranial hypertension, edema, and tumors. Levels of IGF-1 that are clearly associated with adverse reactions are not established to date. Thus, the goal of treatment with hGH is the improvement in growth and final height while avoiding adverse reactions. but monitoring of IGF-1 is not recommended. The target IGF-1 levels to optimize the balance between height gain and potential risks are not established to date (Grimberg et al. 2016), and there are no data that establish a relationship between IGF-1 levels and growth improvement, although a rule of thumb is to keep IGF-1 levels below +2 or 3 SDS.

Assessment

In the somatrogon clinical development program, the Applicant monitored IGF-1 levels every 3 months during treatment with the goal to not exceed +2 SDS. As per protocol, in the somatrogon group, samples for IGF-1 and IGF-1 SDS were to be drawn 4 days post-dose to obtain IGF-1

measurements expected to reflect average levels throughout the week. As shown in Figure 53, predicted IGF-1 concentrations at 96 hours postdose (day 4) had the highest correlation (r^2=0.94) with the weekly average of IGF-1 concentration. The Applicant stated that 23 of the 26 subjects with IGF-1 SDS >2 in the somatrogon group had sampling for measurement of IGF-1 performed at Day 2 or Day 3 post-injection. However, no information was included as to subject ID and the time points of earlier than pre-specified sampling. In the Genotropin group, samples for IGF-1 were collected at any time during the prespecified weeks. The IGF-1 threshold of > +2 SDS on two or more consecutive time points has been used to evaluate the persistent increase in IGF-1 levels above physiologic levels in other hGH programs. Persistent elevation of IGF-1 SDS were to have drug dose decreased by 15% until reaching IGF-1 SDS ≤2.

In the main period of Trial CP-4-006 the number of subjects with at least one IGF-1 SDS value >2 at any time during the study was higher in the somatrogon group (26/119 [24%] subjects) compared to the Genotropin group (3 [3%] subjects). Persistent elevations of IGF-1 SDS (i.e., 2 or more consecutive values of IGF-1 SDS>2) were reported in 14 (13%) subjects in the somatrogon group and in 1 (1%) in the Genotropin group. Twelve of the 14 had their dose reduced. All IGF-1 SDS levels decreased to ≤2 in subjects following a dose reduction. Two out of 14 subjects (ID # (b) (6) and # (b) (6)) with elevated IGF-1 did not have somatrogon dose reduced. However, subject # (b) (6) had a subsequent normalized IGF-1 SDS value at Month 3 of OLE. Subject # (b) (6) continued experiencing persistent elevations of IGF-1 SDS through OLE period and had successive dose reductions (from 0.66 mg/kg/week to 0.35 mg/kg/week) from OLE Month 6 to Month 12, which were followed by gradual decrease in IGF-1 SDS levels (last measurement was 2.98) up to the cut-off date (December 21, 2020). During the OLE period of Trial CP-4-006, the proportion of subjects who met the criteria for persistent IGF-1 SDS levels above 2 [56/212 (26%) subjects] was similar to that reported in the main period (26/119 [24%] subjects). The levels decreased with subsequent somatrogon dose reduction. All subjects were asymptomatic.

No IGF-1-related AEs were reported in subjects with elevated IGF-1 at time of the IGF-1 elevations. No subjects discontinued the trial due to elevated IGF-1 levels.

While the Applicant collected sparse PK/PD samples from Study 004, no analysis/modeling work regarding PK vs. IGF-1 levels was provided for Genotropin. A comparison of PK/PD relationship between Somatrogon and Genotropin therefore could not be conducted.

Because subjects with positive ADA had lower clearance of the drug (refer to Section 6.3.1), the reviewer evaluated the potential association of ADA with chronically elevated IGF-1 SDS in the somatrogon group in Trial CP-4-006. Of the 14 subjects with persistent elevation of IGF-1 SDS in the main period, 11 (79%) subjects had at least one ADA-positive sample, which is a rate similar to overall ADA-positive incidence in the somatrogon arm (77%). In the OLE period of Trial CP-4-006, the incidence of ADA in subjects with elevated IGF-1 SDS levels was 30/56 (54%). IGF-1 and ADA samples were not collected simultaneously, complicating the evaluation of relationship between ADA titers and elevated IGF-1 SDS. Moreover, the fact that all IGF-1 SDS levels normalized with or without dose reduction in subjects who remained ADA positive indicate that positive ADA is not the sole factor contributing to elevated IGF-1 levels.

In the main period of Trial CP-4-004, only 1 of 13 subjects (ID # (b) (6)) in the somatrogon 0.66 mg/kg dose group experienced 2 episodes of persistent elevation of IGF-1 SDS. The first episode (Weeks 10, 14, and 18) resolved with dose reduction and the levels normalized after the second episode (Month 6 and Month 9). No AEs were reported at the time of IGF-1 SDS

increase. This subject tested positive for ADA starting at Month 6 through the entire main and OLE period. No other subjects had persistence elevation of IGF-1 SDS in all treatment groups.

In OLE period, there were a total of 13/48 subjects with persistent elevation of IGF-1. All levels normalized with/without dose reduction. All subjects were asymptomatic, and no AEs were reported.

Conclusion

The difference in the proportion of patients with elevated IGF-1 levels >2 SDS between somatrogon and Genotropin groups may be due to sampling for IGF-1 performed at earlier times (Day 2-3) than the pre-specified time (Day 4) after somatrogon injection as well as higher exposure in some somatrogon-treated subjects, i.e., those with ADA positive status.

Elevations in IGF-1 levels were transient and the levels normalized either at the next visit(s) with or without a dose adjustment in the majority of subjects. All subjects were asymptomatic, and no AEs were reported at time of IGF-1 SDS elevation.

It is reassuring that IGF-1 normalized in all subjects with dose adjustment only and most subjects did not have persistent elevation in IGF-1 SDS for longer than on two consecutive measurement regardless persistence of positive ADA titers.

In conclusion, IGF-1 elevations did not appear to be a concerning safety issue in the somatrogon clinical program. Overall, IGF-1 related AEs and levels of IGF-1 that are associated with these AEs is a monitorable risk. The risk can be mitigated by the monitoring for AEs, recommendations to obtain IGF-1 levels and dose adjustments/treatment discontinuation if the levels are increased above normal range in patients with IGF-1 related AEs (e.g., tumors, glucose abnormalities). However, IGF-1 may require routine monitoring for dose adjustment based on the clinical study designs. This issue is still under discussion at the time of this review.

Dissent

No dissent.

7.7.3. Potential Safety Issues Associated With High Incidence of ADA in the Clinical Program

Issue

As discussed in Section 6.3.1, the high and persistent rate of ADA was observed in the clinical program with somatrogon use that may result in immune responses of varying clinical significance. High titers of ADA and sustained antibody in the circulation can potentially induce immune responses and immune complex deposition at long-term. Epitope spreading can also occur, by novel epitopes formed within ADA immunocomplexes during a primary immune response leads to activation of naïve B cells (Krishna and Nadler 2016). Lastly, there is a potential risk of the interference of anti-CTP antibody with pregnancy tests results and pregnancy/fertility outcomes (refer to Section 7.7.4 for discussion).

Background

Refer to Section 6.3.1. for the discussion of the rate of positive ADA and potential effect of immunogenicity on efficacy of the drug. This section will focus on potential immunogenicity-related safety issues only.

Assessment

- Hypersensitivity AEs

There were no severe and/or serious hypersensitivity reactions in the clinical program. All reactions were mild and resolved without treatment discontinuation. No anaphylactic or angioedema reactions were reported.

The Applicant included the following AEs as potential AEs related to immunogenicity: anti-somatrogon neutralizing antibodies, anaphylactic reaction, angioedema, hypersensitivity. These AEs were also independently analyzed by the review team.

As per the Applicant's analysis, only one subject (subject # (b) (6) in the somatrogon group of Trial CP-4-006, main study) with positive ADA had two AEs of "hypersensitivity." Analysis by the review team revealed that these "hypersensitivity" reactions were mild environmental allergy events of short duration (few hours) with no interruption of study drug.

The Review Team also performed analyses of all AEs reported by PTs suggestive of potential hypersensitivity reactions by grouped query (GQ) (Table 39). Note that even though injection site reactions might be related to hypersensitivity, they are discussed separately in Section 7.7.1. Although there was a slight numerical difference in incidence of injection site reactions between ADA-positive and ADA-negative groups, these differences do not appear to be clinically meaningful. The results of this analysis are briefly summarized below.

The Review Team's analysis based on GQ showed that the main study of Trial CP-4-006, the frequency of immunogenicity-related AEs was low. The incidence of immunogenicity events was higher in the somatrogon group (18 subjects; 17%) compared to Genotropin group (11 subjects; 10%). Most events occurred in three or fewer subjects. The only AEs that occurred in more than two subjects and were seen more frequently in the somatrogon group were conjunctivitis allergic and rhinitis allergic (three subjects each) compared to Genotropin group (one subject with rhinitis allergic). All AEs were nonserious, mostly mild or moderate, self-limiting, and none required drug discontinuation. Allergic rhinitis and conjunctivitis are not unusual events in this age group.

Since ADAs could hypothetically be associated with hypersensitivity reactions, the hypersensitivity reactions in the main period of Trial CP-4-006 were analyzed by ADA status (Table 39). In the somatrogon group, a higher proportion of subjects with hypersensitivity reactions was observed in the ADA-positive (18%) compared to ADA-negative (12%) subjects. The observed difference might be due to the imbalance in the number of subjects per group since there were more ADA-positive subjects than ADA-negative subjects. This explanation is supported by the inverse observation in the Genotropin group, i.e., a higher proportion of subjects with hypersensitivity reactions was observed in the ADA-negative (10%) group (total of 97 subjects) compared to ADA-positive (6%) group (total of 18 subjects).

Table 39. Grouped Queries by Preferred Term and Antibody Status[1], Safety Population, Trial CP-4-006 (Main Period)

	Somatrogon (0.66 mg/kg/Week)		Genotropin (0.034 mg/kg/Day)	
Grouped Query Preferred Term	ADA+ N=84 n (%)	ADA- N=25 n (%)	ADA+ N=18 n (%)	ADA- N=97 n (%)
Hypersensitivity	15 (17.9)	3 (12.0)	1 (5.6)	10 (10.3)
Rash/rash generalized	3 (3.6)	2 (8.0)	0	5 (5.2)
Rhinitis allergic	3 (3.6)	0	0	1 (1.0)
Conjunctivitis allergic	3 (3.6)	0	0	0
Urticaria/idiopathic urticaria	2 (2.4)	0	0	2 (2.1)
Eyelid edema/swelling of eyelid	2 (2.4)	0	0	0
Bronchospasm/bronchial hyperreactivity	1 (1.2)	1 (4.0)	0	1 (1.0)
Pruritus/pruritus generalized	1 (1.2)	0	1 (5.6)	2 (2.1)
Asthma	1 (1.2)	0	0	0
Dermatitis allergic	1 (1.2)	0	0	0
Swelling face	1 (1.2)	0	0	0

Source: adae.xpt; software, Python.
[1] Ant body status for the somatrogon arm combines binding, neutralizing, and anti-CTP antibodies. Antibody status for the Genotropin arm is anti-rhGH.
Hypersensitivity includes asthma, bronchospasm/bronchial hyperreactivity, conjunctivitis allergic, dermatitis allergic, eyelid edema/swelling of eyelid, pruritus/pruritus generalized, rash/rash generalized, rhinitis allergic, swelling face, and urticaria/idiopathic urticaria.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval; CTP, C-terminal peptide; N, number of subjects with ant body status data; n, number of subjects with adverse event; rhGH, human growth hormone

In the main study of Trial CP-4-004, AEs of hypersensitivity were reported in 2 subjects in the somatrogon group (urticaria and rhinitis allergic, 1 subject each). Both subjects were ADA-negative. No subjects in the Genotropin group had hypersensitivity AEs.

There were no new hypersensitivity reactions and no increase in the incidence of hypersensitivity reactions in the OLE periods of both studies CP-4-006 and CP-4-004. Also, there was no evidence of association between hypersensitivity reactions and ADA status.

- Potential impact of ADA on the rate of non-hypersensitivity AEs

Overall, there was no imbalance in frequency or severity of other AEs including the AESI (e.g., tumors, hyperglycemia, edema) between ADA-positive and ADA-negative somatrogon groups in the clinical program (refer to Sections 7.6.1, 7.7.1, and 7.7.2). Few TEAEs were observed slightly more frequently in somatrogon group compared to Genotropin group (e.g., nasopharyngitis, pyrexia, fatigue, nausea). However, the overall rate of these AEs was low, and no imbalance was noted between ADA-positive and ADA-negative subjects. In addition, these AEs are not unusual in this age group. (Guidance 2014).

The incidence of AEs by ADA titer in the somatrogon group was 14/17 (82%) with titer of 0, 10/10 (100%) with titer of 10, 21/25 (84%) with titer of 50, 25/29 (86%) with titer of 250, 16/19 (84%) with titer of 1250, and 9/9 (100%) with titer of >6250. Approximately 50% (49/109) of the subjects treated with somatrogon had ADA titers of 50 or 250. However, the incidence of AEs did not appear to be directly related to the ADA titer.

Conclusion

Overall, no new or increase in frequency of hypersensitivity reactions with somatrogon use compared to Genotropin use was noted in the clinical program. No severe and/or serious hypersensitivity reactions and no anaphylactic reactions were observed with somatrogon use. All

hypersensitivity reactions were mild and resolved without treatment discontinuation. No association between ADA status and titer and potential hypersensitivity reactions was identified during somatrogon treatment. There did not appear to be an association between ADA and frequency and/or severity of other non-hypersensitivity AEs.

Dissent

No dissent

7.7.4. Risks Associated With the Development of Anti-CTP Antibodies

Issue

Somatrogon includes the carboxy-terminal peptide (CTP) present in the beta chain of the human chorionic gonadotropin (hCG), which allows for less frequent injections. The theoretical risks of anti-CTP antibodies are interference with native hCG, leading to incorrect pregnancy tests and adverse effects on fertility and conception.

Background

There is little experience with development of anti-CTP antibodies in drug development. Although the drug would be intended for the pediatric population, there could be adolescents exposed to somatrogon until an age that they still have opened epiphysis, which may be up 15 to 16 years old and therefore potentially of childbearing age. Among subjects with ADA positivity, eleven were also positive for anti-CTP antibodies in Trials CP-4-006 and CP-4-004 (refer to Section 7.2).

To help inform the clinical impact, this issue was discussed in depth with reviewers from the Division of Maternal and Pediatric Health (DPMH), the Division of Urology, Obstetrics and Gynecology (DUOG), and the Division of Biotechnology Review and Research (DBBR3) in the Center for Devices and Radiological Health (CDRH).

Assessment

The Applicant evaluated the effect of somatrogon on fertility in nonclinical studies and there were no treatment-related adverse effects on fertility in rats. However, the impact of anti-CTP antibodies was not evaluated in nonclinical studies. Generally, however, nonclinical studies are not predictive of immunogenicity risk in humans (See Section 7.1)

Anti-CTP antibodies, an unusual finding, were infrequent in the clinical program, were transient and were detected at low concentrations. The Applicant reported a total of 12 subjects with anti-CTP antibodies (3 subjects in CP-4-004, 4 subjects in CP-4-006 OLE, and 4 subjects in the CP-4-004 OLE PEN period) 140 with ADA positivity.

The team, who discussed with the Immunogenicity Review Team, accepted as adequate an analysis from the Applicant that concluded that the risk from anti-CTP antibodies is low: overall, of the 426 positive ADA sample in the program, 2/9% were positive for anti-CTP. In addition, antibodies were transient and mostly of low titer compared to anti-GH ADAs. Acknowledging that there are no available data on the affinity of anti-CTP to hCG, and therefore still an undefined risk, the overall risk for persistent, high titer anti-CTP antibody formation, including long-term, is likely low.

Risk to pregnancy and fertility

DUOG has experience with the development of gonadotropin products and was consulted to provide a clinical perspective on the presence of anti-CTP antibodies and whether these of clinical concern regarding pregnancy and fertility. Dr. Audrey Gassman reviewed information derived from development of Chinese hamster ovary (CHO)-derived gonadotropins (including corifollitropin alfa which is FSH attached to CTP and is approved in Europe for the treatment of infertility), published hCG vaccine data (for pregnancy prevention), and information from the somatrogon development program. Her assessment includes the following:

- *Data from the corifollitropin program can be leveraged to help assess the potential impact on fertility. Corifollitropin is approved in Europe. According to the label, of the 2,511 women treated with corifollitropin who were evaluated for the formation of post-treatment antibodies, only four (0.16%) had evidence of antibody formation. In each case, these antibodies were non-neutralizing and did not interfere with the response to stimulation or the normal physiologic responses of the Hypothalamic-Pituitary-Ovarian axis. Two of these four women became pregnant during the same treatment cycle in which antibodies were detected, suggesting that the presence of non-neutralizing antibodies after stimulation with corifollitropin is not clinically relevant, providing some assurance of the safety.*
- *Data from hCG vaccine programs can also be leveraged to help assess the risk for fertility impairment with somatrogon. A recent published review noted that there is a long history of attempting to develop an hCG vaccine to prevent pregnancy. The review notes that hCG vaccine development has been extremely difficult because the CTP region of hCG β was a poor immunogen and necessitated the use of strong adjuvants to evoke the production of antibodies. This review article states that, "The ability of the anti-hCG titers above 50 ng/ml to prevent pregnancy in sexually active women without derangement of ovulation and menstrual regularity was clearly demonstrated." Although the assays used to develop the hCG vaccine are likely different from those used for somatrogon, it would appear that low levels of anti-CTP antibodies are unlikely to interfere with fertility.*
- *There was a recent report of a false positive pregnancy test that was reported during corifollitropin alfa administration. Based on this report, the EMA added this risk to the product label, "Elonva may cause a false positive hCG pregnancy test if the test is administered during the ovarian stimulation portion of the ART cycle. This may be due to cross-reactivity of hCG pregnancy tests with the carboxy-terminal peptide of the beta subunit of Elonva." Although the false positive level identified with Elonva was a very small quantitative result, it is important for physicians to be aware of this potential cross-reactivity from the CTP protein.*

It is important to note that the above examples do not involve use of a chronic medication (over years) so there remains some uncertainty about the risk with somatrogon. However, it is unlikely that additional clinical studies would inform the risk. Therefore, Dr. Gassman recommended that ideally any patient who develops anti-CTP antibodies should be followed for resolution of the antibodies. It would be challenging to recommend ADA testing for patients using somatrogon in the postmarketing setting, however, and given that the risk of clinical impact appears low, ADA testing specifically for anti-CTP antibodies will not be recommended in labeling. In addition, there is unlikely to be a value in conducting a large postmarketing database or study to directly assess fertility and/or early pregnancy loss given the age of the population treated (pediatrics),

the fact that not all somatrogon-treated patients will attempt to become pregnant, the relatively high background rate of pregnancy loss in the general population (20% of clinically recognized pregnancies), as well as the presence of other risk factors for infertility (such as male factor infertility, polycystic ovarian disease, etc.).

Interference with hCG-based diagnostic tests

CDRH provided expertise on whether anti-CTP antibodies and somatrogon itself (since it contains CTP) can interfere with hCG-based diagnostic tests (refer to CDRH consult review dated May 20, 2021 for full details). Dr. Kotarek indicated that the potential risks associated with both the interference of somatrogon itself and anti-CTP antibodies with pregnancy tests constitute false positive and false negative results. There are potential clinical consequences of inaccurate testing including delayed prenatal care in case of false negative results, and delay of treatment that was contraindicated for pregnancy in case of false positive results. To show that somatrogon itself does not interfere, the Applicant used 4 different home-use urine hCG pregnancy tests and one serum quantitative hCG pregnancy test. Although the Applicant's testing was adequate to show that somatrogon did not interfere with the tests used, different tests may use a different region of hCG for detection and these regions are not typically disclosed to the Agency. Therefore, the tests which the Applicant used do not represent all tests that are on the market. Uncertainty remains that should be considered for labeling. Although the Applicant did not test for interference of anti-CTP antibodies on hCG assays, the same limitations would apply.

Conclusion

Overall, the risks of anti-CTP antibodies appear to be low and can be managed through labeling. No additional premarketing or postmarketing nonclinical or clinical studies are recommended to characterize the risk.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Based on the reviewer's population PK analysis, somatrogon pharmacokinetics is described by a 2-compartment pharmacokinetic model with first order absorption and no lag-time of absorption from the administration compartment. The final model included time varying weight and ADA titer values as the only covariates.

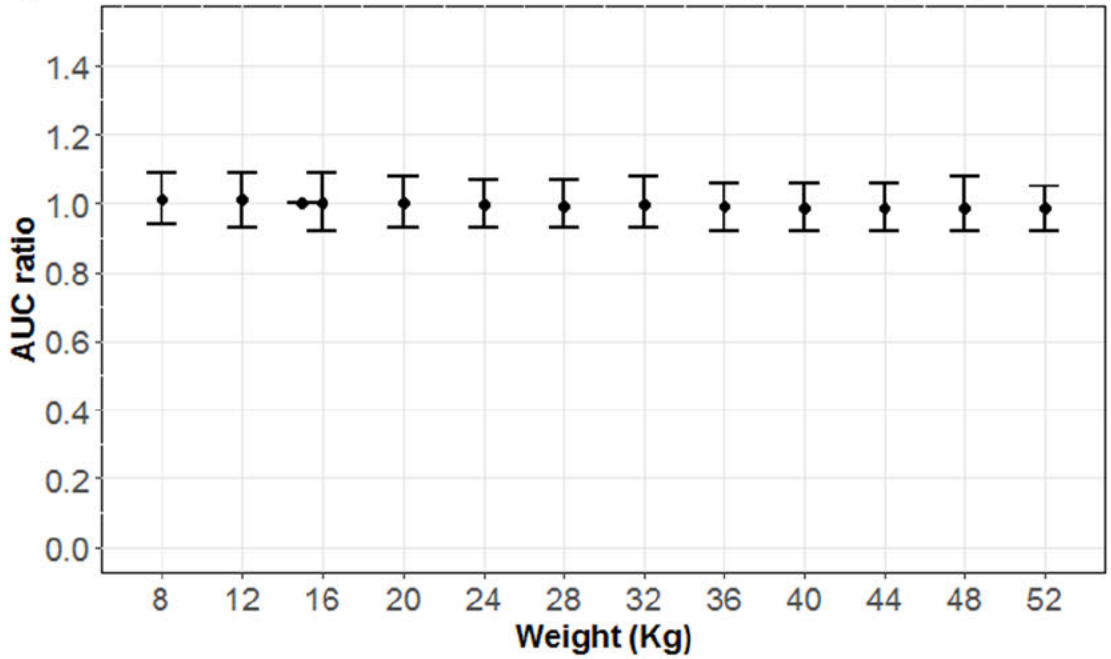
Body Weight

Somatrogon clearance increases with increase in body weight and weight-based dosing provides comparable exposures across body weights anticipated for the patient population (8 to 52 kg).

The impact of body weight on somatrogon exposure was evaluated through Monte Carlo simulation using the reviewer's final PopPK model. The model had time varying body weight and ADA-titer as the only covariates. Therefore, a virtual sample of the pediatric population with uniformly distributed body weight ranging from 8 to 52 kg and with ADA negative status (i.e., ADA titer, 0) was created. Stochastic simulation was used to obtain concentrations over the dosing interval at steady state. Noncompartmental analysis was used to obtain predicted area under the curve (AUC). The virtual sample consisted of 1000 subjects on which 200 stochastic

simulations were performed. For each simulation, the ratio of mean AUC at each weight to mean AUC at 15 kg was calculated. The median and 95% prediction intervals of these ratios are shown in Figure 12. The figure shows that weight-based dosing provides comparable exposures across body weights despite weight-dependent increase in clearance.

Figure 12. Distribution of AUC Ratios at Different Body Weights to Body Weight of 15 kg



Source: Reviewer's independent analysis.
Abbreviation: AUC, area under the curve

More information can be found in the Pharmacometrics review (Section 14.3.1.4.1).

ADA Status

Observed PK data from Trial CP-4-004 and CP-4-006 including open-label extension showed increased somatrogon concentrations in ADA-positive subjects. See Section 14.3.1.4.2.

Based on the population PK analysis, the clearance of somatrogon decreases ~26% after patients developed antidrug antibodies. Table 40 summarizes central tendency and ranges of the selected PK parameters at steady state for all subjects before and after turning ADA positive.

Table 40. Summary Statistics of Model-Predicted Individual PK Parameters for All Subjects in the Phase 2 and Phase 3 Studies Before and After Turning ADA-Positive

Parameter	ADA	Mean (SD)	Median	Min-Max
CL/F (L/h)	-	0.784 (0.337)	0.722	0.27-2.744
	+	0.582 (0.309)	0.552	0.115-1.542
Vc/F (L)	-	7.547 (5.848)	6.07	1.377-41.985
	+	8.31 (7.748)	6.058	1.478-48.29
VP (L)	-	13.921 (7.732)	12.208	3.005-43.07
	+	14.953 (8.505)	12.829	3.697-51.819
Alpha half-life (h)	-	6.386 (3.692)	5.293	1.663-22.67
	+	10.554 (8.696)	6.959	1.707-43.809
Beta half-life (h)	-	351.954 (69.893)	346.664	205.219-550.646
	+	369.052 (74.785)	359.974	221.595-595.33
AUC_{ss} (h·mg/L)	-	19.208 (3.122)	19.408	10.919-28.363
	+	31.162 (14.498)	26.808	12.504-73.647

Parameter	ADA	Mean (SD)	Median	Min-Max
C_{max} (mg/L)	-	0.483 (0.088)	0.484	0.159-0.741
	+	0.628 (0.184)	0.611	0.171-1.212
T_{max} (h)	-	12.954 (3.949)	12	6-26
	+	16.256 (6.214)	14	6-33

Source: Reviewer's independent analysis.
Abbreviations: ADA, antidrug antibodies; AUC_{ss}, area under the curve at steady-state; CL/F, clearance after oral administration; C_{max}, maximum concentration; PK, pharmacokinetics; SD, standard deviation; T_{max}, time to maximum concentration; Vc/F, volume of the central compartment; Vp, volume of the peripheral compartment

More information can be found in the Pharmacometrics review (Section 14.3.1.4.1).

8.2. Drug Interactions

No dedicated drug-drug interaction study was conducted. Based on the class labeling for effect of growth hormone on CYPs and other interactions, Table 41 is proposed for Section 7 Drug Interactions of USPI.

Table 41. Proposed Table for Section 7 of the USPI

Replacement Glucocorticoid Treatment	
Clinical Impact:	Microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue. (b) (6) inhibits 11βHSD-1. Consequently, individuals with untreated GH deficiency have relative increases in 11βHSD-1 and serum cortisol. Initiation of TRADENAME may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations.
Intervention:	Patients treated with glucocorticoid replacement for hypoadrenalism may require an increase in their maintenance or stress doses following initiation of TRADENAME *[see Warnings and Precautions (Section 5 of the USPI]*
Examples:	Cortisone acetate and prednisone may be affected more than others because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.
Cytochrome P450-Metabolized Drugs	
Clinical Impact:	Limited published data indicate that (b) (6) treatment increases cytochrome P450 (CYP450)-mediated antipyrine clearance. TRADENAME may alter the clearance of compounds known to be metabolized by CYP450 liver enzymes.
Intervention:	Careful monitoring is advisable when TRADENAME is administered in combination with drugs metabolized by CYP450 liver enzymes.
Oral Estrogen	
Clinical Impact:	Oral estrogens may reduce the serum insulin-l ke growth factor-1 response to TRADENAME.
Intervention:	Patients receiving oral estrogen replacement may require higher TRADENAME dosages.
Insulin and/or Other (b) (6) Agents	
Clinical Impact:	Treatment with TRADENAME may decrease insulin sensitivity, particularly at higher doses.
Intervention:	Patients with diabetes mellitus may require adjustment of their doses of insulin and/or other (b) (6) agents *[see Warnings and Precautions*

8.3. Plans for Pediatric Drug Development

A juvenile animal toxicity study was not considered to be warranted, because the toxicity profile of somatrogon was consistent with its pharmacological activity and no unexpected findings were noted in adult animals. In addition, in the 26-week repeat-dose monkey study, monkeys were approximately 2.5 to 4 years of age at the initiation of dosing (juvenile/adolescent), but no new or unexpected toxicities were observed in younger animals as compared to older animals.

The proposed indication for somatrogon is treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone. A phase 3 efficacy and safety study was conducted in patients 3 years and above.

8.4. Pregnancy and Lactation

A battery of development and reproductive toxicology studies (fertility, embryo-fetal development, and per-and postnatal development) was conducted in rats. Findings observed were consistent with the pharmacology of growth hormone. The no observed adverse effect level (NOAEL) in all studies was the highest dose tested, 30 mg/kg, corresponding to 45-fold the maximum recommended human dosage (MRHD) based on exposure.

Table 42. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In an embryo-fetal development study in rats subcutaneously administered 3, 10 or 30 mg/kg somatrogon every 2 days during the period of organogenesis from gestation day (GD) 6 to 18, there were no adverse maternal or embryo-fetal effects at doses up to 30 mg/kg (45-fold the maximum recommended human dose (MRHD) based on exposure). In a pre- and postnatal development study in pregnant rats subcutaneously administered 3, 10 or 30 mg/kg somatrogon every 2 days from GD 6 to lactation day 20, there were no treatment-related maternal toxicity or adverse findings in the offspring.
8.2 Lactation	Presence of somatrogon in animal milk was not evaluated.
8.3 Females and Males of Reproductive Potential	Fertility was not affected in animals. This section can be omitted.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Long term carcinogenicity studies and genotoxicity studies have not been performed with somatrogon. In a fertility and early embryofetal development study in rats, subcutaneous doses of 0, 3, 10, or 30 mg/kg somatrogon were administered every 2 days (6-, 22-, or 45-fold the MRHD based on exposure) beginning 4 weeks prior to mating through cohabitation for males and 2 weeks prior to mating up to GD 7 for females. Somatrogon elicited an increase in estrous cycle length, copulatory interval, and number of corpora lutea at doses ≥10 mg/kg, but there was no impact on mating indices, fertility, and number of viable embryos/early embryonic development[A].

[A] Anti-drug antibodies (ADAs) were not measured in the reproductive and developmental studies.

9. Product Quality

Although the Office of Pharmaceutical Quality (OPQ) Review team has assessed BLA 761184 with respect to microbiology, facilities, and immunogenicity assays and has determined that it

meets all of those applicable standards to support the identity, strength, quality, and purity that it purports, the DS and DP discipline has unresolved quality issues. The deficiencies include (b) (4) Therefore, from an OPQ perspective, this BLA is not deemed ready for approval in its present form until the above-mentioned issues are satisfactorily resolved. As such, OPQ recommends a Complete Response (CR) action from a product quality perspective.

9.1. Device or Combination Product Considerations

The Center for Devices and Radiological Health (CDRH) reviewed the proposed device, a disposable pre-filled pen injector, and recommend approval of device constituent parts of the combination product (pen-Injector) pending an inspection of Pfizer Manufacturing Belgium NV facility. A pre-approval inspection was recommended based on the analysis of the Applicant's inspection history indicating that it has not been inspected over the past 3 and based on the existing for-cause pending inspection. The inspection has not been performed at the time of this review completion (refer to CDRH consults from May 10, 2021 and June 22, 2021).

The somatrogon drug product is a single-patient-use, disposable prefilled pen designed for subcutaneous injection. The pen encloses a 3 mL (b) (4) clear glass cartridge containing the somatrogon drug product solution and together they form a single integral product, intended exclusively for use in the given combination. There are 2 mechanically identical somatrogon prefilled pen presentations; 24 mg-containing a volume of 1.2 mL somatrogon at 20 mg/mL and 60 mg – containing a volume of 1.2 mL somatrogon at 50 mg/mL. Needles are not included in the carton containing the pen. Both pen presentations are mechanically identical. Each pen presentation contains multiple doses of somatrogon drug product solution. The dose is variable, set within the range of 10 to 600 µL, which is selected using a manual dial dose setting mechanism and injected by a manually driven piston.

CDRH assessment included device description, labeling, design controls, risk analysis and design verification, which were all found to be adequate. No deficiencies were identified in any of these assessments. The following notes were added:

- Labeling adequately covers the device requirements for labeling. CDRH recommended pen needles listed on the device carton.
- Risk analysis: the pen is not novel and is like other pens currently on the market. It is recommended that all users receive training on the correct way to inject and use all aspects of the pen injector prior to beginning therapy.
- CDRH found deficiencies in the design verification and sent several Information Requests (IRs) during the review, to which the Applicant provided adequate responses and resolved the pending deficiencies. The final assessment found no deficiencies.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The inspection for this BLA consisted of two domestic clinical sites and of the co-Applicant (OPKO Health, Inc.) of Study CP-4-006. Based on the inspections of the two clinical sites and of the co-Applicant, the Office of Scientific Investigation (OSI) concluded that the inspectional findings support validity of data as reported by the Applicant under this BLA (Section 20).

Financial disclosure documentation was reviewed. No issues were identified that could influence the outcome of the trials (Refer to Section 23 in the Appendix).

11. Advisory Committee Summary

No Advisory Committee meeting was held for the following reasons:

- This was not the first drug in class, the application did not raise significant public health questions on the role of the biologic.
- The discussion of immunogenicity-related issues would not benefit from advisory committee discussion at this time until the high immunogenicity rate is better understood and factors that contribute to the immunogenicity of the product are identified and potentially addressed.

III. Appendices

12. Summary of Regulatory History

The Investigational New Drug (IND) 079745 was submitted by Modigenetech, Ltd., on July 19, 2010, to investigate the use of MOD-4023 (also referred to as somatrogon) for the treatment of growth hormone deficiency (GHD) (b) (4) On September 29, 2010, FDA designated MOD-4023 as an orphan drug product for the treatment of GHD. In a meeting held on September 13, 2011, the Sponsor (then PROLOR-Biotech Ltd.) presented a design for an initial phase 2 clinical study in pediatric subjects with GHD. This meeting also discussed the design and validation of immunogenicity test methods.

An end-of-phase 2 (EOP2) meeting was held with the current Sponsor of the IND (OPKO Biologics Ltd. [OBL]) on March 11, 2013, to discuss the development program and planned phase 3 study (b) (4)

Another EOP2 meeting was held with OBL on March 23, 2015, to discuss the proposed indication for the treatment of children with growth failure due to inadequate secretion of endogenous growth hormone. At this meeting, FDA expressed concerns with the treatment duration of OBL's planned phase 3 study, stating that 12 months of treatment may not be sufficient to evaluate the long-term safety and efficacy of MOD-4023 (i.e., final adult height). OBL agreed to submit data from pediatric subjects following 4 years of treatment in an extension of the phase 2 study, as well as data from an open-label extension of the phase 3 study. FDA provided additional recommendations regarding the immunogenicity sampling and analysis plan and sample size calculations, to which OBL agreed. FDA also recommended that OBL consider including a lower dose of MOD-4023 (0.48 mg/kg/week) in addition to the planned dose of 0.66 mg/kg/week, which OBL agreed to consider in conjunction with their review of the completed phase 2 study data. FDA agreed to accept a single phase 3 study for BLA filing, with the phase 2 study data to be included for review as supportive evidence of effectiveness. FDA expressed concerns for OBL's use of a different formulation in the pivotal trials (frozen liquid in vial) versus the to-be-marketed formulation (to be administered via a prefilled, single-patient-use, multidose disposable pen [autoinjector]), and made recommendations for bridging the formulations. In addition, FDA provide guidance about conducting human factors studies for the final combination product (autoinjector) and its instructions for use.

FDA provided additional guidance to OBL via written responses to address chemistry, manufacturing, and controls (CMC) and clinical strategies for OBL's plan to change the drug presentation from a frozen liquid vial to an autoinjector device (refer to letters issued on May 20 and August 19, 2016). FDA provided additional advice related to the biocomparability studies planned for the new formulation in written responses issued on May 10, 2018.

IND 132494 was submitted by Pfizer, Inc. (Pfizer), on May 24, 2018, for further development of MOD-4023 for the treatment of GHD in adult and pediatric subjects. OBL provided a letter of authorization to cross-reference the previous development work conducted under IND 079745. The initial IND submission included protocol C0311002 entitled *A Phase 3, Randomized, Multicenter, Open-Label, Crossover Study Assessing Subject Perception of Treatment Burden With Use of Weekly Growth Hormone (Somatrogon) Versus Daily Growth Hormone (Genotropin) Injections in Children With Growth Hormone Deficiency*.

On October 16, 2018, Pfizer submitted a human factors validation study protocol for the autoinjector presentation (24 mg/1.2 mL and 60 mg/1.2 mL). FDA provided recommendations on December 13, 2018, March 21, 2019, and July 11, 2019. Pfizer provided responses to the recommendations on February 7, 2019, and April 4, 2019.

A pre-BLA meeting was held on December 16, 2019, to discuss Pfizer's planned application seeking an indication for the treatment children with GHD. (b) (4) This meeting discussed the format and content of the planned BLA for all relevant disciplines, and there were no agreements made for late submission of application components.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Pharmacology

13.1.1.1. Primary Pharmacology

Refer to Section 15.1 for a discussion of the primary pharmacology of somatrogon. There was no evidence for off-target binding activity of somatrogon.

13.1.1.2. Safety Pharmacology

No treatment-related adverse effects were noted in safety pharmacology endpoints evaluated during repeat dose toxicology studies in monkeys (cardiovascular system, CNS, and respiratory system) and rats (CNS and respiratory system).

13.1.2. Pharmacokinetics

Absorption

Repeat-Dose Pharmacokinetics/Toxicokinetics

Pharmacokinetic evaluation was incorporated into pivotal repeat dose toxicology studies conducted in rats (4 weeks in duration) and monkeys (4 and 26 weeks in duration). Similar to single dose exposures, repeated subcutaneous administration of somatrogon resulted in systemic exposures (maximum plasma concentration (C_{max}) and area under the curve (AUC) values) that increased in an approximately dose proportional manner and were not significantly influenced by

sex in both rats and monkeys. In rats, twice weekly subcutaneous administration generally resulted in increased C_{max} and AUC values, longer half-lives, prolonged T_{max}, and a two-fold accumulation in AUC and C_{max} at Week 4 of dosing. In an embryofetal development study where pregnant rats were administered somatrogon every 2 days, a similar dose proportional increase in systemic exposure (C_{max} and AUC values) was observed from gestation day 6 to 18. However, no consistent evidence of accumulation was observed with repeated administration in pregnant rats.

Monkeys subcutaneously administered somatrogon twice weekly for a duration of 4 weeks did not show accumulation of the test article; similar C_{max}, T_{max}, and AUC values were observed on Days 1 and 19. Monkeys administered somatrogon twice weekly for 26-weeks of duration showed evidence of slight accumulation. Consistent with the long-acting nature of somatrogon, half-life and T_{max} values were typically increased and clearance (CL/F) values were decreased when compared to recombinant human growth hormone (rhGH).

13.1.3. Toxicology

Single-Dose Toxicology

Non-Good Laboratory Practices (GLP) single-dose toxicology studies were performed where somatrogon was administered subcutaneously to rats (0, 3, 6, 36, or 180 mg/kg) and monkeys (1.8 or 90 mg/kg). No adverse findings were noted.

Repeat-Dose Toxicology

Pivotal GLP-compliant repeat dose toxicology studies with somatrogon were conducted in rats and monkeys. Results with somatrogon (MOD-4023) are summarized as follows:

Trial Number and Title: TP-4-003: A 4-Week Subcutaneous Toxicity Study of MOD-4023 in Sprague-Dawley Rats with a 2-Week Recovery

Due to a lack of adverse findings, the NOAEL was the highest dose examined (268-fold[5] the maximum recommended human dose, based on AUC).

[5] Four-week rat study (TP-4-003) 180 mg/kg, $AUC_{0\text{-}72h}$ on Day 26 = 3280 µg·h/mL. Extrapolated $AUC_{0\text{-}168h}$ = 7544 µg·h/mL. Clinical $AUC_{0\text{-}168h}$ for the 0.66 mg/kg/week dose = 28.1 µg·h/mL.

Table 43. Information for the 4-Week Repeat Dose Toxicity Study in Rats

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 3.6, 36 and 180 mg/kg on Days 1, 5, 8, 12, 15, 19, 22, and 26
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) mM citrate, (b) (4) mM NaCl
Species/strain:	Rat/CD® [Crl:CD®(SD)]
Number/sex/group:	15/10/10/15/sex in each group
Age:	6 weeks
Satellite groups/unique design:	5/11/11/11/sex in each group
Deviation from study protocol affecting interpretation of results:	None

Source: Prepared by the Nonclinical Reviewer
Abbreviation: GLP, good laboratory practices

Table 44. Observations and Results for the 4-Week Repeat Dose Toxicity Study in Rats

Parameter	Major Findings
Mortality	None
Clinical signs	Increase incidence of scabs was observed in the 180 mg/kg group starting on day 8 of the dosing period.
Body weights/Food consumption	Increased body weight gain, body weight, and food consumption was noted at doses ≥36 mg/kg in males and females and resulted in a statistically significant increases in body weight for rats in the 180 mg/kg group beginning on day 5 in females and day 8 in males.
Ophthalmoscopy	Not conducted.
Electrocardiogram	Not conducted.
Hematology	Statistically significant and dose-related decreases in erythrocytes (≥36 mg/kg), hemoglobin (180 mg/kg) and hematocrit (180 mg/kg) were observed. Decreases in red cell mass ranged from 5 to 12% and were associated with a statistically significant increase (31%) in reticulocytes (180 mg/kg females), indicating a regenerative response in the bone marrow. Platelets were increased at doses ≥36 mg/kg in both sexes (up to 31%). These changes were reversible and were not considered clinically relevant as they occurred at high multiples to the clinical dose (≥61 times based on AUC).
Clinical chemistry	Relative to predose levels, insulin-like growth factor-1 (IGF-1) serum concentrations increased in all dose groups without dose dependency on both Day 1 and Day 26, indicating that somatrogon was pharmacologically active. While dose proportional increases in IGF-1 levels were not observed, this finding is not unusual as healthy animals with normal pituitary gland function were used. Increases in triglyceride (males and females) and cholesterol (males) levels were observed in rats treated with 180 mg/kg somatrogon.
Urinalysis	No adverse findings noted.
Gross pathology	No adverse findings noted.

Parameter	Major Findings
Organ weights	Consistently with the pharmacology of growth hormone, subcutaneous somatrogon administration resulted in increases in several absolute organ weights that coincided with increases in body weights including adrenals (≥3.6 mg/kg for males and 180 mg/kg females), heart (≥36 mg/kg males and 180 mg/kg females), kidney (≥36 mg/kg for females and 180 mg/kg in males), liver (≥36 mg/kg in females and 180 mg/kg males), lung (≥36 mg/kg in females), ovaries (≥36 mg/kg in females), spleen (≥36 mg/kg in females and 180 mg/kg in males), and thymus (≥36 mg/kg in females and 180 mg/kg in males). Several increases in female organ weights persisted throughout the recovery period (heart, kidney, and lung). Increased liver weights persisted in both sexes throughout the recovery period.
Histopathology Adequate battery: Yes	Minimal to mild, irreversible feminization of the mammary gland in somatrogon-treated males and partially reversible minimal to moderate hyperplasia in females dosed with ≥36 mg/kg somatrogon was observed, consistent with growth hormone pharmacology. Increased minimal extramedullary hematopoiesis (EMH) observed in the spleen of two males dosed at 180 mg/kg was not considered adverse due to the lack of any hematological correlate in the effected rats. EMH has been observed in rats treated with rhGH (Jorgensen et al. 1988). A dose-dependent increase in the incidence and severity (minimal to mild) of tubular mineralization in the cortico-medullary junction of the kidney of female rats was observed. This is a common spontaneous background finding in female rats that has been associated with low calcium: phosphorus ratios and high food consumption (Rao 2002) and may have been exacerbated by the increase in food consumption. A dose-dependent increase in the incidence and severity (minimal to moderate) of periportal vacuolation in the liver was partially reversible in males. These changes were consistent with fat accumulation, higher food consumption, and higher triglycerides and were considered a likely indirect effect of the test article (increase in food consumption). All above changes were generally reversible and were not considered adverse.
Immunogenicity	While antidrug antibodies against human growth hormone and against the c-terminal peptide domain of somatrogon were observed across all study groups, pharmacodynamic activity was maintained in all animals and pharmacokinetics were not affected. Therefore, ADAs did not impact the evaluation of safety of somatrogon.

Source: Prepared by the Nonclinical Reviewer

Study Number and Title: M04008: A 26-Week Subcutaneous Toxicity Study of MOD-4023 in Rhesus Monkeys With a 4-Week Recovery

Due to a lack of adverse findings, the NOAEL was the highest dose examined (150-fold[6] the maximum recommended human dose).

Table 45. Information for the 26-Week Repeat Dose Toxicity Study in Monkeys

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	MOD-4013: 0, 1.5, 15, 30 mg/kg every 5 days Bio-tropin®: 3.6 mg/kg/day
Route of administration:	Subcutaneous injection
Formulation/vehicle:	(b) (4) mM citrate, (b) (4) mM NaCl
Species/strain:	Rhesus monkeys (*Macaca mulatta*)/China origin
Number/sex/group:	4/sex/group
Age:	2.7-4 years old
Satellite groups/unique design:	2/sex/group
Deviation from study protocol affecting interpretation of results:	None

Source: Prepared by the Nonclinical Reviewer

[6] Twenty-six-week monkey study (M04008) NOAEL = 30 mg/kg, AUC_{0-t} or AUC_{0-120h} on Day 118 = 3445 µg·h/mL in males, 2574 µg·h/mL in females, and 3009.5 µg·h/mL combined. Extrapolated Combined AUC_{0-168h} = 4213.3 µg·h/mL. Clinical AUC_{0-168h} for the 0.66 mg/kg/week dose = 28.1 µg·h/mL.

Table 46. Observations and Results for the 26-Week Repeat Dose Toxicity Study in Monkeys

Parameter	Major Findings
Mortality	None.
Clinical signs	Increases incidence of soft and watery feces was observed in all somatrogon-treated male groups (without dose-relationship) compared to controls.
Body weights	No treatment-related changes in body weight were observed.
Ophthalmoscopy	No adverse findings noted.
Electrocardiogram	No adverse findings noted.
Hematology	No adverse findings noted.
Clinical chemistry	Increases in serum insulin-like growth factor-1 (IGF-1) levels were observed in all somatrogon-treated monkeys. Consistent with findings in rats, dose responsive increases in IGF-1 levels did not occur, possibly because healthy monkeys with normal pituitary function were evaluated.
Urinalysis	No adverse findings noted.
Gross pathology	No adverse findings noted.
Organ weights	A two-fold increase in mandibular salivary glands weight observed in females at 180 mg/kg was not considered adverse because there were no microscopic correlates, and was not clinically relevant because it occurred at 150-fold the clinical exposure
Histopathology Adequate battery: Yes	An increased incidence of mixed inflammatory cells in the subcutis and deep dermis at the injection site was observed in all somatrogon-treated groups and resolved during the recovery period.
Immunogenicity	ADAs against hGH and to a lesser extent against CTP were observed in all treated groups. ADAs were generally not neutralizing based on the sustained increase in IGF-1 levels.

Source: Prepared by the Nonclinical Reviewer

Genotoxicity

No genetic toxicity studies were conducted, because somatrogon is a protein based biotherapeutic that is not expected to interact with DNA.

Carcinogenicity

Carcinogenicity studies were not performed. The toxicological profile of somatrogon in rats and monkeys is generally consistent with the exaggerated pharmacology of growth hormone in healthy animals.

Reproductive and Developmental Toxicity

Findings observed in development and reproductive toxicology studies in rats were generally consistent with the pharmacology of growth hormone. The production of antidrug antibodies was not evaluated in development and reproductive toxicology studies. Safety margins were calculated based toxicokinetic data from the embryo-fetal study and a clinical $AUC_{0\text{-}168h}$ of 28.1 µg·h/mL at 0.66 mg/kg/week in phase 2 study, Trial CP-4-004.

Fertility and Early Embryonic Development

In a fertility and early embryofetal development study in rats, subcutaneous doses of 0, 3, 10, or 30 mg/kg every 2 days beginning four weeks prior to mating through cohabitation for males and two weeks prior to mating up to gestation day (GD) 7 for females, had no adverse impact on fertility or early embryonic development. Increased estrous cycle length, longer copulatory intervals, and an increased number of corpora lutea were observed in rats treated with ≥10 mg/kg somatrogon. However, these findings were not considered adverse as they did not negatively impact fertility or reproductive performance. Therefore, the NOAEL for fertility and reproductive performance was the highest dose tested (45-fold the maximum recommended human dose).

Embryo-Fetal Development

In a pivotal embryo-fetal development study, pregnant rats were subcutaneously administered 0, 3, 10 or 30 mg/kg somatrogon every 2 days from gestation days 6 to 18. Pharmacologically-mediated increase in maternal body weight and body weight gain was observed at doses ≥10 mg/kg. As no adverse findings were noted, the NOAEL for maternal toxicity and embryo-fetal development was the highest dose examined (45-fold the maximum recommended human dose).

Prenatal and Postnatal Development Including Maternal Function

In a pre- and postnatal development study, pregnant rats were subcutaneously administered 3, 10 or 30 mg/kg somatrogon every 2 days from gestation day 6 to lactation day 20. Consistent with the pharmacological activity of somatrogon, a statistically significant increase in body weight was observed in dams (≥10 mg/kg) and offspring (30 mg/kg). No treatment-related maternal toxicity or adverse findings in the offspring were noted. Therefore, the NOAEL for maternal and developmental toxicity was 30 mg/kg (45-fold the maximum recommended human dose).

13.2. Individual Reviews of Studies Submitted to the BLA

Not applicable

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Not applicable

14.2. In Vivo Studies

14.2.1. Study CP-4-001: Phase 1 Single-Ascending Dose Study in Adult Healthy Volunteers

Title

A phase I, Randomized, Double-Blinded, Placebo-Controlled, Single-Dose, Dose-Escalation Study to Evaluate the Safety and Pharmacokinetics of a Long Acting hGH Product (somatrogon, also called MOD4023), in Healthy Volunteers

Design

This study was a phase 1, randomized, double-blind, placebo-controlled, single-dose, study designed to evaluate the safety, tolerability, PK, immunogenicity, and PD of MOD-4023 administered at doses of 4, 7, or 21 mg to healthy male subjects. Twenty-four (24) healthy subjects were enrolled into three cohorts, each with eight subjects (six active; two placebo) to receive SC injections of either MOD-4023 or placebo.

The drug was administered as a single SC dose: 4 mg as one injection to the arm, 7 mg as one injection to the arm, and in the 21 mg dose group as two equal-volume injections (one to the arm and one to the thigh).

Blood samples for MOD-4023 PK were drawn at 0 (predose, up to 60 minutes before injection), 2, 4, 6, 8, 10, 12, 24 hours and 2 (48±2 hours), 3 (72±2 hours), 4 (96±2 hours), 7 (168±2 hours), 10, and 14 days after injection. Blood samples for IGF-I levels were drawn at 0 (predose, up to 60 minutes before injection), 6, 12, 24 hours and 2 (48±2 hours), 3 (72±2 hours), 4 (96±2 hours), 7 (168±2 hours), 10, and 14 days after injection. Blood samples for antibodies to MOD-4023 were drawn at predose and after injection at 14±2 and 30±2 days.

Measurement of plasma concentrations of MOD-4023, IGF-1 and detection of antibodies to MOD-4023 were performed using validated assays.

IGF-1 SD scores were calculated from appropriate reference data from the same assay and a demographically matched subject base.

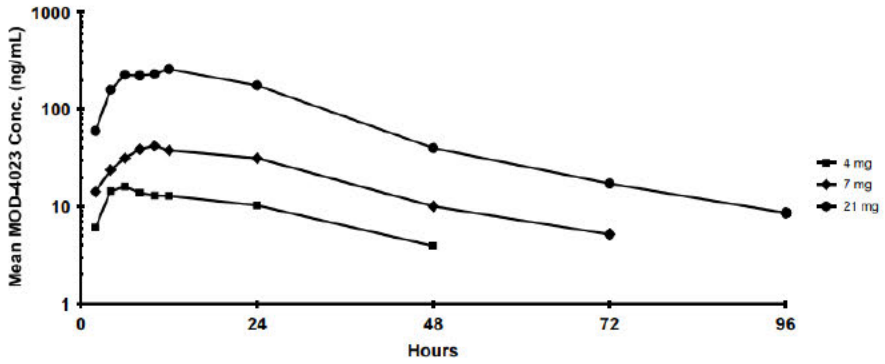
Subject Disposition

A total of 24 subjects were screened, enrolled, and randomized. All subjects completed the study, meeting the minimum number planned for analysis. No subjects withdrew from the study.

Pharmacokinetic Results

Mean MOD-4023 concentration-time profiles and PK parameters of MOD-4023 in healthy volunteers following subcutaneous administration of 4, 7, or 21 mg MOD-4023 are shown in Figure 13 and Table 47.

Figure 13. Mean Serum MOD-4023 Concentration Versus Time Profiles for Healthy Volunteers Following Subcutaneous Injection of 4, 7, or 21 mg MOD-4023



Source: Figure 2 of CP-4-001-SAP.pdf.
Abbreviation: MOD-4023, somatrogon

Exposure expressed as C_{max} and AUC (AUC_{0-t} and $AUC_{0-\infty}$) increased more than the increase in dose. Correspondingly, CL/F (dose divided by $AUC_{0-\infty}$) decreased with the increase in dose from 85.81 to 68.90 and 37.08 mL/hr/kg at the 4, 7, and 21 mg doses. $T_{1/2}$ appeared to be dose independent.

Median T_{max} was 7 to 12 hours and mean $T_{1/2}$ was 21 to 24 hours following SC injection of 4, 7, and 21 mg MOD-4023.

Table 47. MOD-4023 Pharmacokinetic Parameters in Healthy Volunteers Following Subcutaneous Administration of 4, 7, or 21 mg MOD-4023 (n=6 Per Dose Arm) by Noncompartmental Analysis

Dose (mg)	C_{max} (ng/mL)	T_{max} (Hours)	AUC_{0-t} (ng·h/mL)	AUC_{0-inf} (ng·h/mL)	CL/F (mL/h/kg)	$T_{1/2}$ (Hours)
4	18.7±9.6 [19.6]	4-24 [7]	493±153 [449]	592±133 [582]	85.8±15.2 [90.7]	21.5±9.8 [18.5]
7	46.4±27.5 [34.6]	8-24 [10]	1429±744 [1298]	1533±761 [1339]	68.9±22.7 [69.7]	20.8±8.1 [19]
21	268.6±111.9 [237]	6-12 [12]	7918±1552 [7305]	8034±1574 [7392]	37.1±6.6 [39.3]	23.6±4.8 [23.7]

Source: Adapted from Table 8 of CP-4-001-SAP.pdf.
Minimum-maximum [median] for T_{max}, mean±standard deviation [median] for other parameters.
Abbreviations: AUC_{0-t}, area under the curve from time zero to time t; AUC_{0-inf}, area under the curve from time zero extrapolated to infinity; CL/F clearance after oral administration; C_{max}, maximum concentration; MOD-4023, somatrogon; $T_{1/2}$, half-life

Immunogenicity Results

Serum samples collected from all subjects prior to dosing and at 14 days and 30 days following MOD-4023 administration were negative for anti-MOD-4023 antibodies. Therefore, immunogenicity was not a factor in evaluating PK and PD in this study.

Pharmacodynamic Results

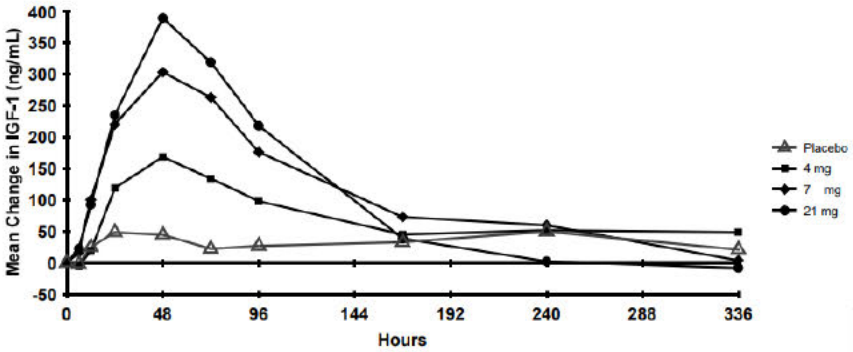
Mean serum IGF-1 change from baseline concentration-time profiles and PD parameters based on IGF-1 change from baseline concentrations in healthy volunteers following subcutaneous administration of 4, 7, or 21 mg MOD-4023 are shown in Figure 14 and Table 48.

At all dose levels, the IGF-1 response peaked at 48 hours and then declined to about 50 ng/mL above baseline levels at 168 hours.

The IGF-1 response was dose-related but not dose proportional. The C_{max}, AUC_{0-t}, and AUC_{0-168} were approximately dose proportional from 4 mg to 7 mg but the AUC_{0-t} following 21 mg of

MOD-4023 was approximately the same as that following 7 mg. The C_{max} following 21 mg was only about 30% greater than that following 7 mg. Mean IGF-1 response is also presented as a standard deviation score in Figure 15.

Figure 14. Mean Serum IGF-1 Change From Baseline Concentration Versus Time Profiles for Healthy Volunteers Following Subcutaneous Injection of Placebo or 4, 7, or 21 mg MOD-4023



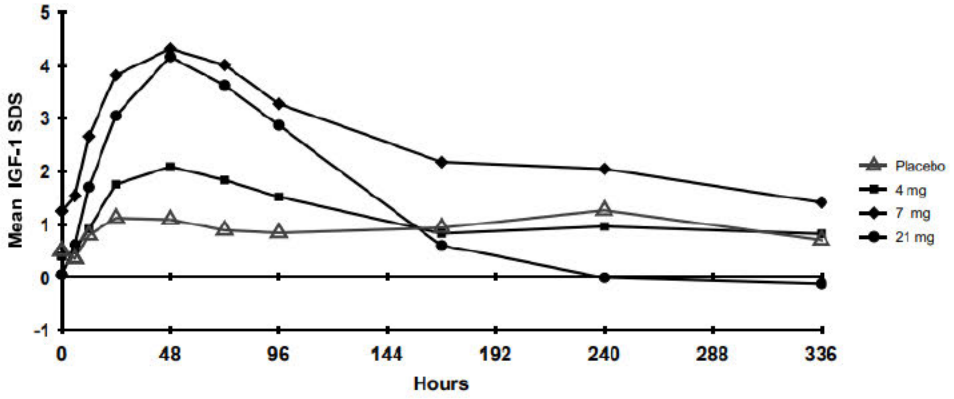
Source: Figure 6 of CP-4-001-SAP.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; MOD-4023, somatrogon

Table 48. IGF-1 Pharmacodynamic Parameters (Mean±SD [Median]) in Healthy Volunteers Following Subcutaneous Administration of Placebo or 4, 7, or 21 mg MOD-4023

Dose	C_{max} (ng/mL)	T_{max} (Hours)	AUC_{0-t} (ng·h/mL)	AUC_{0-168} (ng·h/mL)
Placebo	75±37 [70]	100±88 [72]	11,243±8527 [9167]	5161±3936 [3582]
4	175±30 [176]	48±15 [48]	24,178±11,137 [20,988]	15,882±5167 [16,514]
7	304±59 [331]	48±0 [48]	36,768±10,646 [36,107]	29,696±5939 [30,161]
21	390±100 [393]	48±0 [48]	35,656±10,162 [38,908]	34,118±8586 [38,166]

Source: Adapted from Table 9 of CP-4-001-SAP.pdf.
Abbreviations: AUC_{0-168}, area under the curve from 0 to 168 h; AUC_{0-t}, area under the curve from time zero to time t; C_{max}, maximum concentration; MOD-4023, somatrogon; SD, standard deviation; T_{max}, time to maximum concentration

Figure 15. Mean Serum IGF-1 SD Scores Versus Time Profiles for Healthy Volunteers Following Subcutaneous Injection of Placebo or 4, 7, 21 MOD-4023



Source: Figure 8 of CP-4-001-SAP.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; MOD-4023, somatrogon; SD, standard deviation

14.2.2. Study CP-4-007: Phase 1 Single-Ascending Dose Study in Adult Caucasian and Japanese Healthy Volunteers

Title

A Randomized, Double-blind, Vehicle-controlled, Parallel-group, Single-dose Trial to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Three Doses of Long-acting hGH Product (Somatrogon, also called "MOD-4023") in Healthy Caucasian and Japanese Volunteers.

Design

This study was a phase 1, randomized, double-blind, vehicle-controlled, single-dose, 3 dose level study in healthy Caucasian and Japanese male volunteers. After a 4-week screening period, eligible male subjects were stratified by ethnic group and randomized to 1 of 6 groups as shown in Table 49. Each subject received a single SC injection according to the randomization.

Table 49. MOD-4023 Dose and Number of Subjects by Ethnic Group

			Number of Subjects	
Group	Treatment	Dose Volume	Caucasian	Japanese
1A	MOD-4023 2.5 mg	0.13 mL	6	6
1V	Vehicle	0.13 mL	1	1
2A	MOD-4023 2.5 mg	0.38 mL	6	6
2V	Vehicle	0.38 mL	1	1
3A	MOD-4023 2.5 mg	0.75 mL	6	6
3V	Vehicle	0.75 mL	1	1

Source: Table 9.1-1 of cp-4-007-report-body.pdf.
Abbreviation: MOD-4023, somatrogon

Blood samples for the measurement of serum concentrations of MOD-4023 were obtained before (0, predose) and at the following times (nominal) after the dose: 2, 4, 6, 8 10, 12, 18, 24, 36, 48, 72, 96, 168, and 336 hours. Plasma concentrations of IGF-1 were measured in the blood samples collected at 0, 6, 12, 24, 48, 72, 96, 168, and 336 hours. Blood samples for binding and neutralizing Abs (NAb) to MOD-4023, native human growth hormone (hGH) and carboxy-terminal peptide (CTP) were collected at predose and after injection at 14±1 hours and 30±2 days.

Measurement of plasma concentrations of MOD-4023, IGF-1 and detection of antibodies to MOD-4023 were performed using validated assays.

IGF-1 SD scores were calculated from appropriate reference data from the same assay and a demographically matched subject base.

Subject Disposition

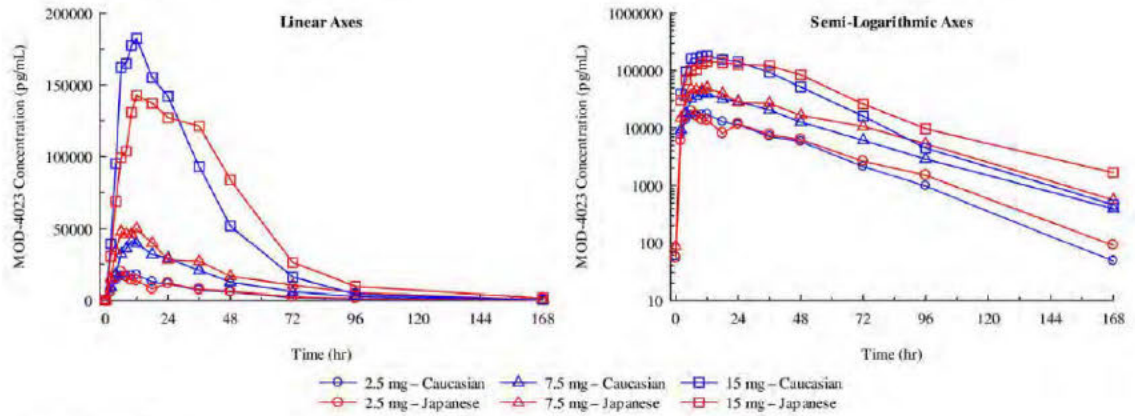
A total of 42 subjects was enrolled and randomized, of which half were Japanese and half Caucasian. Six (6) subjects were randomized to vehicle (placebo, 3 in each ethnic group) and 36 subjects were randomized to MOD-4023 (18 in each ethnic group), of which 12 were randomized to each dose group (2.5 mg, 7.5 mg and 15 mg; 6 in each ethnic group). All subjects completed the study, meeting the minimum number planned for analysis and none withdrew prematurely. All subjects were included in the safety, PD and PK analyses.

Pharmacokinetic Results

When the small number of subjects and associated variability are taken into account, there does not appear to be a difference between Japanese and Caucasian subjects with respect to PK parameters for the 2.5 mg and 7.5 mg cohorts (Figure 16 and Table 50). For the 15 mg cohort, the geometric mean C_{max} was lower and the median T_{max} was longer in Japanese compared to Caucasian subjects although the geometric mean values for $AUC_{(inf)}$ were comparable, possibly suggesting a slower rate of absorption.

For both Caucasian and Japanese subjects, there was a greater than proportional increase in $AUC_{(inf)}$ with dose.

Figure 16. Arithmetic Mean Serum Concentrations of MOD-4023 After SC Injection of a Single 2.5 mg, 7.5 mg, or 15 mg Dose of MOD-4023 to Healthy Caucasian and Japanese Subjects



Source: Figure 1 of CP-4-007-PK-report.pdf.
Abbreviations: MOD-4023, somatrogon; SC, subcutaneous

Table 50. Summary of Pharmacokinetic Parameters for MOD-4023 After SC Injection of a Single 2.5 mg, 7.5 mg, or 15 mg Dose of MOD-4023 to Healthy Caucasian and Japanese Subjects by NCA

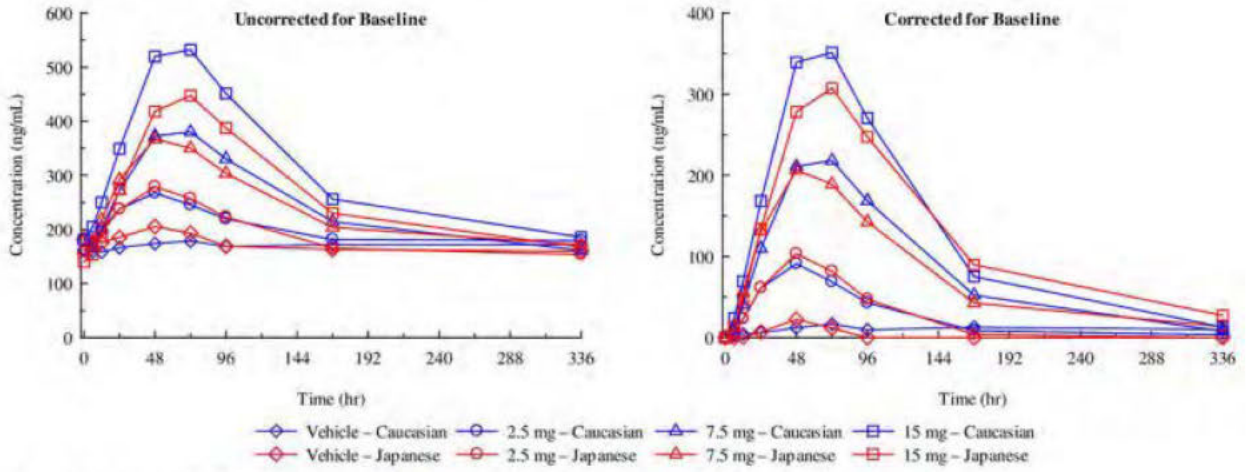
	MOD-4023 Dose		
Parameter	**2.5 mg**	**7.5 mg**	**15 mg**
Caucasian			
C_{max} (ng/mL)	16.8 (66.7) (5)	37.7 (104) (6)	183.5 (34.5) (6)
T_{max} (h)	10 [4-24] (5)	15 [6-24] (6)	10 [6-12] (6)
AUC_{0-t} (h·ng/mL)	581.4 (62.5) (5)	1531.7 (49.2) (6)	6610.0 (34.9) (6)
AUC_{inf} (h·ng/mL)	505.0 (63.6) (3)	1551.8 (47.6) (6)	6264.1 (35.7) (5)
$T_{1/2}$ (h)	20.7 (5.67) (3)	24.5 (18.5) (6)	18.2 (7.64) (5)
CL/F (L/h)	4.95 (63.6) (3)	4.83 (47.6) (6)	2.39 (35.7) (5)
Vz/F (L)	148 (70.3) (3)	171 (66.3) (6)	62.8 (40.3) (5)
Japanese			
C_{max} (ng/mL)	17.5 (76.3) (5)	50.6 (39.2) (6)	107.0 (147) (6)
T_{max} (h)	6 [4-24] (5)	12 [6-18] (6)	15 [10-48] (6)
AUC_{0-t} (h·ng/mL)	605.4 (55.6) (5)	2169.8 (30.2) (6)	5924.3 (94.3) (6)
AUC_{inf} (h·ng/mL)	487.1 (44.5) (3)	2164.3 (33.8) (5)	6017.1 (92.1) (6)
$T_{1/2}$ (h)	21.0 (42.0) (3)	22.3 (9.1) (5)	20.9 (34.2) (6)
CL/F (L/h)	5.1 (44.5) (3)	3.5 (33.8) (5)	2.5 (92.1) (6)
Vz/F (L)	156 (98.7) (3)	112 (39.5) (5)	75.2 (151) (6)

Source: Table 3 of CP-4-007-PK-report.pdf.
Values are geometric means (geometric coefficient of variation) (N) except T_{max}, for which the medians (N) [range] are reported.
Abbreviations: AUC_{0-t}, area under the curve from time zero to time t; AUC_{inf}, area under the curve extrapolated to infinity; CL/F, clearance after oral administration; C_{max}, maximum concentration; MOD-4023, somatrogon; NCA, noncompartmental analysis; SC, subcutaneous; $T_{1/2}$, half-life; T_{max}, time to maximum concentration; Vz/F, apparent volume of distribution during terminal phase

Pharmacodynamic Results

There were no apparent differences in the arithmetic mean plasma concentrations of IGF-1, either uncorrected or corrected for baseline, between Japanese and Caucasian subjects for the vehicle, 2.5 mg, and 7.5 mg cohorts, although those for the Japanese were lower than for the Caucasians after a dose of 15 mg (Figure 17). However, within each dosing cohort, the geometric mean values for baseline corrected C_{max} and AUEC (area under the effect curve) were comparable (Table 51), suggesting no difference in response between the two ethnic groups.

Figure 17. Arithmetic Plasma Concentrations of IGF-1 After SC Injection of a Single 2.5 mg, 7.5 mg, or 15 mg Dose to Healthy Caucasian and Japanese Subjects



Source: Figure 4 of CP-4-007-PK-report.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; SC, subcutaneous

Table 51. Summary of Pharmacodynamic Parameters for Baseline-Corrected IGF-1 After SC Injection of a Single 2.5 mg, 7.5 mg, or 15 mg Dose of MOD-4023 to Healthy Caucasian and Japanese Subjects

	Dose			
Parameter	**Vehicle**	**2.5 mg**	**7.5 mg**	**15 mg**
Caucasian				
C_{max} (ng/mL)	21.9 (11.8) (3)	89.9 (17.5) (5)	221 (25.1) (6)	360 (7.87) (6)
T_{max} (h)	72.1 [48.0-168] (3)	48.0 [48.0-48.0] (5)	72.0 [48.0-72.5] (6)	72.0 [48.0-72.0] (6)
AUEC (h·ng/mL)	3361 (65.5) (3)	8267 (33.5) (5)	26969 (26.5) (6)	43268 (15.2) (6)
Japanese				
C_{max} (ng/mL)	19.0 (88.2) (3)	99.4 (31.5) (5)	207 (19.7) (6)	307 (26.1) (6)
T_{max} (h)	48.0 [48.0-48.0] (3)	48.0 [48.0-48.0] (5)	48.0 [48.0-72.0] (6)	72.0 [48.0-96.1] (6)
AUEC (h·ng/mL)	663 (164) (3)	9522 (64.3) (5)	24566 (32.3) (6)	40893 (18.2) (6)

Source: Table 5 of CP-4-007-PK-report.pdf.
Values are geometric means (geometric coefficient of variation) (N) except T_{max}, for which the medians (N) [range] are reported.
Abbreviations: AUEC, area under the effect curve; C_{max}, maximum concentration; IGF-1, insulin-like growth factor-1; MOD-4023, somatrogon; SC, subcutaneous; T_{max}, time to maximum concentration

Immunogenicity Results

Overall, all but 1 subject had negative result on MOD-4023 binding specificity test. At the EOS visit (Day 30), 1 Japanese subject [redacted] (b) (6) from the 15 mg dose group had a positive result for the MOD-4023 binding specificity (value 24.8%) and negative results for the NAb for MOD-4023, native hGH and CTP Abs (-43% inhibition).

14.2.3. Study CP-4-011: Phase 1 PK Comparability Study Between Prefilled Pen (PEN) and Liquid in Vial (VIAL)

Title

A phase 1, Single-Center, Randomized, Cross-Over, Clinical Study Investigating the Comparability of Somatrogon in Two Different Drug Product Presentations

Design

This was a phase 1, single-center, open-label, randomized, 2×2 crossover (Ref Test | Test Ref) study with a washout period of two weeks in healthy male volunteers. The total duration of subject participation in the study was up to 60 days: Day -28 to Day -1 of Screening, dosing on Day 0, two weeks washout and observation, crossover dosing on Day 14 with end of study (EOS) on Day 30±2 days. The study was conducted at a single clinical study site in the United States.

The Test formulation was the single subject use, multidose, disposable prefilled PEN intended for SC injection. The drug product primary container was a 3 mL glass cartridge filled with 50 mg/mL somatrogon that was stored at 2 to 8°C.

The Reference formulation was a frozen liquid formulation intended for SC administration. The single-use frozen vials were to be stored at -20±5°C. Prior to dosing, remove the vial(s) from the freezer and thaw overnight in the refrigerator at 2 to 8°C prior to dosing.

The dose of somatrogon to be used in this clinical study was 12 mg of somatrogon delivered from a VIAL or by the PEN. Doses were administered once each as a SC injection by study staff in the morning of dosing day once in the upper arm.

Somatrogon serum concentrations were determined from samples collected at 0 (predose, up to 1 hour before injection), 6, 12, 18 hours (±15 min) postdose on Day 0/14, Day 1/15 (24±2 hours and 36±2 hours postdose), Day 2/16 (48±4 hours postdose), Day 3/17 (72±4 hours postdose), Day 4/18 (96±4 hours postdose), Day 5/19 (120±4 hours postdose), and Day 7/21 (168±4 hours postdose).

The blood samples for PD analysis were collected at 0 (predose, up to 1 hr before injection), 6, 12 hours (±15 min) postdose on Days 0/14, Days 1/15 (24±2 hours), Days 2/16 (48±4 hrs postdose), Days 3/17 (72±4 hours postdose), Days 4/18 (96±4 hours postdose), Days 7/21 (168±4 hours postdose), and Days 10/24 (240±4 hours postdose).

Blood samples for antidrug antibodies (ADAs) to somatrogon, and, if positive for ADAs, anti-CTP, r-hGH, and NAbs to somatrogon, were taken at Screening, predose on Day 14 (-2 days), and 30±2 days.

Measurement of plasma concentrations of MOD-4023, IGF-1 and detection of antibodies to MOD-4023 were performed using validated assays.

PK and PD analysis were performed using noncompartmental methods.

Subject Disposition

There were 49 subjects enrolled in this study, including 26 subjects in VIAL-PEN group (administered with somatrogon via VIAL first in Treatment Period 1, followed by somatrogon

via PEN in Treatment Period 2) and 23 subjects in PEN-VIAL group (administered with somatrogon via PEN first in Treatment Period 1, followed by somatrogon via VIAL in Treatment Period 2). Of the 49 enrolled subjects, 7 subjects (i.e., 4 from the VIAL-PEN group and 3 from the PEN-VIAL group) did not complete the study, including two subjects terminated early due to consent withdrawal, four subjects lost to follow up, and one subject terminated early by the Investigator's judgment.

Pharmacokinetics

A total of 49 subjects were enrolled and included in Parameter Analysis Set (PK). Data from one subject in the treatment period of somatrogon via PEN (Test Product) and three subjects in the treatment period of somatrogon via VIAL (Reference Product) were not included for both PK and PD data analysis. The details of excluding from PK analysis are summarized in Table 52.

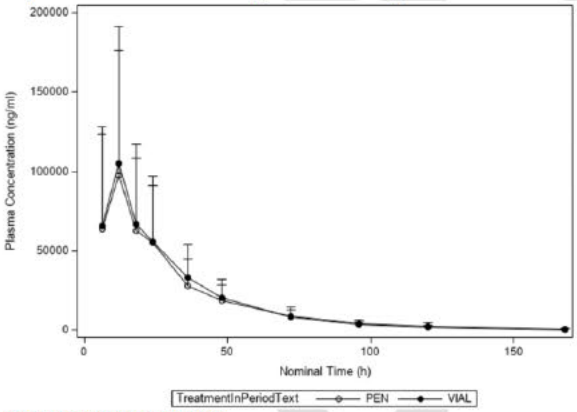
Table 52. Data Not Included in the Parameter Analysis

Number	Treatment	Sequence	Period	Reason of Exclusion
1 subject	PEN	VIAL-PEN	2	Withdrew consent
1 subject	VIAL	PEN-VIAL	2	Withdrew consent
1 subject	VIAL	PEN-VIAL	2	Lost to follow up
1 subject	VIAL	PEN-VIAL	2	Positive DoA and breathalyzer on day 13 admission

Source: Table 5 of CP-4-011-report-body.pdf.
Abbreviation: DoA, drug of abuse

The somatrogon serum concentration-time profiles are displayed in Figure 18. Statistical comparisons of PK parameters of somatrogon are presented in Table 53.

Figure 18. Mean±SD Serum Somatrogon Concentration-Time Profiles Following Single 12 µg SC Injections in Healthy Male Subjects



Source: FDA's analysis.
Abbreviations: SC, subcutaneous

The PK parameters of AUC_t and AUC_∞ after SC injection of somatrogon via PEN (Test Product) were bioequivalent to the injection of somatrogon via VIAL (Reference Product), while lower limit of the 90% CI for C_{max} of somatrogon after PEN (Test Product) was modestly lower (0.74) than the prespecified limit of 0.80. The Applicant's bioequivalence analyses were verified by FDA reviewers.

Table 53. Statistical Comparison of Somatrogon Pharmacokinetic Parameters Following Single Subcutaneous Injections in Healthy Male Subjects

PK Parameter†	PEN (Test)		VIAL (Reference)		PEN/VIAL
	N	GLSM	N	GLSM	GMR (90% CI)
C_{max} (pg/mL)	48	71150	46	78791	90.30 (74.24, 109.84)
AUC_t (h*pg/mL)	46[a]	2385782	46	2517373	94.77 (87.05, 103.18)
AUC_∞ (h*pg/mL)	37[a,b]	2544288	42[c]	2642923	96.27 (87.64, 105.75)

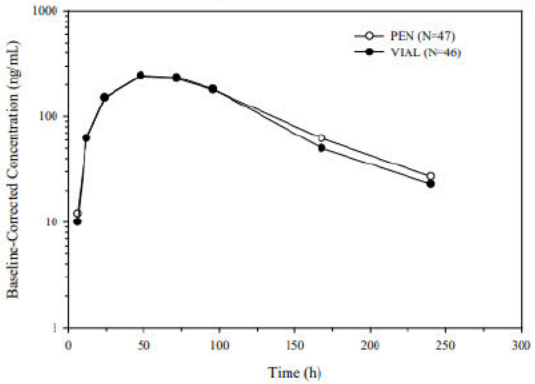
† Back-transformed least squares mean and CI from ANOVA model performed on natural log-transformed values.
[a] AUC_t and AUC_∞ values in two (2) subjects in the test (PEN) treatment group were not evaluable due to lost to follow up and then not used in the statistical analysis.
[b] Nine (9) subjects' AUC_∞ values in the test (PEN) treatment group were not reported because λ_z_period <2.
[c] Four (4) subjects' AUC_∞ values in the reference (VIAL) treatment group were not reported because λ_z_period <2.
GLSM=Geometric least-squares mean; GMR=Geometric least-squares mean ratio; CI=Confidence interval;
GMR and 90% CI: Reported as percentage.
Source: Table 14.2.13

Source: Table 7 of CP-4-011-report-body.pdf.
Abbreviations: ANOVA, analysis of variance; AUC_∞ area under the curve extrapolated to infinity; AUC_t, area under the curve at time t; C_{max}, maximum concentration; PK, pharmacokinetics

Pharmacodynamics

The mean baseline-corrected IGF-1 serum concentration-time profiles are displayed in Figure 19. The mean baseline-corrected values of IGF-1 after SC injection of somatrogon via PEN were comparable to those after injections via VIAL.

Figure 19. Mean Baseline-Corrected IGF-1 Concentration-Time Profiles Following Single 12 mg Subcutaneous Injections of Somatrogon in Healthy Male Subjects



Source: Figure 3 of CP-4-011-report-body.pdf.
Abbreviation: IGF-1, insulin-like growth factor-1

Immunogenicity

No subject was tested positive for ADAs during the study period.

Conclusions

While AUCs met the prespecified bioequivalence criteria, the 90% confidence interval of C_{max} did not fall within 80 to 125%. C_{max} of pen presentation was 10% lower than that of vial, based on the ratio of geometric means. This lower C_{max} is not a concern because similar PD response were observed between pen and vial presentations and pen presentation was used in the phase 3 study (Trial 006).

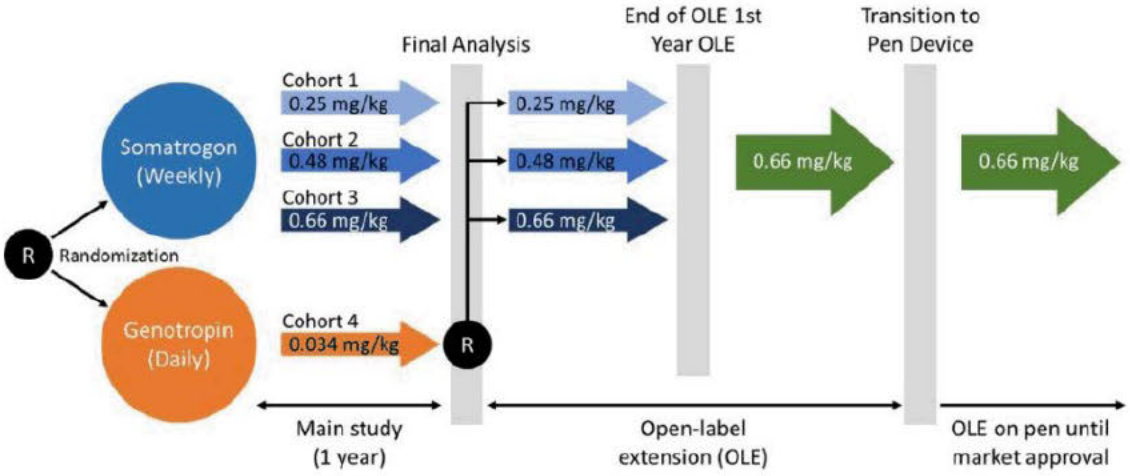
14.2.4. Study CP-4-004: Phase 2 Dose Finding Study

CP-4-004 was an Open-label, phase 2, safety and dose-finding study that compared the safety, tolerability, and efficacy of three doses of somatrogon compared to Genotropin in the main study period.

By August 2019, the study covers the 12-month main study periods (Periods I and II), the 1-year open-label extension (OLE, Period III), 3-year long-term OLE (Period IV), and an additional 12-month exposure to the PEN (Period V).

The somatrogon presentation was frozen vial (hereafter referred to as vial) during the main study and OLE until Period V. Genotropin was dosed at 0.034 mg/kg administered once daily throughout. A study schematic is shown in Figure 20.

Figure 20. Trial CP-4-004 Design Schematic



Source: Figure 3 of isi.pdf.

Eligible patients were randomized in a 1:1:1:1 ratio to undergo the following treatment schedule consisting of a Screening Period lasting up to 6 weeks and two Treatment Periods (Treatment Periods I and II), which comprise the Main Study.

- Period I: open-label 6-month repeated dosing including PK/PD sampling.
- Period II: an additional open-label 6-month continuous repeated dosing.

Due to the differences in dosing regimen, blinding was not possible, no party was blinded to study drug allocation at any time. In order to introduce naïve patients to their allocated MOD-4023 dose in a gradual manner, a stepwise dose increase was implemented in Period I (Table 54).

Table 54. Overview of Study Drug Dosing, Trial CP-4-004, (Main Period)

Initial Treatment Arm		Period I [a]					Period II [b]
		Week 1	Week 2	Week 3	Week 4	Week 5 – Month 6	Months 7-12
Cohort 1	Somatrogon	0.25 mg/kg/week					
Cohort 2		0.25 mg/kg/week		0.48 mg/kg/week			
Cohort 3		0.25 mg/kg/week		0.48 mg/kg/week		0.66 mg/kg/week	
Cohort 4	Genotropin	0.034 mg/kg/day					

Source: Module 5.3.5.1 CP-4-004 CSR, Section 9.1.1.
a. Dose could be decreased for safety reasons.
b. Dose adjustment allowed for safety or efficacy reasons.

After completing the 12-month main study period (Periods I and II), subjects could enter into the OLE period (Periods III through V). In Period III (OLE; Year 1), subjects who had been initially

randomized to somatrogon remained on the same somatrogon dose they had received in the main study period, and subjects who had been randomized to Genotropin were randomized at the start of the OLE to receive 1 of the 3 somatrogon doses.

After 12 months in the OLE, subjects entered Period IV (LT-OLE; Years 2-4) at which point all were switched to somatrogon 0.66 mg/kg administered once weekly. Subjects transitioned into Period V when they switched from the vial presentation of somatrogon to the single-patient-use, prefilled disposable pen device (hereafter referred to as pen), at the same dose. The somatrogon pen was the proposed commercial dose and presentation (same as used in Trial CP-4-006). Subjects could remain on treatment until registration of somatrogon. Table 55 provides an overview of study drug dosing in Trial CP-4-004 OLE periods.

Table 55. Overview of Study Drug Dosing, Trial CP-4-004 (OLE)

Initial Treatment Arm		Period III OLE 12-Month Duration [a] Month 13 to Month 24	Period IV LT-OLE [a, b] Starting at Month 25 (Year 3)	Period V LT-OLE PEN [a, c]
Cohort 1	Somatrogon	0.25 mg/kg/week	All eligible subjects received somatrogon 0.66 mg/kg/week	For each subject, Period V begins at switch to the pen.
Cohort 2		0.48 mg/kg/week		
Cohort 3		0.66 mg/kg/week		
Cohort 4	Genotropin	Randomized switch to somatrogon 0.25, 0.48, or 0.66 mg/kg/week		

Source: Module 5.3.5.1 CP-4-004 OLE CSR, Section 9.1.1.
a. Somatrogon dose could be modified for pre-specified safety or efficacy reasons.
b. Duration is through switch to the pen.
c. Duration is through marketing approval in each country.
Abbreviations: LT, long-term; OLE, open-label extension

PK/PD sampling

In the main study, patients were to be further randomized within each cohort to one of three blocks for PK/PD sampling. Following the second dose administration at the patient's target dose level, limited (i.e., population-based) PK and PD sampling was to be performed as described in Table 56, and Figure 21.

Table 56. PK/PD Sampling[1] Scheme of the MOD-4023 Population (Period I)

	Dosing Scheme					
Cohort	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cohort 1	0.25 mg/kg/week		0.25 mg/kg/week			
Cohort 2	0.25 mg/kg/week		0.48 mg/kg/week		0.48/mg/kg/week	
Cohort 3	0.25 mg/kg/week		0.48 mg/kg/week		0.66 mg/kg/week	

Source: modified based on Table 2 of cp-4-404-report-body.pdf.
[1] PK/PD sampling was performed at Week 2 in Cohort 1, Week 4 in Cohort 2, and Week 6 in Cohort 3.
Abbreviations: MOD-4023, somatrogon; PD, pharmacodynamics; PK, pharmacokinetics

Figure 21. PK/PD Sampling Scheme of MOD-4023 Population (Period I)

Visit (V2, V3, V4)	a			b	c	d	e	f	g
Time after dosing:	0 h	6 h	12 h	24 h	48 h	72 h	96 h	120 h	168 h
Block 1	X			X	X		X		
Block 2		X			X	X		X	
Block 3			X	X		X			X

Source: Table 3 of cp-4-404-report-body.pdf.
Abbreviation: MOD-4023, somatrogon

Four PK and PD samples per patient were collected in one of the three specified time series: i) 0, 24, 48, 96; ii) 6, 48, 72, 120; and iii) 12, 24, 72, 168 hours postdose, after the second

administration of the targeted somatrogon dose, i.e., at Week 2 (V1), 4 (V2), and 6 (V3) for the 0.24, 0.48, and 0.66 mg/kg cohort, respectively. The Day 4 samples at Week 6 in the 0.25 mg/kg cohort, at Week 2 and 6 in the 0.48 mg/kg cohort and at Week 2 and 4 in the 0.66 mg/kg cohort were also collected.

In addition, the following PK samples were collected:

- Day 4 postdose at Week 10, 14, 18, 22 and 26, Month 9 and Month 12 (Year 1, Main Study).
- Day 4 postdose at Month 1, 3, 6, 9, and 12 during the first year of OLE (Year 2).
- Predose at baseline, Day 4 postdose at Month 3, 6, and both predose and Day 4 postdose at Month 12 of each year or early termination until switch to pen device (Years 3 to 4).
- Predose for the first dose and Day 4 postdose at Week 4, Month 3, Month 6, Month 9, and both predose and Day 4 postdose at Month 12. (OLE PEN Year 1).
- Day 4 postdose every 6 months while the study is running (OLE PEN Year 2 and beyond).

Immunogenicity Sampling

Blood samples for immunogenicity testing were acquired predose at the time points summarized in Table 57.

Table 57. Immunogenicity Sampling by Study Period and Treatment, Trial CP-4-004

Study Period		Study Treatment	Immunogenicity Sampling
Screening			Somatrogon ADAs: Not done hGH ADAs: Screening in all subjects [a]
Main study period	Period I Month 1-6	• Weekly somatrogon at 0.25, 0.48, or 0.66 mg/kg/week • Daily Genotropin at 0.034 mg/kg/day	Somatrogon ADAs: Weeks 1 and 26 in somatrogon arm. hGH ADAs: Weeks 1 and 26 in Genotropin arm.
	Period II Month 7-12	• Weekly somatrogon at 0.25, 0.48, or 0.66 mg/kg/week • Daily Genotropin at 0.034 mg/kg/day	Somatrogon ADAs: Month 12 in somatrogon arm. hGH ADAs: Month 12 in Genotropin arm.
OLE	Period III Month 13-24	• Weekly somatrogon at 0.25, 0.48, or 0.66 mg/kg/week	Somatrogon ADAs: Visit 0 [b], Month 3 [c] and Month 6. hGH ADAs: Not routinely done [d].
LT-OLE	Period IV Month 25 to switch to pen	• Weekly somatrogon at 0.66 mg/kg/week	Somatrogon ADAs: Visit 0, Month 3 [e], Month 12 [f], ET [g]. hGH ADAs: Not routinely done [d].
LT-OLE PEN	Period V Switch to pen to EOS	• Weekly somatrogon at 0.66 mg/kg/week	Somatrogon ADAs: Visit 0 (switch day), Week 4, Month 3, 6, 9, 12, every 6 months thereafter, EOS/ET. hGH ADAs: Not routinely done [d].

Source: Module 5.3.5.1 Study CP-4-004 CSR, Appendix 16.1.1, Protocol Amendment 8, Appendices 1, 2, 3.

a. Positive result is exclusion criterion.
b. Applicable to Genotropin subjects who switched to somatrogon.
c. Applicable to Genotropin subjects who switched to somatrogon to 0.66 mg/kg/week.
d. hGH Ab specificity testing in somatrogon-treated subjects who tested positive in screening and confirmatory assays.
e. For subjects switching to somatrogon 0.66 mg/kg/week from a lower dose.
f. Of each year before switch to the somatrogon pen.
g. Where applicable.

Abbreviations: ADA, antidrug antibodies; EOS, end of study; ET, early termination hGH, human growth hormone; LT, long-term

Pharmacokinetics Results

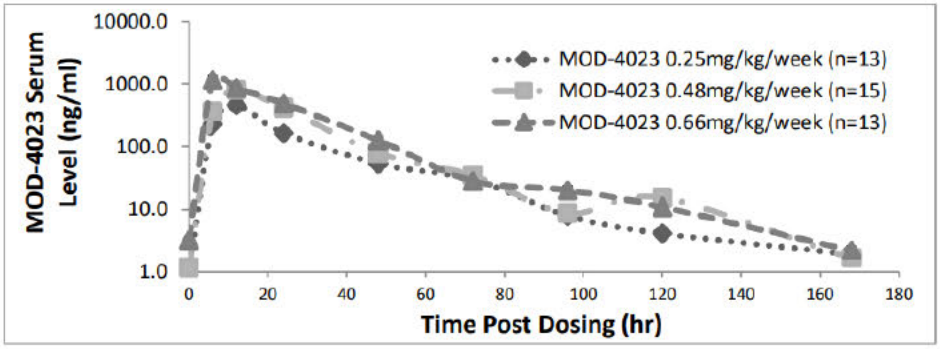
PK data from main study and open-label periods were combined for population PK analysis. See pharmacometrics review for more details.

Although the PK characteristics of MOD-4023 in pediatric GHD patients were determined from the population-based PK models, a naïve-pooled approach was also used to generate the mean

concentration-time profile of MOD-4023 based on sparse sampling during the main study period. Results of the naïve-pooled analysis are presented in Figure 22 and Figure 23 for MOD-4023.

Based on PK parameters reported in Table 58, In pediatric patients with GHD, somatrogon exposure increases in a dose proportional manner for doses of 0.25, 0.48, and 0.66 mg/kg/week.

Figure 22. Mean Weekly Trend of Plasma Concentration-Time Profile of MOD-4023 at the Final Randomization Dose (PP Population; Periods I and II)



Source: Figure 3 of cp-4-004-report-body.pdf.
Abbreviations: MOD-4023, somatrogon; PP, per protocol

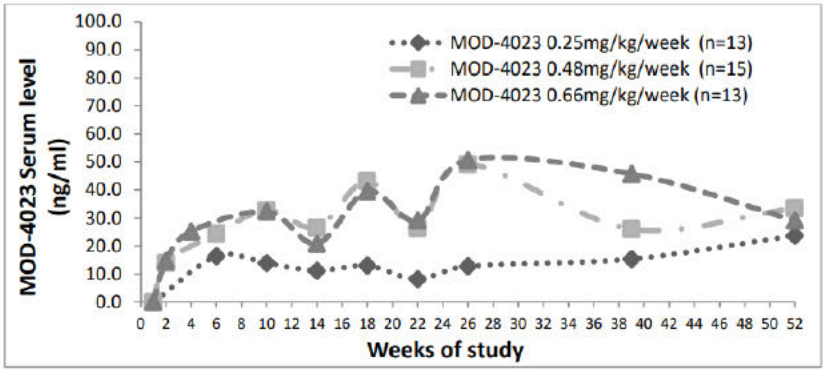
Table 58. Mean PK Parameters for MOD-4023 Based on Naïve Pooled Estimate (PP Population; Periods I and II)

	MOD-4023		
PK Parameter	0.25 mg/kg/wk (N=13)	0.48 mg/kg/wk (N=13)	0.66 mg/kg/wk (N=13)*
$T_{1/2}$ (h)	36.1	18.3	22.4
T_{max} (h)	12	12	6
$AUC_{0\text{-}inf\ obs}$ (ng/mL·h)	10,930	20,492	28,085
C_{max} (ng/mL)	460	810	1151

Source: Table 28 of cp-4-004-report-body.pdf.
* Patient 08003, who was wrongly included in the study and dosed in Cohort 3. Patient diagnosed with psychosocial dwarfism following study completion and eliminated from the efficacy analysis.
Abbreviations: $AUC_{0\text{-}inf\_obs}$, area under the curve from 0 to infinite calculated based on observed data; C_{max}, maximum concentration; MOD-4023, somatrogon; PK, pharmacokinetics; PP, per protocol; $T_{1/2}$, half-life; T_{max}, time to maximum concentration

The mean Day 4 MOD-4023 drug levels over the 12 months of weekly administration are presented in Figure 23.

Figure 23. Mean Day 4 MOD-4023 Drug Level for Patients Completing 12 Months of Treatment (PP Population; Periods I and II)



Source: Figure 5 of cp-4-004-report-body.pdf.
Abbreviations: MOD-4023, somatrogon; PP, per protocol

Pharmacodynamic Results

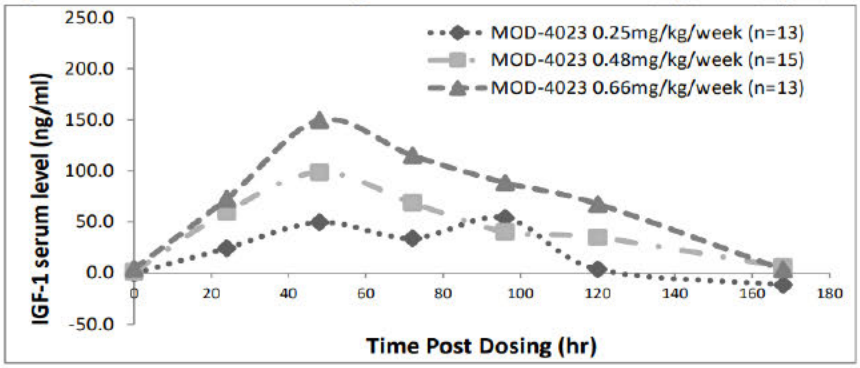
Main Study Period

The mean IGF-1 change from baseline trends over a one-week dosing interval are shown in Figure 24. The mean IGF-1 SDS trends over the same interval are shown in Figure 25 and the mean IGF-1 SDS trends over the course of the first year of therapy are shown in Figure 26.

Serum IGF-1 level reached maximum concentration around 48 hours after single dosing of MOD-4023 at different dose levels. For cohort 2 and 3, serum IGF-1 SDS peaked around 48 hours to a level beyond 0 and were within 2 SDS over a week. IGF-1 SDS for Cohort 1 (0.25 mg/kg/week) did not increase above 0 and dropped during the second part of the week and reached suboptimal mean value (around -2 SDS) by Day 5.

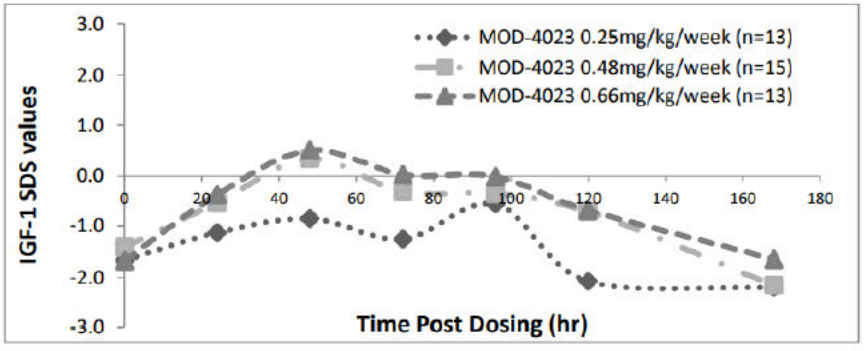
Over 12 months, MOD-4023 provided an IGF-1 response within the normal range, reaching an optimal average value of 0 SDS in Cohorts 2 and 3, and not exceeding +2 SDS when monitoring the weekly profile on Day 3 or 4 postdosing or when monitoring it on monthly basis through 12 months (Figure 26). MOD-4023 0.48 and 0.66 mg/kg/week resulted in comparable IGF-1 SDS to that of Genotropin 0.034 mg/kg/day.

Figure 24. Mean IGF-1 Change From Baseline - Weekly Trend (PP Population; Periods I and II)



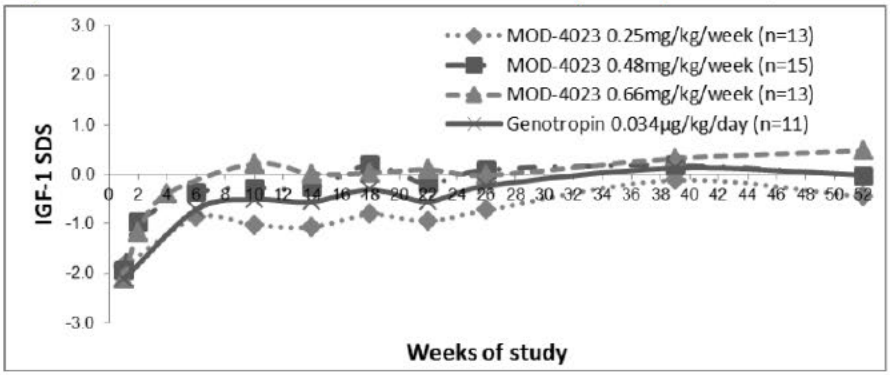
Source: Figure 6 of cp-4-004-report-body.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; MOD-4023, somatrogon; PP, per protocol

Figure 25. Mean IGF-1 SDS - Weekly Trend (PP Population; Periods I and II)



Source: Figure 7 of cp-4-004-report-body.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; MOD-4023, somatrogon; PP, per protocol; SDS, standard deviation score

Figure 26. Mean IGF-1 SDS - 12 Month Trend (PP Population; Periods I and II)



Source: Figure 8 of cp-4-004-report-body.pdf.
Abbreviations: IGF-1, insulin-like growth factor 1; MOD-4023, somatrogon; PP, per protocol; SDS, standard deviation score

Open-Label Extension Periods

Summaries of IGF-1 SDS at the end of Period III (Year 1 OLE) and Periods IV to V (Years 2-4 and PEN) are provided in Table 59 and Table 60, respectively. The observed mean IGF-1 SDS was lowest for the 0.25 mg/kg/week treatment group at the end of Year 1. The mean IGF-1 SDS for all cohorts in Period III and subjects in Year 2 were similar and increased at Year 3 and the end of Period V (PEN). Mean IGF-1 SDS values were consistently within the target therapeutic range and remained below 2 SDS across all time points in Periods III to V.

Table 59. Summary of IGF-1 SDS at End of Period III (Year 1 OLE) - Full Analysis Set

	0.25 mg/kg/wk (N=16)	0.48 mg/kg/wk (N=17)	0.66 mg/kg/wk (N=15)	Total Year 1 (N=48)
IGF-1 SDS (Z) at End of Year				
n	14	16	13	43
Mean (SD)	0.19 (0.89)	0.96 (0.92)	0.72 (0.95)	0.64 (0.96)
Median	0.12	1.21	0.49	0.58
Minimum, Maximum	-1.66, 2.25	-0.66, 2.64	-0.83, 2.41	-1.66, 2.64

Abbreviations: N = number of subjects that entered the study period; n = subjects with IGF-1 SDS at end of period.
Source: Table 35 of cp-4-004-ole-report-body.pdf.
Abbreviations: IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS, standard deviation score

Table 60. Summary of IGF-1 SDS at End of Period IV (Years 2-4 OLE) and Period V (PEN)—Full Analysis Set

	Year 2 (N=44)	Year 3 (N=43)	Year 4 (N=38)	PEN (N=40)
IGF-1 SDS (Z) at End of Year				
n	41	38	1	35
Mean (SD)	0.65 (1.08)	1.05 (0.82)	0.29 (-)	1.29 (0.81)
Median	0.68	1.09	0.29	1.25
Minimum, Maximum	-2.23, 2.69	-0.96, 2.92	0.29, 0.29	-0.34, 2.71

Abbreviations: N = number of subjects that entered the study period; n = subjects with IGF-1 SDS at end of period.
Source: Table 36 of cp-4-004-ole-report-body.pdf.
Abbreviations: IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS, standard deviation score

Immunogenicity Results

ADA Incidence

Main Study Period (First Year)

Among 42 somatrogon-treated subjects, 10 subjects (23.8%) tested ADA-positive for somatrogon, five from the 0.48 mg/kg dose group and five from the 0.66 mg/kg dose group. No subjects receiving the lowest dose (0.25 mg/kg/week) developed ADAs. No somatrogon-treated subjects tested positive for NAbs.

Open-Label Extension (OLE) Periods

Incidence of ADA and NAb against somatrogon in CP-4-004 OLE study period is summarized in Table 61.

Table 61. ADA and Nab, Trial CP-4-004 (OLE Period)

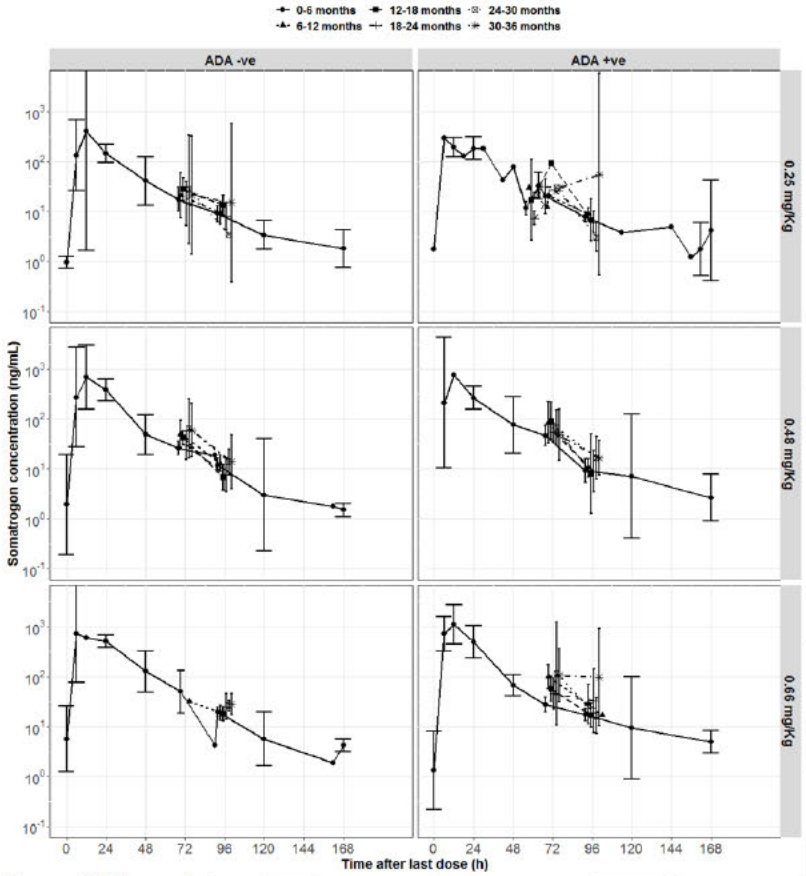
Study	N	ADA+	NAb
Overall	48	19 (39.6%)	0
Year 1 (3 dose groups together)	48	12 (25%)	0
Year 2 (0.66 mg/kg dose group)	44	11 (25%)	0
Year 3 (0.66 mg/kg dose group)	43	11 (26%)	0
Year 4 (0.66 mg/kg dose group)	38	2 (5%)	0
PEN period Year 1	40	15 (38%)	0
PEN period Year 2	35	13 (37%)	0

Source: FDA's analysis
Abbreviations: ADA, antidrug antibodies; NAb, neutralizing antibodies; OLE, open-label extension

Impact of ADA on PK

All available somatrogon concentrations after a dose during Study CP-4-004 was plotted by ADA status (Figure 27).

Figure 27. Somatrogon Concentration-Time Profile After Last Dose in Different Epochs of Treatment for Patients With and Without ADA in Trial CP-4-004



Source: FDA's analysis.
Mean and 95% confidence intervals are presented. Only subjects who originally assigned to somatrogon 0.25 mg/kg, 0.48 mg/kg and 0.66 mg/kg were included. Not all subjects were switched to 0.66 mg/kg at Month 24. Those switched to 0.66 mg/kg at Month 24 were included in the panels for the 0.66 mg/kg group.
Abbreviation: ADA, antidrug antibodies

When ADA-positive versus ADA-negative subjects were compared, concentrations at 72 hours or 96 hours after dose during different epochs were similar in dose cohorts of 0.25 and 0.48 mg/kg. For subjects receiving 0.66 mg/kg, in 4 out of 6 epochs of treatment (i.e., 6 to 12 months, 12 to 18 months, 18 to 24 months, and 30 to 36 months), ADA-positive subjects appeared to have higher concentrations than ADA-negative subjects at 96 hours after the last dose (Table 62). But the differences were not statistically significant due to large variability in somatrogon concentrations. Due to sparse sampling and no drug accumulation with weekly dosing, the same comparison could not be done with other time points after a dose.

Table 62. Mean and 95% CI of Somatrogon Concentration at 96 hours After Last Dose in Different Epochs of Treatment for Patients With and Without ADA, Trial CP-4-004

	ADA-			ADA+		
0.66 mg/kg	Mean	N	95% CI	Mean	N	95% CI
0-6 months	23.03	38	(19.15, 26.91)	20.62	25	(15, 26.25)
6-12 months	21.19	12	(14.6, 27.79)	35.85	5	(4.79, 66.92)
12-18 months	19.53	11	(13.85, 25.2)	19.6	7	(9.38, 29.83)
18-24 months	28.46	8	(14.05, 42.86)	148.07	8	(-53.85, 349.99)
24-30 months	26.67	6	(21.88, 31.46)	17.47	3	(4.71, 30.23)
30-36 months	28.63	3	(16.25, 41.02)	164.79	3	(-207.89, 537.47)

Source: FDA's analysis.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval

On September 15, 2021, the Applicant submitted an amendment to include clinical data from the data cut-off date of November 1, 2019 used for the original BLA to December 21, 2020. In the amendment, the Applicant also provided additional PK data for the first months after a subject is switched to the pen (PEN Period Year 1) in Study 004 (note: Depending on the time of enrollment into Study 004, the subject could be switched to pen device, which is the to-be-marketed product, in Years 2 to 4 of OLE). Summary of PK data by ADA status are shown in Table 63. Mean somatrogon concentration at different visits during PEN Period Year 1 were higher in ADA-positive subjects, compared to those in ADA-negative subjects. But the differences were not statistically significant due to large variability in somatrogon concentrations. The overall trend is consistent with what was observed in the data submitted in the original BLA (Table 62).

We note that somatrogon concentrations during PEN Period Year 1 were higher than those presented in Table 62. The difference is probably mainly due to sample collection time. In Table 62, all data were collected 96 hours after dose. In Table 63, the data were collected 72 hours or 96 hours after dose.

Table 63. Mean and 95% CI of Somatrogon Concentration (ng/mL), Trial CP-4-004 (PEN Period Year 1)

	ADA-			ADA+		
0.66 mg/kg	**Mean**	**N**	**95% CI**	**Mean**	**N**	**95% CI**
Month 1 PEN Period Year 1	68.7	25	(32.3, 105.0)	106.1	15	(42.3, 169.0)
Month 3 PEN Period Year 1	73.8	24	(44.1, 103.6)	107.5	13	(45.6, 169.5)
Month 6 PEN Period Year 1	86.9	23	(6.4, 167.5)	159.9	15	(37.9, 282.0)
Month 9 PEN Period Year 1	51.6	22	(29.3, 74.0)	97.9	13	(18.4, 177.3)
Month 12 PEN Period Year 1	49.1	21	(2.9, 95.2)	79.2	13	(-32.8, 190.1)

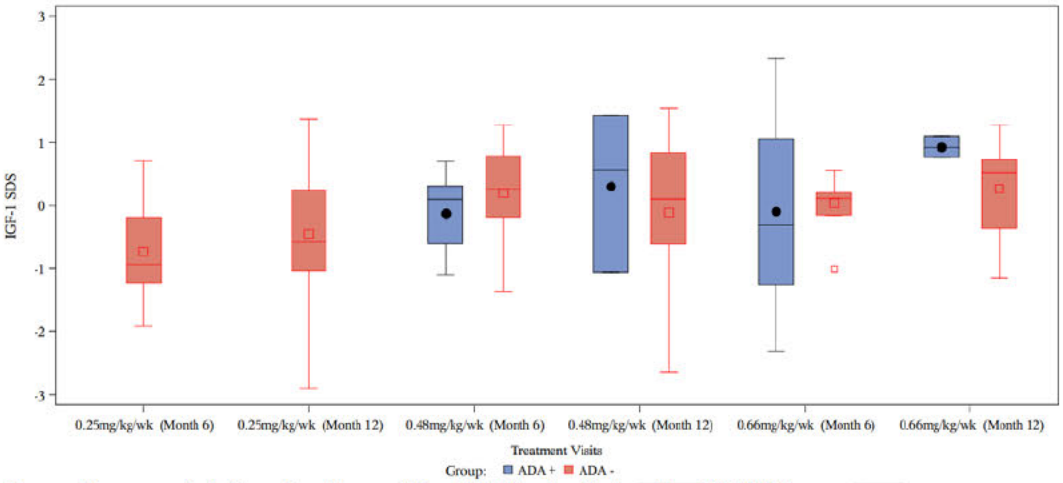
Source: FDA's analysis.
Per protocol, Day 4 postdose PK samples were taken during the open-label phase and could be taken on Day 3 or 4 postdose. The Applicant did not specify the time since last dose in the dataset. A subject was considered ADA+ if the subject tested positive during PEN Year 1.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval

Impact of ADA on PD

Main Study Period

To evaluate the impact of ADA on PD, IGF-1 SDS over time in subjects randomized to somatrogon dosing cohorts were plotted by ADA status. As may be seen in Figure 28 and Table 64, no subject treated with 0.25 mg/kg/wk developed ADA during the main study. For the 0.48 mg/kg/wk and the 0.66 mg/kg/wk dosing groups, the range of IGF-1 SDS scores among those who are ADA-positive overlap those who are ADA-negative.

Figure 28. Box Plot of IGF-1-SDS Over Time by Dose and ADA Status in Somatrogon, Trial CP-4-004 (Main Period)



Source: Response to Information Request (Serial #33) submitted on May 10, 2021
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor 1; SDS, standard deviation score

Table 64. Descriptive Summary of IGF-1-SDS by Dose and ADA Status in Somatrogon, Trial CP-4-004 (Main Study)

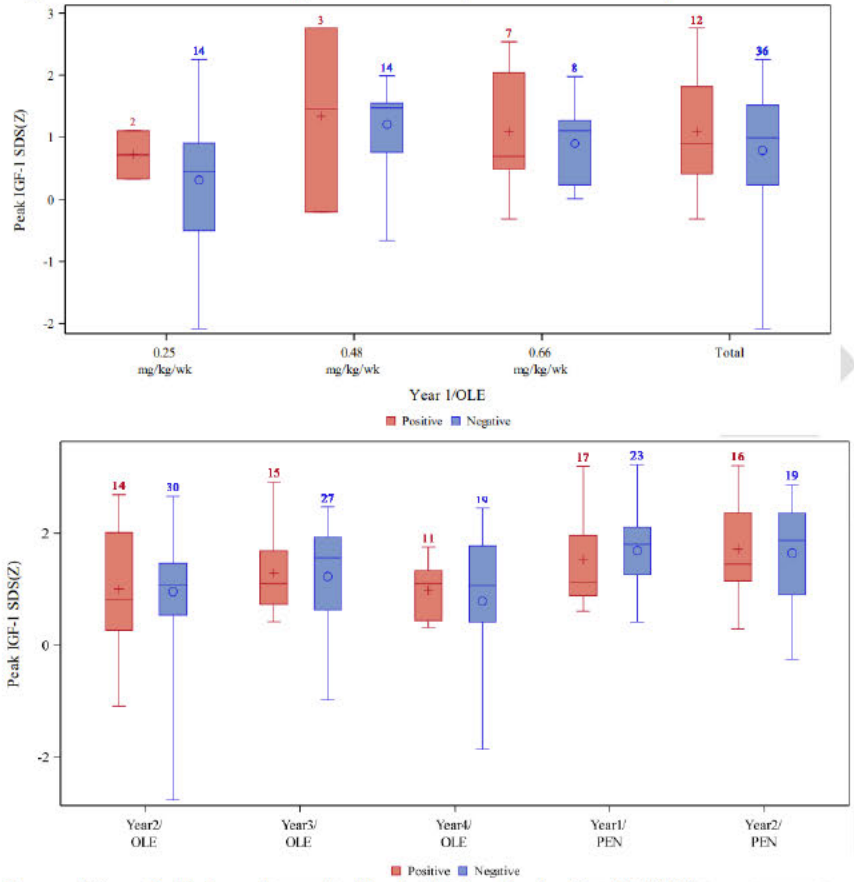
		0.25 mg/kg/wk (N=13)		0.48 mg/kg/wk (N=15)		0.66 mg/kg/wk (N=14)	
Visit in Main Period	Statistics	ADA +	ADA -	ADA +	ADA -	ADA +	ADA -
Month 6	n	0	13	5	10	5	9
	Mean (SD)		-0.73 (0.80)	-0.12 (0.72)	0.19 (0.86)	-0.10 (1.84)	0.04 (0.47)
	Median		-0.94	0.09	0.26	-0.32	0.11
	Range (min, max)		-1.92, 0.70	-1.10, 0.69	-1.37, 1.27	-2.30, 2.34	-1.01, 0.55
Month 12	n	0	13	3	12	2	12
	Mean (SD)		-0.46 (1.19)	0.31 (1.26)	-0.11 (1.34)	0.93 (0.23)	0.26 (0.72)
	Median		-0.57	0.56	0.10	0.93	0.52
	Range (min, max)		-2.91, 1.37	-1.06, 1.43	-2.64, 1.54	0.76, 1.09	-1.15, 1.27

Source: Response to Information Request (Serial #33) submitted on May 10, 2021.
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor-1; SD, standard deviation; SDS, standard deviation score

Open-Label Extension Periods

Plots of IGF-1 SDS by ADA status are provided in Figure 29. Summaries of IGF-1 SDS by ADA status are provided for Period III (Year 1 OLE) and Periods IV to V (Years 2 to 4 and PEN) in Table 65 respectively. The mean IGF-1 SDS remained similar between ADA-positive and ADA-negative subjects across all study periods.

Figure 29. IGF-1 SDS by ADA Status, Trial CP-4-004 (End of Periods III-V (Years 1-4 OLE + PEN))



Source: Figure 8 of isi-supplement.pdf submitted on September 15, 2021.
Upper whisker represents maximum, and the lower whisker represents minimum. The circle and plus in the box are mean; line in the box is median. Box is first and third quartiles.
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor 1; OLE, open-label extension; PEN, period V; SDS, standard deviation score

Table 65. IGF-1 SDS, Trial CP-4-004 End of Periods III to V (Years 1 to 4 OLE + PEN Years 1 to 2))

	Year 1							
	0.25 mg/kg/wk		0.48 mg/kg/wk		0.66 mg/kg/wk		Total	
	N=16		N=17		N=16		N=48	
IGF-1 SDS (Z)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	2	14	3	14	7	8	12	36
Mean (SD)	0.72 (0.55)	0.31 (1.17)	1.34 (1.48)	1.21 (0.71)	1.09 (1.00)	0.90 (0.68)	1.09 (1.01)	0.79 (0.97)
Median	0.72	0.44	1.46	1.48	0.69	1.11	0.90	0.99
Min, max	0.33, 1.11	-2.08, 2.25	-0.20, 2.76	-0.66, 1.99	-0.32, 2.54	0.01, 1.98	-0.32, 2.76	-2.08, 2.25

	Year 2		Year 3		Year 4		PEN Year 1		PEN Year 2	
	N=44		N=43		N=38		N=40		N=35	
IGF-1 SDS (Z)	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	14	30	15	27	11	19	17	23	16	19
Mean (SD)	1.00 (1.14)	0.96 (0.99)	1.29 (0.73)	1.23 (0.84)	0.98 (0.48)	0.79 (1.15)	1.53 (0.83)	1.69 (0.69)	1.71 (0.91)	1.64 (0.92)
Median	0.82	1.07	1.10	1.56	1.10	1.06	1.12	1.80	1.44	1.87
Min, max	-1.08, 2.69	-2.76, 2.67	0.42, 2.92	-0.96, 2.47	0.31, 1.75	-1.84, 2.44	0.60, 3.20	0.41, 3.23	0.29, 3.21	-0.24, 2.87

Source: Table of isi-supplement.pdf submitted on September 15, 2021.
Abbreviations: IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS (z), number of standard deviations

Dose Selection for Phase 3

Over 12 months, Somatrogon 0.48 and 0.66 mg/kg/week resulted in comparable IGF-1 SDS to that of Genotropin 0.034 mg/kg/day. Somatrogon 0.66 mg/kg/week was selected to be tested in the phase 3 study (CP-4-006) because, in terms of height increase (primary efficacy endpoint), 0.66 mg/kg/week was better than 0.25 and 0.48 mg/kg/week, and the closest to Genotropin 0.034 mg/kg/day.

14.2.5. Study CP-4-006: Phase 3 Study in Pediatric Patients

CP-4-006 was a phase 3 registration study that evaluated the efficacy, safety, and tolerability of somatrogon 0.66 mg/kg administered once weekly delivered via a single-patient-use, prefilled disposable pen containing 1.2 mL of 20 or 50 mg/mL somatrogon compared with Genotropin 0.034 mg/kg administered once daily using a commercially available pen.

Following completion of the 12-month main study period, subjects were eligible to enter the LT-OLE period where they will be able to continue to receive treatment until registration of somatrogon. Subjects who received somatrogon in the main study period and who participated in the LT-OLE continued on the same dose of somatrogon (0.66.mg/kg administered once weekly). Subjects who had received Genotropin during the main study period were switched to somatrogon at a dose of 0.66 mg/kg administered once weekly for the LT-OLE period. Every 3 months doses were assessed and adjusted, if needed, based on body weight. Doses could also be decreased for safety reasons according to prespecified criteria.

PK samples were collected at period at Day 1 (baseline), Day 10 (Day 4 after the last dose), Month 1, Month 3, Month 6, Month 9, and Month 12 after the first dose during the Main study period.

PD samples were collected predose at baseline and at 4 days after dose at Months 1, 3, 6, 9, and 12.

After Month 12, during the first year of LT-OLE, PK and PD assessments were conducted every 3 months (on Day 3 or 4) postdose for all patients. In addition, for subjects originally assigned to Genotropin, predose PK samples were collected at Month 13 (1 month after the first dose of somatrogon).

Blood samples for immunogenicity testing were acquired predose at the time points summarized in Table 66.

Table 66. Study CP-4-006 Immunogenicity Sampling by Study Period and Treatment

Study Segment	Study Treatment	Immunogenicity Sampling	
Pre-dosing		Somatrogon ADAs:	Baseline in the somatrogon arm.
		hGH ADAs:	Screening in all subjects [a], baseline in Genotropin arm.
Main study period	• Somatrogon 0.66 mg/kg/week • Genotropin 0.034 mg/kg/day	Somatrogon ADAs:	Day 10, Months 1, 3, 6, 9, 12 in somatrogon arm; Month 12 [b] in Genotropin arm.
		hGH ADAs [c]:	Months 1, 3, 6, 9, 12 in Genotropin arm.
LT-OLE	• Somatrogon 0.66 mg/kg/week	Somatrogon ADAs:	All subjects: Months 12.5, 13, 15, 18, 21, 24, EOS/ET.
		hGH ADAs:	Not routinely done [c].

Source: Module 5.3.5.1 Study CP-4-006 CSR, Appendix 16.1.1, Protocol Amendment 2 (US Version 5.0), Appendix A.

a. Positive result is exclusion criterion.
b. For subjects switching to somatrogon 0.66 mg/kg/week at the start of the OLE.
c. hGH Ab specificity testing in somatrogon-treated subjects who tested positive in screening and confirmatory assays.

Abbreviations: Ab, ant body; ADA, antidrug antibodies; hGH, human growth hormone; LT, long-term; OLE, open-label extension

Pharmacokinetics and Pharmacodynamics Results

PK/PD data from this study, combined with data from Study -004, were analyzed using a population PK approach. See Pharmacometrics Review for more details.

Immunogenicity Results

- Incidence of ADA

Incidence of ADA and NAb against somatrogon for Trials CP-4-006 and -006 OLE period is summarized in Table 67.

Table 67. ADA and Nab, Trials CP-4-006 and CP-4-006 (OLE Period)

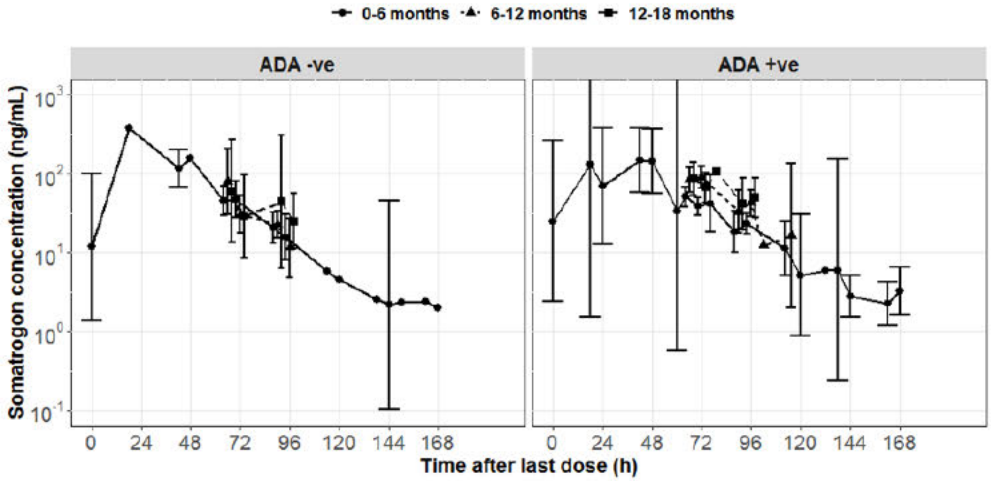
Study	N	ADA+	NAb
CP-4-006 Main			
Somatrogon	109	84 (77%)	2 (2%)
Genotropin	115	18 (16%)	0
CP-4-006 OLE (at Month 12 OLE)			
Previously randomized to somatrogon	104	78 (75%)	3[1] (3%)
Previously randomized to Genotropin	108	36 (33%)	0

Source: FDA's analysis
[1] One of these three subjects (# (b) (6)) is also included among those NAb positive in the main period.
Abbreviations: ADA, antidrug antibodies; NAb, neutralizing antibodies; OLE, open-label extension

Impact of ADA on PK

All available somatrogon concentrations after a dose during Study CP-4-006 were plotted by ADA status (Figure 30).

Figure 30. Somatrogon Concentration-Time Profile After Last Dose in Different Epochs of Treatment for Patients With and Without ADA, Trial CP-4-006



Source: FDA's analysis.
Abbreviation: ADA, antidrug antibodies

Across all epochs of treatments (i.e., 0 to 6 months, 6 to 12 months, and 12 to 18 months), ADA-positive subjects had higher concentrations than ADA-negative subjects at 72 and 96 hours after the last dose (Table 68). Moreover, the mean somatrogon concentrations 72 hours after the last dose were statistically significant between ADA-negative and ADA-positive subjects in the epoch of 6 to 12 months because the mean somatrogon concentration of ADA-negative subjects were outside of the 95% CI of somatrogon concentration of ADA-positive subjects and vice versa. Same observation was made for somatrogon concentrations 96 hours after the last day in

the epoch of 6 to12 months. These data indicated that the presence of ADA increased somatrogon concentration.

Table 68. Mean and 95% Confidence Interval of Somatrogon Concentration (ng/mL) After 72 and 96 hours of Last Dose Across Different Epochs of Treatment, Trial CP-4-006

	ADA-			ADA+		
0.66 mg/kg	Mean	N	95% CI	Mean	N	95% CI
72 hours after dose						
0-6 months	70.94	22	(41.35, 100.54)	77.09	77	(40.15, 114.03)
6-12 months	40.23	16	(22.57, 57.9)	175.84	54	(105.54, 246.15)
12-18 months	57.51	9	(21.32, 93.71)	133.39	25	(26.26, 240.52)
96 hours after dose						
0-6 months	27.32	18	(12.45, 42.19)	47.39	43	(15.4, 79.37)
6-12 months	24.94	13	(4.71, 45.16)	81.33	36	(43.66, 118.99)
12-18 months	28.67	4	(1.67, 55.66)	105.24	17	(4.65, 205.83)

Source: FDA's analysis.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval

In the amendment submitted on September 15, 2021, the Applicant provided PK data for Year 1 of OLE treatment, which is Month 12 to Month 24 since the first dose in Study 006. Summary of PK data by ADA status are shown in Table 69. Data in the "OLE Month 6" row in Table 69 include data presented in the "12-18 months" row in Table 68. Mean somatrogon concentration at OLE Month 6 and Month 12 visits were higher in ADA-positive subjects, compared to those in ADA-negative subjects. The difference was statistically significant at OLE Month 6 visit. The overall trend is consistent with what was observed in the data submitted in the original BLA. When the analysis was done separating the subjects who were originally randomized to Genotropin, at OLE Month 6, ADA-positive subjects (n=23) had higher concentration than ADA-negative subjects (n=36) (124 versus 97 ng/mL, mean conc, P=0.634); at OLE Month 12, ADA-positive subjects (n=27) had lower concentration than ADA-negative subjects (n=38) (17.3 versus 26.3 ng/mL, mean conc, P=0.626).

Table 69. Mean and 95% CI of Somatrogon Concentration (ng/mL), Trial CP-4-006 (Year 1 of OLE Treatment)

	ADA-			ADA+		
0.66 mg/kg	Mean	N	95% CI	Mean	N	95% CI
OLE Month 6 (month 18 since first dose)	88.4	49	(51.7, 125.0)	160.7	74	(104.5, 217.0)
OLE Month 12 (month 24 since first dose)	20.3	56	(-1.8, 42.4)	34.4	97	(20.8, 47.9)

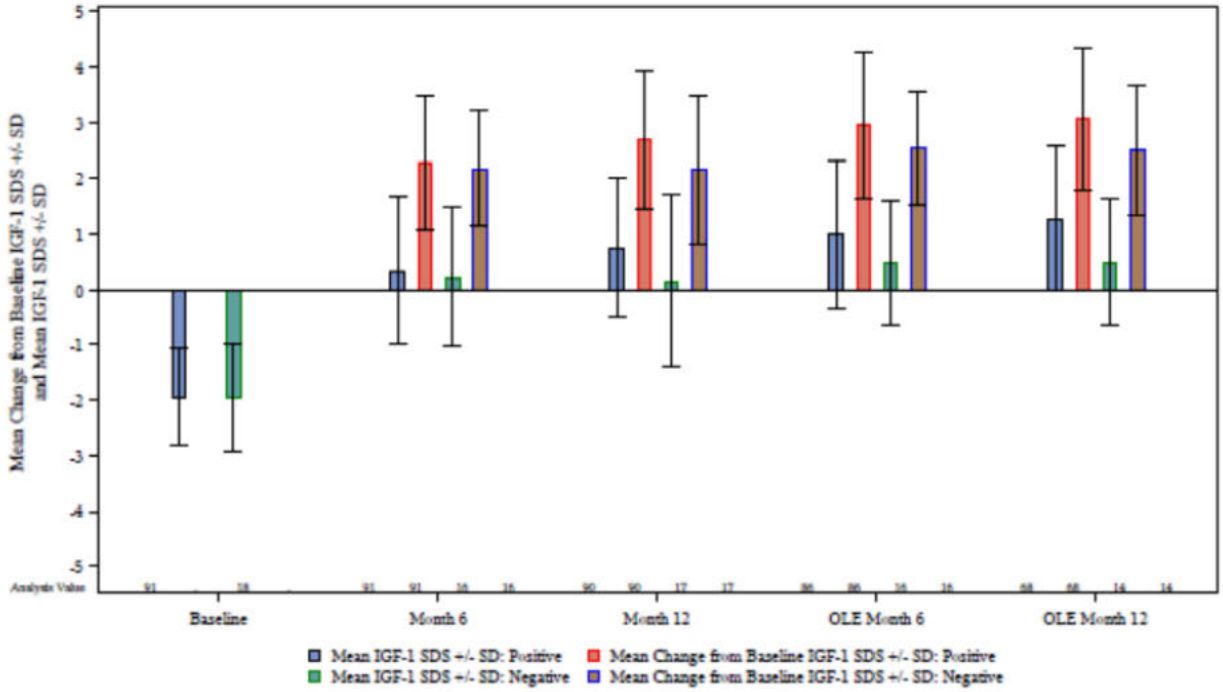
Source: FDA's analysis.
Note: Per protocol, Day 4 postdose pharmacokinetics samples were taken during the OLE phase and could be taken on Day 3 or 4 postdose. The Applicant did not specify the time since last dose in the dataset.
Abbreviations: ADA, antidrug antibodies; CI, confidence interval; OLE, open-label extension

We note that somatrogon concentrations at OLE Month 6 were higher than those at OLE Month 12 visits for both ADA-positive and ADA-negative. The reason for this apparent difference is not known. However, the difference does not appear to impact efficacy based on annual height velocity and IGF-1 SDS.

Effect of ADA on PD

To evaluate the effect of ADA on PD, IGF-1 SDS over time in subjects randomized to somatrogon dosing cohorts were plotted by ADA status. As may be seen in Figure 31 and Table 70, and Table 71. Overall, while testing ADA-positive tended to be associated with numerically higher mean and median IGF-1 SDS values and greater changes from baseline, there was considerable overlap between ADA-positive and ADA-negative subjects.

Figure 31. IGF-1-SDS and Change From Baseline by ADA Status Over Time, Trial CP-4-006 (Main and OLE Somatrogon to Somatrogon)



Source: Figure 14.2.2.3c of isi-appendix-tables-figures.pdf.
* Baseline is the main period baseline for the study. ADA positive is defined as those who tested negative at the baseline and then tested positive after receiving drug at any time during the study (main + OLE), as well as those who tested positive at the baseline and then had increase in titer after receiving drug (4×baseline titer value).
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor 1; OLE, open-label extension; SDS, standard deviation score

Table 70. Summary of IGF-1 SDS by ADA Status, Trial CP-4-006 (Main and OLE Full Analysis Set Group: Originally Randomized to Somatrogon)

		Originally Randomized to Somatrogon			
		ADA+		ADA-	
Visit	Variable	Observed	Change From Baseline	Observed	Change From Baseline
Baseline	N	91	N/A	18	N/A
	Mean (SD)	-1.95 (0.88)		-1.94 (0.98)	
	Median	-1.88		-1.81	
	(Min, max)	-4.39, -0.62		-3.65, -0.21	
Month 3	N	91	91	18	18
	Mean (SD)	0.1 (1.45)	2.05 (1.22)	0.22 (1.41)	2.16 (1.22)
	Median	-0.04	2.04	0.15	2.15
	(Min, max)	-3.32, 3.69	-0.5, 5.13	-2.09, 3.41	0.20, 5.28
Month 6	N	91	91	16	16
	Mean (SD)	0.33 (1.32)	2.28 (1.21)	0.23 (1.27)	2.17 (1.03)
	Median	0.49	2.24	0.05	2.11
	(Min, max)	-3.54, 2.99	-0.44, 5.57	-1.67, 3.10	0.46, 4.97
Month 9	N	91	91	17	17
	Mean (SD)	0.62 (1.28)	2.57 (1.37)	0.39 (1.45)	2.38 (1.20)
	Median	0.77	2.62	0.81	2.27
	(Min, max)	-3.86, 2.99	-0.39, 5.20	-2.76, 2.46	-0.51, 4.33
Month 12	N	90	90	17	17
	Mean (SD)	0.75 (1.26)	2.68 (1.24)	0.15 (1.55)	2.15 (1.32)
	Median	0.82	2.72	0.57	2.12
	(Min, max)	-3.64, 3.22	0.02, 6.11	-3.2, 2.77	-0.27, 3.90
OLE Month 3	N	87	87	16	16
	Mean (SD)	0.81 (1.41)	2.78 (1.38)	0.21 (1.24)	2.26 (1.22)
	Median	1.15	2.62	0.24	1.85
	(Min, max)	-3.64, 2.93	-0.30, 5.79	-1.65, 2.92	0.60, 4.79
OLE Month 6	N	86	86	16	16
	Mean (SD)	0.99 (1.32)	2.96 (1.31)	0.48 (1.11)	2.53 (1.02)
	Median	1.13	2.96	0.58	2.46
	(Min, max)	-3.24, 3.72	-0.17, 5.43	-1.56, 2.17	0.69, 4.21
OLE Month 9	N	79	79	13	13
	Mean (SD)	1.21 (1.29)	3.15 (1.26)	0.94 (1.28)	2.71 (1.27)
	Median	1.43	3.33	1.25	2.37
	(Min, max)	-3.07, 4.0	-0.12, 5.59	-1.87, 2.39	0.38, 4.80
OLE Month 12	N	68	68	14	14
	Mean (SD)	1.28 (1.29)	3.07 (1.28)	0.49 (1.14)	2.51 (1.16)
	Median	1.59	3.03	0.52	2.54
	(Min, max)	-4.2, 3.36	-0.54, 5.78	-1.55, 2.58	0.54, 4.66

Source: Table 18 of isi-supplement.pdf submitted on September 15, 2021.
Baseline is the main period baseline for the study. ADA positive defined as those who tested negative at baseline and positive after receiving drug at any time during the study (main + OLE), as well as those who tested positive at baseline and had an increase in titer after receiving drug (4×baseline titer value).
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS, standard deviation score

Table 71. Summary of IGF-1 SDS by ADA Status, Trial CP-4-006 (Main and OLE Full Analysis Set Group: Originally Randomized to Genotropin)

		Originally Randomized to Genotropin			
		ADA+		ADA-	
Visit	Variable	Observed	Change from Baseline	Observed	Change from Baseline
OLE Month 3	N	37	37	67	67
	Mean (SD)	0.69 (1.31)	2.47 (1.24)	0.94 (1.44)	2.64 (1.26)
	Median	0.52	2.72	1.18	2.66
	(Min, max)	-1.87, 3.0	-0.29, 4.49	-3.36, 3.5	-0.15, 4.99
OLE Month 6	N	35	35	66	66
	Mean (SD)	1.15 (1.27)	2.94 (1.34)	0.88 (1.35)	2.57 (1.21)
	Median	1.23	2.97	0.91	2.62
	(Min, max)	-1.47, 3.44	0.36, 5.49	-2.75, 3.37	-0.61, 5.24
OLE Month 9	N	29	29	62	62
	Mean (SD)	1.15 (1.12)	2.79 (1.38)	1.02 (1.44)	2.71 (1.27)
	Median	1.58	2.73	1.12	2.83
	(Min, max)	-1.76, 2.46	-0.18, 5.26	-2.84, 3.57	0.20, 5.70
OLE Month 12	N	27	27	45	45
	Mean (SD)	1.48 (1.07)	3.12 (1.27)	1.20 (1.21	2.84 (1.03)
	Median	1.50	3.04	1.07	2.92
	(Min, max)	-0.75, 3.90	0.53, 7.12	-2.86, 3.68	0.34, 4.57

Source: Table 19 of isi-supplement.pdf submitted on September 15, 2021.
ADA positive defined as those who tested negative at baseline and tested positive after receiving drug at any time during the study (main + OLE), as well as those who tested positive at baseline and had an increase in titer after receiving drug (4×baseline titer value).
Abbreviations: ADA, antidrug antibodies; IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS, standard deviation score

14.3. Pharmacometrics Review

14.3.1. Population PK Analysis

14.3.1.1. Review Summary

The Applicant developed two population PK models of somatrogon for different purposes using data from a phase 3 efficacy and safety trial in pediatric subjects 6 to 12 years old. In both models, somatrogon PK was described by a two-compartment model, with first order absorption constant and absorption lag time. The two models differed in the way the impact of body weight on somatrogon PK parameters was characterized. In the first model PK parameters were normalized by body weight (Equation (1.1)) while in the second model, PK parameters were allometrically scaled by body weight (Equation (1.2)). However, the models predicted different parameter estimates for a typical 15 kg child. Further review determined that the population PK model of somatrogon could be optimized to characterize factors influencing PK variability of somatrogon. The following issues were identified: Both models were over-parameterized; attempting to reproduce the results of the weight-normalized PopPK model gave different estimates than reported by the Applicant; both models did not evaluate the impact of ADA-titer values on somatrogon PK.

In order to best characterize the PK of somatrogon, the reviewer developed an alternative PopPK model using PK data from phase 2 and phase 3 studies. Like the Applicant's models, the alternative model was also a two-compartment model, with first-order absorption kinetics, but with no lag time. Also, unlike both Applicant's models, the alternative model's clearance parameters were weight normalized while volume parameters were allometrically scaled.

Therefore, somatrogon clearance increases proportionally while volume of distribution increases more than proportionally with body weight. The alternative model also included ADA-titer as statistically significant covariate of somatrogon clearance. Higher ADA-titers were associated with lower somatrogon clearance.

The average estimates of somatrogon PK parameters for the reviewer's alternative model were: CL/F=0.59 (l/h/17 kg), V2/F=3.9 (L/17 kg), Q=0.02 (L/h/17 kg), V3=8.7 (L/17 kg) and Ka=0.047 (h^{-1}). For the factors associated with PK variability; the weight allometric exponent for scaling V2 was 1.62, the percent decrease in CL for subjects with ADA-titer of × 50 dilution factor was 23%, the percent decrease in CL for subjects with ADA-titer of × 250 dilution factor was 35%, the percent decrease in CL for subjects with ADA-titer of × 1250 dilution factor was 58%, and the percent decrease in CL for subjects with ADA-titer of × 6250 dilution factor was 66%. Unexplainable between subject variability in PK parameters were estimable for CL and V2 with estimates of 22% and 67% respectively; the corresponding ETA shrinkages were 26% and 35% respectively.

The developed alternative model can be used to support labelling of Somatrogon as outlined in Table 72.

Table 72. Reviewer's Comments on the Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Somatrogon dosing is based on body weight. This dosing strategy ensures comparable somatrogon exposure across all pediatric body weights	In addition to body weight, ADA titer was also a significant covariate on clearance. Prediction based on reviewer's PK/PD model indicated that ADA positive patients had higher probability of IGF-1 SDS ≥ 2 than ADA negative patients. However, there was no association between the probability of IGF-1 SDS ≥ 2 and ADA titer levels.
	Extrinsic factor		
Derive exposure metrics for exposure-response analyses	Predicted individual PK parameters were used in exposure-efficacy analyses		The use of predicted individual PK parameters in E-R analyses is acceptable since the model performance was reasonable as indicated by the GOF plots
Predict exposures at alternative dosing regimen			The model was not used to assess predicted exposures at other doses

Source: Reviewer's independent analysis.
Abbreviations: ADA, antidrug antibodies; E-R exposure-response; GOF, goodness of fit; IGF-1, insulin-like growth factor-1; PK, pharmacokinetics; SDS, standard deviation score

14.3.1.2. Introduction

The Applicant developed two population PK models to describe the same PK data collected from children 6 to 12 years old who participated in the phase 3 study. The models were developed at different periods and for different purposes. The first PopPK model (dated May 26, 2020) was developed through re-estimation of structural model parameters and re-evaluation of covariate model after a previously developed PopPK model based on phase 2 adult and children PK data (hereafter named PHASE-2 PopPK-MODEL) failed external validation using the phase 3 children only data. In this model clearance and volume parameters were normalized by body weight (hereafter named Weight-Normalized PopPK model). In the second PopPK model (dated August 5, 2020) structural model parameters from the previous PHASE-2 PopPK-MODEL were

fixed to PHASE-2 PopPK-MODEL parameters, but covariates were re-assessed, and stochastic parameters were re-estimated. In this second model, clearance and volume parameters were allometrically scaled by body weight (hereafter named Allometric PopPK model). The two models yielded different population average parameter estimates. For example, for a typical 15 kg child, the PK parameter estimates from the first PopPK model were CL=0.315 L/h, V1=6.98 L, Q=0.015 L/h, V2=69.5 L, Ka=0.41/h, absorption lag time (ALAG1) = 1 hour, while the corresponding estimates for the second PopPK model were CL=0.472 L/h, V1=10.9 L, Q=0.013 L/h, V2=2.37 L, KA=0.41/h, ALAG1=0.35 hours. Parameter estimates with large difference between the two models are V2 and ALAG1. Individual PK parameters from the Weight-Normalized PopPK model were used for PKPD modeling to evaluate the relationships between somatrogon exposure and IGF-1 levels overtime. The individual PK parameters from this model were not used for providing summary of PK parameters in Section 12.3 of the US-FDA label. In contrast, individual PK parameters from the Allometric PopPK model were not used for PKPD modeling but were used for labeling Section 12.3 of the US-FDA label. Section 1.3 compares the developments of the Applicant's two PopPK models.

14.3.1.3. Applicant's PopPK Model Development

14.3.1.3.1. Data

Both Allometric and Weight-normalized PopPK models were developed using sparse pharmacokinetic samples collected from the same phase 3 study. The study design, study population, and timing of blood samples collection are presented in Table 73. However, the first PopPK model used a NONlinear Mixed Effects Modeling datafile that contained 826 PK observations while the second PopPK model used a datafile containing 826 PK observations from 109 subjects.

Table 73. Summary of the Phase 3 Study

Trial	Population	Study Design	Dosage	PK Sampling
CP-4-006	Prepubertal children with GHD who are naïve to treatment with rhGH	Randomized, open-label, active-controlled, parallel-group, multicenter, phase 3 study to investigate the efficacy and safety of somatrogon compared to Genotropin	Somatrogon 0.66 mg/kg/week or Genotropin 0.034 mg/kg/day	PK and anti-somatrogon antibody assessments were conducted in the main study treatment period at Day 1 (baseline), Day 10, Month 1, Month 3, Month 6, Month 9, and Month 12 after the first dose. Sparse samples for PD (IGF-1, IGFBP-3) were collected predose at baseline and at 4 days after dose at months 1, 3, 6, 9, and 12.

Source: Reviewer's independent analysis.
Abbreviations: GHD, growth hormone deficiency; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; PD, pharmacodynamics; PK, pharmacokinetics; rhGH, recombinant human growth hormone

Table 74 provides summary statistics of the baseline demographic and laboratory characteristics in the analysis datasets.

Table 74. Summary of Baseline Demographic and Laboratory Characteristics

Variable		Value
	N	109
Body weight (kg)	Mean ± sd	19.7 ± 7.1
	Median	19.3
	min - max	8 - 46.1
Age (year)	Mean ± sd	7.8 ± 2.7
	Median	7.9
	min - max	3 - 12
Baseline Creatinine CL (mL/min)	Mean ± sd	49.7 ± 15.3
	Median	48.9
	min - max	22 - 93.3
Male	N (%)	82 (75.2%)
Female	N (%)	27 (24.8%)
White	N (%)	81 (74.3%)
Asian	N (%)	24 (22%)
American Indian or Alaska Native	N (%)	1 (0.9%)
Other or missing	N (%)	3 (2.8%)

Repository artifact ID FI-9428500. Line 1 substituted.

N:number of patients; sd=standard deviation; kg=kilogram; min=minimum; max=maximum; CL=clearance

Source: Applicant's Population Modeling Analysis Report (Report number PMAR-EQDD-C031b-DP3-1093, page 27 of 231).

14.3.1.3.2. Base Model

Development of both Allometric and Weight-Normalized PopPK models started by external validation of a previous PHASE-2 PopPK-MODEL using the sparse data from the phase 3 study. The previous PHASE-2 PopPK-MODEL failed external validation. The base structural model for the Weight-Normalized model was a 2-compartment PK model with delayed first order absorption kinetics and body weight as covariate on clearance and volume parameters parameterized as shown in equation (1.1). All parameters of the base model, including random effects parameters, were re-estimated.

$$P_i = P_{pop} \times \frac{BodyWeight}{77} \times e^{\eta} \quad (1.1)$$

$$Where:$$
$$P_i = individual\ predicted\ parameter\ value$$
$$P_{pop} = Typical\ population\ (mean)\ value\ for\ 77\ Kg$$
$$\eta = inter-individual\ random\ effect$$

The base structural model for the Allometric model was the same as the PHASE-2 PopPK-MODEL, which was a 2-compartment PK model with delayed first order absorption kinetics and PK parameters allometrically scaled by body weight as shown in equation (1.2). All parameters of the base model were fixed to values estimated in the PHASE-2 PopPK-MODEL. Inter-subject variability parameter for KA was fixed to a PHASE-2 PopPK-MODEL value but was re-estimated for CL and V parameters.

$$P_i = P_{pop} \times \left(\frac{BodyWeight}{15}\right)^{\theta} \times e^{\eta} \quad (1.2)$$

Where:

$\theta = Weight\ effect\ on\ clearance\ and\ volume\ parameters$

14.3.1.3.3. Covariate Analysis

In both model developments, graphical exploration of parameter-covariates relationships was used to guide selection of relations to be statistically tested during covariate model development. Goodness-of-fit (GOF) plots were also used to guide structural model modification and covariate selections. GOF plots included ratios of observed-to-population predicted values versus time and observed versus population predicted values were examined. Covariates that were included in graphical assessments included age, sex, height, BMI, body surface area, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, creatinine clearance, serum creatinine and antidrug antibody (ADA) status for Allometric model.

For Weight-normalized model a factor indicating decrease in clearance after day 125 was included in the model while for Allometric model a factor indicating proportional decrease in clearance for subjects who ADA positive was included. In addition, a factor indicating higher clearance in the phase 3 study compared to clearance estimated in the phase 2 PopPK-model was estimated.

No additional covariates were identified for both models.

14.3.1.3.4. Final Model

For both the Allometric and the Weight-Normalized PopPK models, the covariate models were the final models. The parameter estimates of the final Allometric and Weight-Normalized PopPK model are listed in Table 75 and Table 76, respectively.

Table 75. Parameter Estimates of the Applicant's Final Allometric PopPK Model

Parameter	Fixed	Estimate	SE	RSE (%)	CV (%)	Shrinkage (%)
CL/F (L/hr)	0.472					
Vc/F (L)	10.9					
Q/F (L/hr)	0.0135					
Vp/F (L)	2.37					
Ka (1/hr)	0.313					
Lag time (hr)	0.353					
Body Weight on CL/F & Q/F	1.26					
Body Weight on Vc/F & Vp/F	1.74					
Proportional Change in Apparent Clearance for Positive ADA Status		-0.258	0.01	-3.876		
Proportional Change in Apparent Clearance for Study CP-4-006 Compared to Study CP-4-004		0.0661	0.00309	4.675		
Variance on CL/F		0.295	0.0814	27.6	58.6	26.0
Covariance on CL/F & Vc/F		0.35	0.124	35.4		
Variance on Vc/F		0.456	0.192	42.1	76.0	36.3
Variance on Ka	0.449				75.3	57.6
Variance on ADAT		0.0301	0.0172	57.1	17.5	43.6
Correlation (CL/F & Vc/F)		0.955	0.0125	1.31		
Residual SD		0.815	0.00836	1.026	112.2	

Fixed=parameters being fixed; Estimate=parameters being estimated; SE=standard error; RSE=relative standard error; CV=coefficient of variation; CL/F=apparent clearance from central compartment; Vc/F=apparent central compartment volume; Q/F=apparent clearance between peripheral and central compartment; Vp/F=apparent peripheral compartment volume; Ka=absorption rate constant; L=liter; mL=milliliter; hr=hour; ug=microgram; ng=nanogram; SD=standard deviation in log scale

Source: Applicant's Population Modeling Analysis Report (Report number PMAR-EQDD-C031b-DP3-1093, page 39 of 231).

Table 76. Parameter Estimates of the Applicant's Final Weight-Normalized PopPK Model

Parameter	Estimate	Inter-individual Variability*
FCTR		—†
Through Day 125	1.0	
After Day 125	0.890255	
SCALE	KG/77	—†
Clearance/F (L / hour)	1.62012 • SCALE • FCTR	1.091
V_1/F (L)	35.8774 • SCALE	1.251
Distributional Clearance/F (L / hour)	0.0793539 • SCALE	0.748
V_2/F (L)	357.084 • SCALE	0.8744
Absorption Rate (/ hour)	0.416988	1.043
Absorption Lag (hours)	0.998283	—†

* Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.

† Inter-individual variability was not permitted for this term

‡ KG is weight in kg; the value of 77 kg (median value in adults) is applied to center the parameter estimates

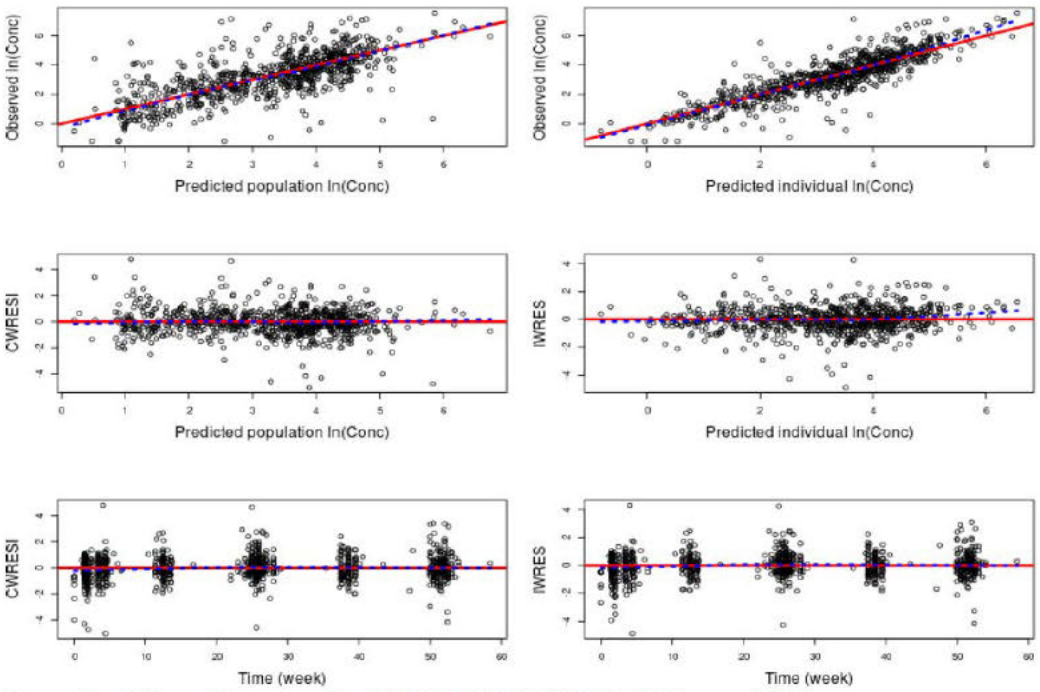
FCTR = Factor for time-related step-change in apparent clearance, SCALE = Scaling term for systemic parameters

Standard errors were not obtained.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 6/1938.
Abbreviations: F, bioavailability; PKPD, pharmacokinetics/pharmacodynamics; PopPK, population pharmacokinetics; sqrt, square root; V1, apparent volume of the central compartment; V2, apparent volume of the peripheral compartment

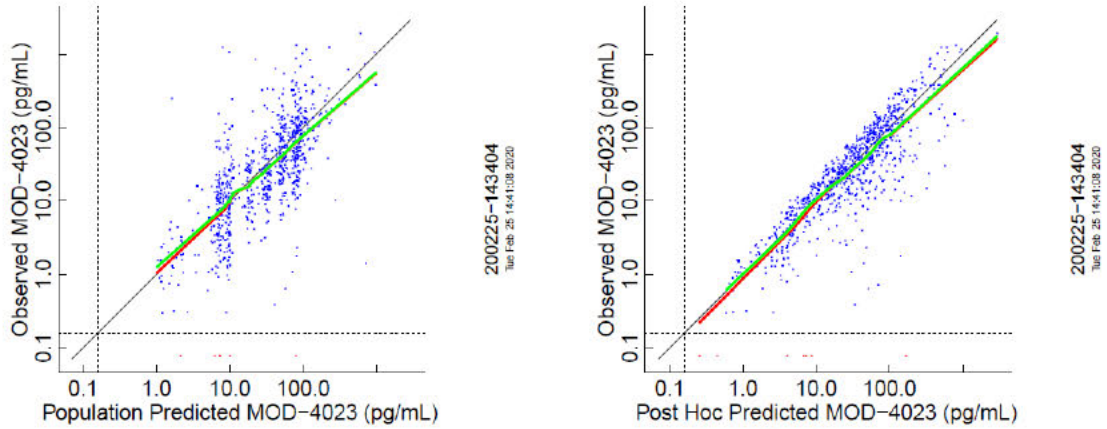
The goodness-of-fit plots for the final Allometric and the Weight-Normalized PopPK models are shown in Figure 32 and Figure 33, respectively.

Figure 32. GOF of the Applicant's Final Allometric PopPK Model



Source: PopPK report (report number PMAR-EQDD-C031b-DP3-1093), page 42/231.
Abbreviations: GOF, goodness-of-fit; PopPK, population pharmacokinetics

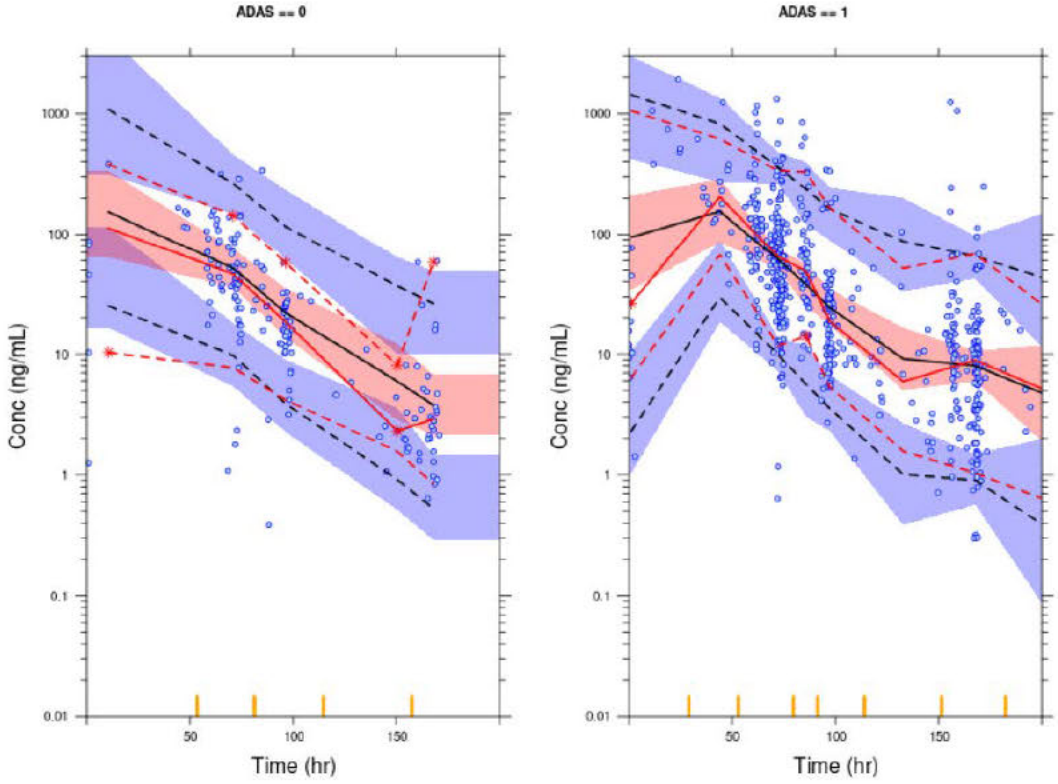
Figure 33. GOF of the Applicant's Final Weight-Normalized PopPK Model



Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 31/1938.
Abbreviations: GOF, goodness-of-fit; MOD-4023, somatrogon; PopPK, population pharmacokinetics

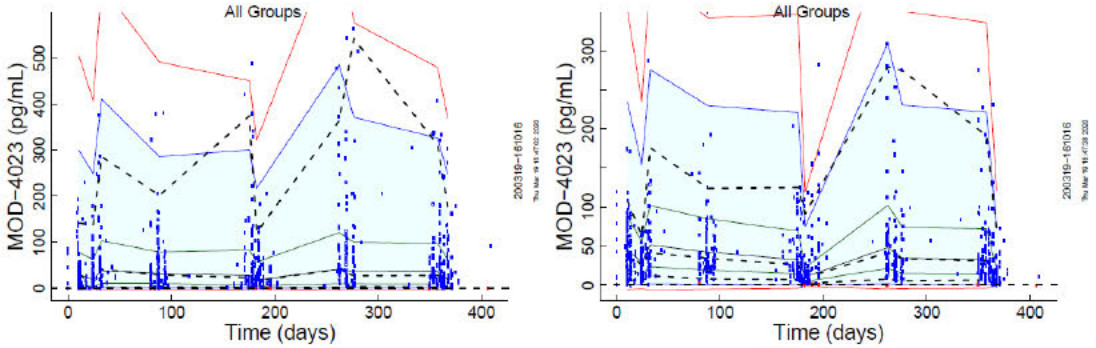
The Visual Predictive Check plot for the final Allometric and the Weight-Normalized PopPK models are shown in Figure 34 and Figure 35, respectively.

Figure 34. VPC of the Applicant's Final Allometric PopPK Model



Source: Population PK report (number PMAR-EQDD-C031b-DP3-1093), page 56/231.
Abbreviations: PopPK, population pharmacokinetics; VPC, visual predictive check

Figure 35. VPC of the Applicant's Final Weight-Normalized PopPK Model



Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 34/1938.
Abbreviations: PopPK, population pharmacokinetics; MOD-4023, somatrogon; VPC, visual predictive check

14.3.1.3.5. Reviewer's Comments

Although both models provide adequate description of the data, they were over-parameterized. Upon repeating the Applicant's analyses, the reviewer found that the Applicant's Allometric PopPK model had large conditional number (18392) and large coefficient of correlations among parameters. The correlated parameters are given in Table 77.

Table 77. Coefficients of Correlation Among Model Parameters Indicating Unidentifiability of V2, CL, and Covariance Parameters (BSV-V_2 Versus BSV-CL)

Correlated Parameters	Coefficient of Correlation	Implication
OMEGA(2,1)−CL	0.98	Covariance (between BSV-V_2 and BSV-CL) is unidentifiable with CL
V_2−CL	0.96	V_2 is unidentifiable with CL
OMEGA(2,1)−V_2	0.99	Covariance (between BSV-V_2 and BSV-CL) is unidentifiable with V_2

Source: Reviewer's independent analysis.
The repeat of the Applicant's weight-normalized PopPK model did not yield the same parameter estimates as those reported by the Applicant. Table 78 shows that using the same dataset and the model from the Applicant, parameter estimation yielded different estimates compared to those reported by the Applicant in Table 76. The model had large conditional number (1.221e+009) and large coefficients of correlation among parameters indicating unidentifiability.
Abbreviations: BSV; between-subject variability; CL, clearance; RSE, relative standard error; V_2, volume of central compartment

The Applicant's Weight-normalized model was therefore not acceptable for sequential PKPD modeling. Despite adequate description of the PK data, the Allometric model was also unsuitable due to unidentifiability among some of the parameters.

Table 78. Parameter Estimates of the Applicant's Weight-Normalized Model Where the Estimation Was Repeated by the Reviewer

Parameter	Description	Estimate (RSE)
OFV	Objective function value	17627.590
CL	Clearance (L/h/77 kg)	1.805 (8%)
V_2	Volume of central compartment (L/77 kg)	40.74 (6%)
Q	Intercompartment clearance (L/h/77 kg)	0.07272 (6%)
V_3	Volume of peripheral compartment (L/77 kg)	208.1 (84%)
K_a	Absorption rate constant (/h)	0.4012 (9%)
ALAG1	Absorption lag-time (h)	0.9883 (4%)
TIMEFCT	Factor for step change in CL at day 125	0.8809 (1%)
ECL	Between-subject variability of CL	1.083 (4%)
ECL_cor_EV2	Correlation between BSV-CL and BSV-V_2	0.994 (0%)
EV2	Between-subject variability of V_2	1.262 (2%)
ECL_cor_EQ	Correlation between BSV-CL and BSV-Q	0.7002 (14%)
EV2_cor_EQ	Correlation between BSV-V_2 and BSV-Q	0.7014 (14%)
EQ	Between-subject variability of Q	1.007 (21%)
ECL_cor_EV3	Correlation between BSV-CL and BSV-V_3	0.302 (118%)
EV2_cor_EV3	Correlation between BSV-V_2 and BSV-V_3	0.383 (92%)
EQ_cor_EV3	Correlation between BSV-Q and BSV-V_3	0.6612 (24%)
EV3	Between-subject variability of V_3	1.385 (17%)
EKA	Between-subject variability of K_a	1.086 (FIXED)
PROP	Proportional residual error	0.5741 (0%)
ADD	Additive residual error	360 (0%)

Source: Reviewer's independent analysis.
Abbreviations: BSV, between-subject variability; RSE, relative standard error

Table 79. Coefficient of Correlation Among Model Parameters Indicating Unidentifiability of V_3, CL, K_a, ALAG1, Variance, and Covariance

Correlated Parameters	Coefficient of Correlation	Implication
V_3-CL	0.95	Unidentifiable
K_a-CL	-0.95	
K_a-V_3	-0.98	
ALAG1-V_3	0.95	
ALAG1-K_a	-0.94	
OMEGA(2,1)–ECL	0.94	
OMEGA(3,2)–OMEGA(3,1)	0.98	
OMEGA(4,2)–OMEGA(4,1)	0.99	

Source: Reviewer's independent analysis.
Abbreviations: ALAG1, absorption lag time; CL, clearance; ECL, enhanced chemiluminescence; K_a, absorption rate constant V_2, volume of central compartment; V_3, volume of peripheral compartment

Decrease in somatrogon clearance among patients who developed ADA was surprising. The suggested explanation was that ADA conjugated with somatrogon thus limiting its elimination. This hypothesis could be tested by examining the impact of ADA titer on somatrogon clearance. If ADA-somatrogon conjugate had less clearance, then subjects with higher ADA titer would have lower clearance compared to subjects with lower ADA titer. The Applicant did not evaluate the impact of ADA titer on somatrogon clearance.

14.3.1.4. Reviewer's PopPK Model Development

14.3.1.4.1. Introduction

Due to the deficiencies in both of the Applicant's PopPK models, the reviewer developed an alternative PopPK model to describe both the phase 2 and phase 3 PK data in pediatric subjects. The goal was to obtain a parsimonious PopPK model that adequately described the PK data and therefore used for sequential PKPD modeling and labeling PK parameters in the USPI.

14.3.1.4.2. Data

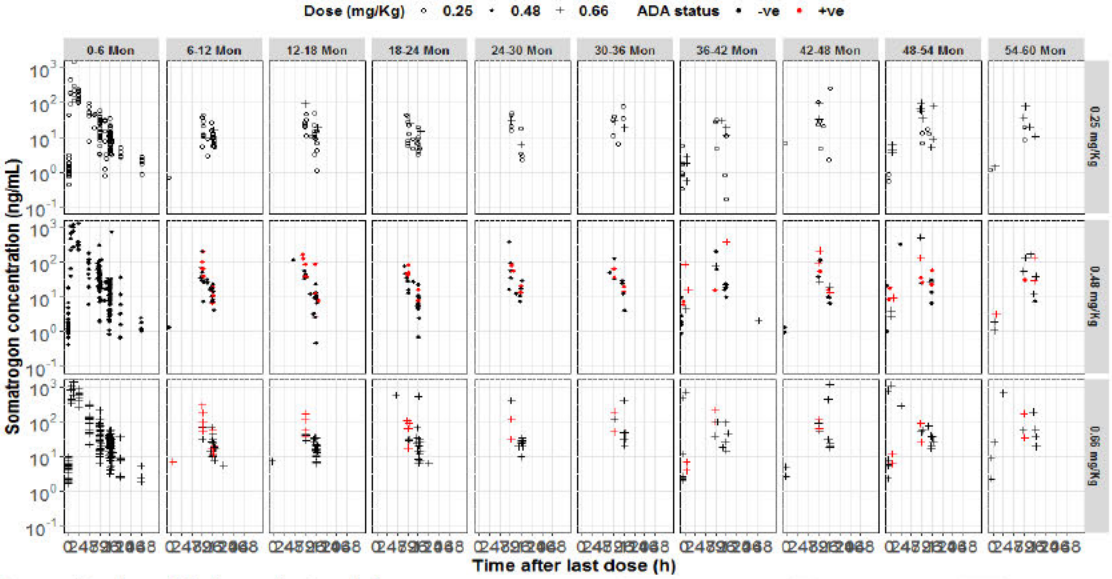
The Applicant's final NONlinear Mixed Effects Modeling datasets for PHASE2 PopPK model and Allometric PopPK model were pooled to make a combined phase 2 and phase 3 PK dataset for modeling. Only pediatric data were included in this dataset. The summaries of the study design, study population, and timing of blood samples collection are presented in Table 73 for phase 3 and Table 80 and Figure 37 show somatrogon concentration versus time after last dose in different periods of treatment in phase 2 and phase 3 studies, respectively. No subjects were ADA-positive in the 0.25 mg/kg treatment group and in the first 6 months for the phase 2 study. In the phase 3 study, few subjects were ADA-positive at 0.5 months, but about 85 subjects were ADA-positive by the 6th month of treatment.

Table 80. Summary of the Phase 2 Study

Trial	Population	Design	Dosage	PK Sampling
CP-4-004	Prepubertal growth hormone-deficient children	Randomized, open-label, parallel group safety and dose-finding study	Somatrogon at 0.25, 0.48, and 0.66 mg/kg/week and rhGH at 0.034 mg/kg/daily. Patients in the 0.25 mg/kg/week cohort received 0.25 mg/kg weekly during the entire Period I. Patients in the 0.48 mg/kg/week cohort received two 0.25 mg/kg weekly doses prior to receiving 0.48 mg/kg weekly for the rest of Period I. Patients in the 0.66 mg/kg/week cohort received two 0.25 mg/kg weekly doses, two 0.48 mg/kg weekly doses and followed by a dose of 0.66 mg/kg weekly for the rest of Period I.	Four PK and PD samples per patient were collected in one of the three specified time series: i) 0, 24, 48, 96; ii) 6, 48, 72, 120; and iii) 12, 24, 72, 168 hours postdose, after the second administration of the targeted somatrogon dose, i.e., at Week 2, 4, and 6 for the 0.24, 0.48, and 0.66 mg/kg cohort, respectively. The Day 4 samples at Week 6 in the 0.24 mg/kg cohort, at Week 2 and 6 in the 0.48 mg/kg cohort and at Week 2 and 4 in the 0.66 mg/kg cohort were also collected. In addition, the Day 4 samples after the doses at Week 10, 14, 18, 22 and 26, the trough samples at Months 9, 12, 15, 18, 21, and 24, and the Day 3 or 4 samples after the dose at Month 30 and 36 were also collected. Antibodies to somatrogon were tested at Visit 1 (Baseline), Visit 10 (Week 26, the end of Period I) and Visit 12 (Month 12, the end of Period II), every 6 months in open-label extension study.

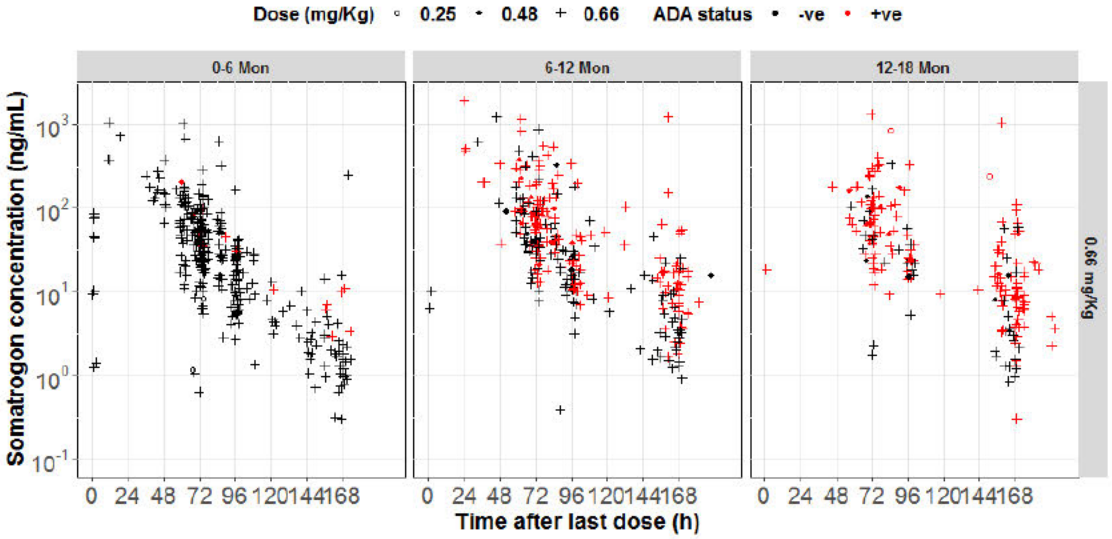
Source: Reviewer's summary of data supplied by the Applicant.
Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; rhGH, recombinant human growth hormone

Figure 36. Somatrogon Concentration-Time Profile After Last Dose in the Different Epochs of Treatment for Patients With and Without ADA in the Pediatric Phase 2 Study



Source: Reviewer's independent analysis.
Red points, ADA-positive; black points, ADA-negative subjects
Abbreviations: ADA, antidrug antibodies

Figure 37. Somatrogon Concentration-Time Profile After Last Dose in the Different Epochs of Treatment for Patients With and Without ADA in the Pediatric Phase 3 Study



Source: Reviewer's independent analysis.
Abbreviations: ADA, antidrug antibodies

14.3.1.4.3. Model Development

The steps below were followed in developing an alternative PopPK model.

A one-compartment (1CMT) PK model was tested using FOCE+I for SAEM + IMP methods for estimation of model parameters. Precise parameters were estimate for this model expect for variance of KA. Residual errors were described by combined plus proportional residual error model.

A two-compartment (2CMT) model was subsequently tested using SAEM + IMP method for estimation of model parameters. Based on likelihood ratio test, the 2CMT model provided a better model fit (OFV=12853) compared to 1CMT model (OFV=13246). Parameters were precisely estimated except for V2. This model was adopted for covariate model building. Residual errors were described by a proportional error model.

Residual error modeling was used to determine the best residual error model. Time varying residual error model (Time varying RUV) and model with interindividual variability of residuals (IIV on RUV) were better candidates for proportional residual error model. The IIV on RUV was eventually adopted in the final model.

We also tested a modeling strategy where observed and predicted data are transformed to normality using box-cox transformation (data transform both sides). This improved the model fit (OFV=12243 versus OFV=12853 for 2CMT).

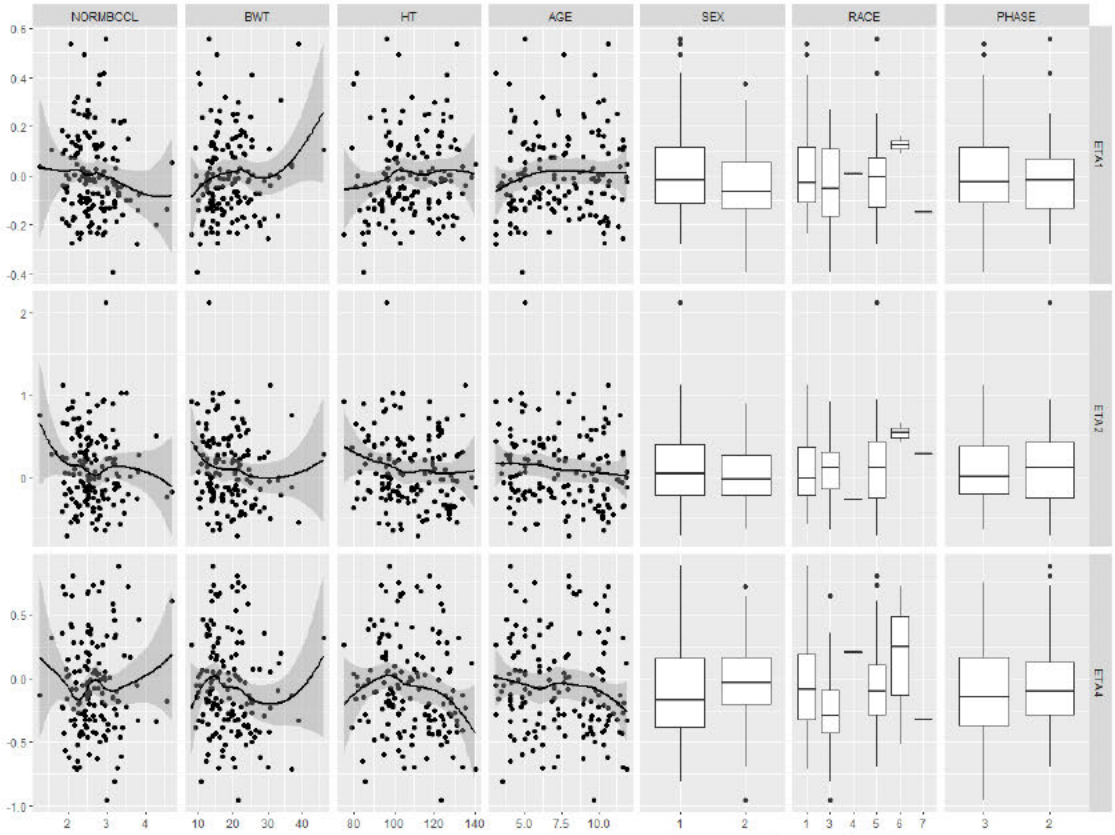
Body weight was tested as a time varying covariate on structural model parameters (Clearance and volume). Three covariate models were tested: (i) Fixed allometry, where clearance and volume parameters were scaled by the ratio of individual's weight to 70 kg raised to fixed exponents of 0.75 for clearance or 1 for volume parameters $\left(\frac{WT}{70}\right)^{0.75 \text{ or } 1}$; (ii) Estimated allometry, where clearance and volume parameters were scaled by the ratio of individual's weight to median body weight raised to estimated exponents $\left(\frac{WT}{median(WT)}\right)^{\theta}$; and (iii) Weight-normalized, where clearance and volume parameters were scaled by the ratio of individual's weight to median weight $\left(\frac{WT}{median(WT)}\right)$. The model with estimated allometry provide better fit (OFV=12174) compared to fixed allometry (OFV=12186) and weight-normalized (OFV=12196) models. The allometry exponent for clearance was estimated to be 1.02 and was therefore fixed to this value in the subsequent models.

ADA status was also tested as time varying covariate on clearance. ADA status as covariate on CL improved model fit (OFV=12094 versus OFV=12174 for Estimated-allometry model)

ADA titer values were also tested as time varying covariate on clearance. This improved model fit (OFV=12015 versus OFV=12094 for ADA-status model)

Graphical exploration parameter-covariate relationships were performed to identify any additional covariates. Figure 38 shows that among the assessed covariates (Weight-normalized baseline Creatinine-Clearance (NORMBCCL), baseline weight (BWT), height (HT), baseline Age (AGE), sex, race, and study phase (PHASE)), none indicated relationship with ETA for clearance (ETA1) nor ETA for volume (ETA2). No relationship with IIV on RUV (ETA4) was found.

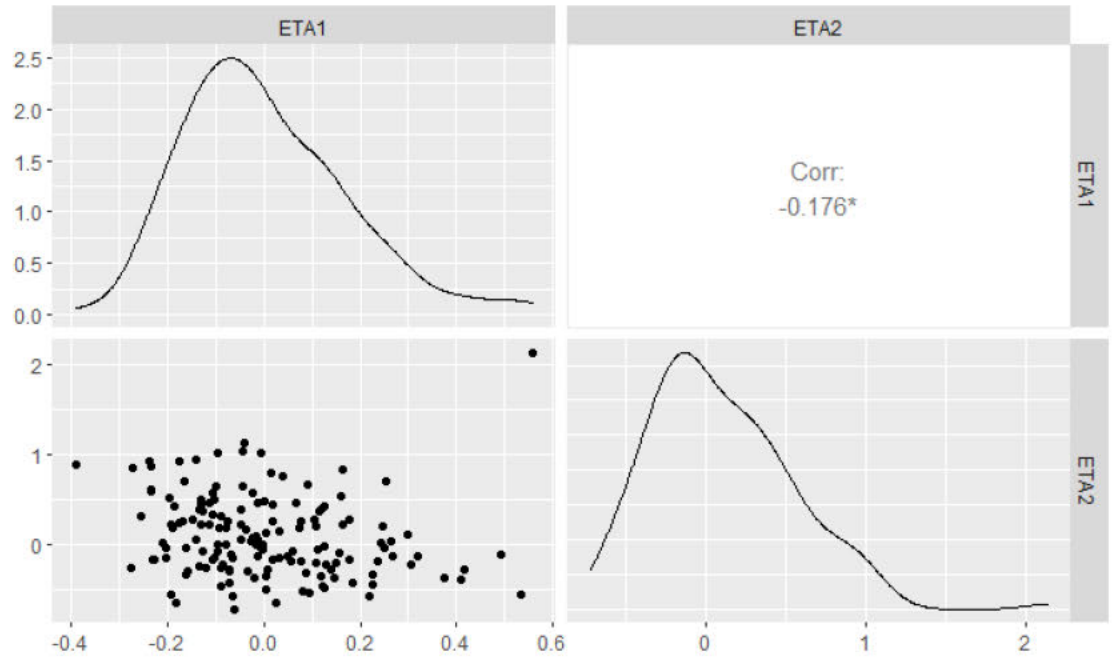
Figure 38. ETA Versus Covariate Plots for the Penultimate Covariate Model



Source: Reviewer's independent analysis.

Graphical exploration of ETA versus ETA plots (Figure 39) revealed correlation between variance of CL and variance of V2. Covariance between ETA1 and ETA2 improved model fit ($\Delta OFV = 15$) but the model conditional number increased (12000) and the covariance was unidentifiable with variance of CL (coefficient of correlation, 0.91). This model was not adopted.

Figure 39. ETA Versus ETA Plot



Source: Reviewer's independent analysis.

14.3.1.4.4. Final Model

The final model included time varying weight and ADA titer values as the only covariates. Parameter estimates of the final model are given in Table 81. Eta shrinkage of ETA for CL, V_2, and PROP were 26.1%, 35.1%, and 15.8%, respectively. Goodness-of-fit plots for the final model are given in Figure 40. The final model conditional number was 24.8 and no model parameter estimates had large correlation (i.e., coefficient of correlation >0.9).

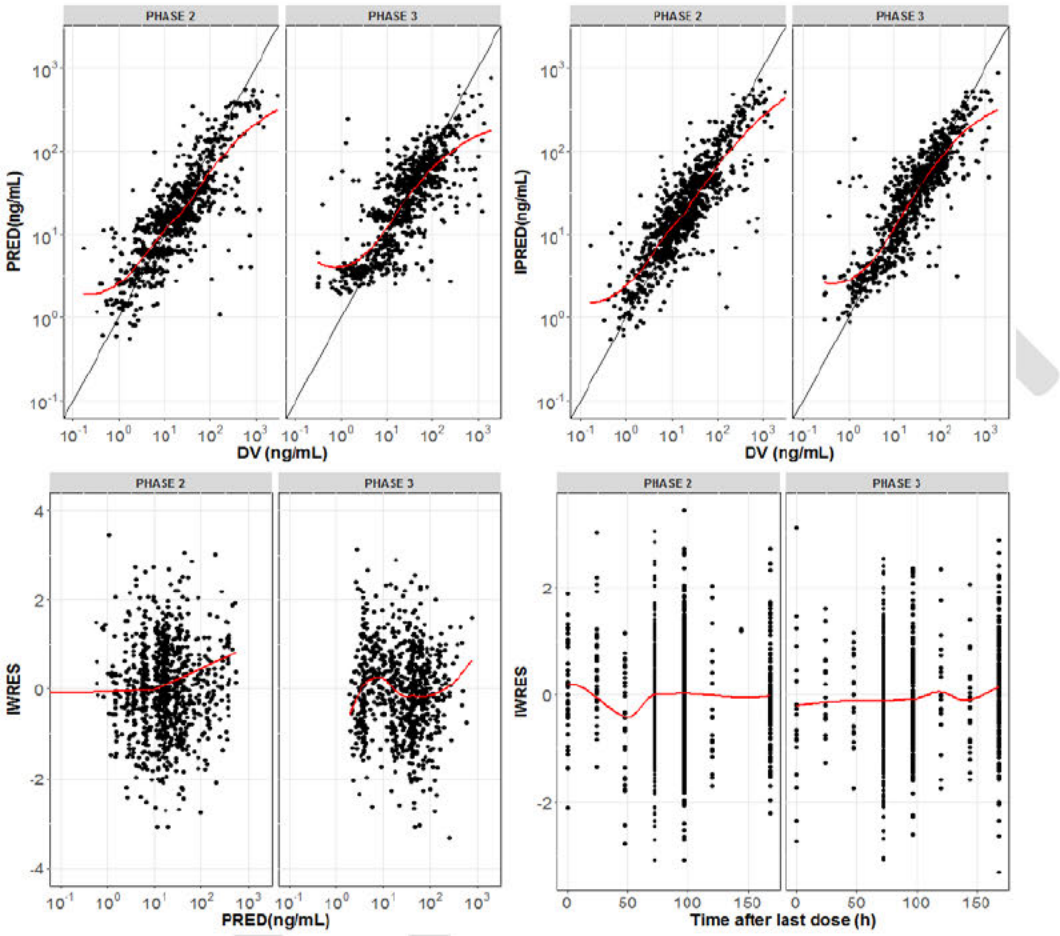
Table 81. Parameter Estimates of the Reviewer's Final PopPK Model

Parameter	Description	Estimate (RSE)
OFV	Objective function value	11697.889
CL	Clearance (L/h/17 kg)	0.5888 (5%)
V_2	Volume of central compartment (L/17 kg)	3.923 (17%)
Q	Intercompartment clearance (L/h/17 kg)	0.0205 (9%)
V_3	Volume of peripheral compartment (L/17 kg)	8.735 (31%)
K_a	Absorption rate constant (/h)	0.0475 (4%)
PROP	Proportional residual error	0.725 (6%)
WTCL	Allometric exponent for scaling CL by time varying weight	1.02 (FIXED)
WTV	Allometric exponent for scaling V_2 by time varying weight	1.621 (9%)
T50CL	Percent decrease in CL for subjects with titer of ×50 dilution factor	-0.2315 (15%)
T250CL	Percent decrease in CL for subjects with titer of ×250 dilution factor	-0.3462 (9%)
T1250CL	Percent decrease in CL for subjects with titer of ×1250 dilution factor	-0.5847 (6%)

Parameter	Description	Estimate (RSE)
T6250CL	Percent decrease in CL for subjects with titer >×6250 dilution factor	-0.6621 (12%)
ECL	Between-subject variability for CL	0.2206 (11%)
EV2	Between-subject variability for V_2	0.6754 (16%)
EKA	Between-subject variability for K_a	0 (fixed)
EPROP	Between-subject variability for PROP	0.4225 (8%)

Source: Reviewer's independent analysis.
Abbreviations: PopPK, population pharmacokinetics; RSE, relative standard error

Figure 40. GOF Plots



Source: Reviewer's independent analysis.
Abbreviations: GOF, goodness-of-fit

14.3.1.4.5. Model-Predicted PK parameters

The reviewer's final PopPK model parameters were used to derive individual PK parameters (at baseline body weight) which were subsequently used to simulate somatrogon concentration-time profile at steady state (assuming no change in body weight). The profiles were analyzed to obtain AUC and C_{max} at steady state. Table 82 summarizes central tendency and ranges of the selected PK parameters at steady state.

Table 82. Summary Statistics of Model-Predicted Individual PK Parameters

Parameter	Mean (SD)	Median	Min-Max
CL/F (L/h)	0.669 (0.299)	0.613	0.215-2.339
VC/F (L)	5.834 (4.715)	4.346	1.202-31.411
Q/F (L/h)	0.023 (0.008)	0.021	0.01-0.057
VP (L)	10.891 (6.594)	9.155	2.575-43.994
K_a (/h)	0.048 (0)	0.048	0.048-0.048
Alpha half-life (h)	5.777 (3.283)	4.721	1.581-20.358
Beta half-life (h)	320.226 (66.746)	311.445	196.564-554.995
Accumulation factor	1.022 (0.004)	1.021	1.011-1.033
Effective half-life (h)	30.084 (1.532)	30.003	25.733-33.95
AUC_{ss} (h·mg/L)	19.25 (3.175)	19.405	10.955-28.476
C_{max} (mg/L)	0.5 (0.089)	0.504	0.168-0.766
T_{max} (h)	12.219 (3.75)	11.000	6-25

Source: Reviewer's independent analysis.
Abbreviations: AUC_{ss}, area under the curve at steady-state; CL/F, clearance after oral administration; C_{max}, maximum concentration; K_a, absorption rate constant; max, maximum; min, minimum; PK, pharmacokinetics; Q/F, apparent intercompartmental clearance; SD, standard abbreviation; T_{max}, time to maximum concentration; VC/F, apparent volume of distr bution for central compartment; VP, apparent volume of distribution for peripheral compartment

In addition, the reviewer's final PopPK model parameters were used to derive individual PK parameters before and after turning ADA positive. The derived PK parameters were subsequently used to simulate somatrogon concentration-time profile after single dose and steady state. The profiles were analyzed to obtain AUC and C_{max} at steady state.

Table 40 summarizes central tendency and ranges of the selected PK parameters at steady state for all subjects before turning ADA positive and Table 83 summarizes the PK parameters at steady state for subjects who became ADA positive.

Table 83. Summary Statistics of Model-Predicted Individual PK Parameters for All Subjects in the Phase 2 and Phase 3 Studies Before Turning ADA-Positive

Parameter	ADA	Mean (SD)	Median	Min-Max
CL/F (L/h)	-	0.784 (0.337)	0.722	0.27-2.744
VC/F (L)	-	7.547 (5.848)	6.070	1.377-41.985
Q/F (L/h)	-	0.027 (0.009)	0.025	0.01-0.056
VP (L)	-	13.921 (7.732)	12.208	3.005-43.07
K_a (/h)	-	0.048 (0)	0.048	0.048-0.048
Alpha half-life (h)	-	6.386 (3.692)	5.293	1.663-22.67
Beta half-life (h)	-	351.954 (69.893)	346.664	205.219-550.646
Accumulation factor	-	1.023 (0.004)	1.023	1.012-1.035
Effective half-life (h)	-	30.531 (1.535)	30.674	26.241-34.338
AUC_{ss} (h·mg/L)	-	19.208 (3.122)	19.408	10.919-28.363
C_{max} (mg/L)	-	0.483 (0.088)	0.484	0.159-0.741
T_{max} (h)	-	12.954 (3.949)	12.000	6-26

Source: Reviewer's independent analysis.
Abbreviations: ADA, antidrug antibodies; AUC_{ss}, area under the curve at steady-state; CL/F, clearance after oral administration; C_{max}, maximum concentration; K_a, absorption rate constant; max, maximum; min, minimum; PK, pharmacokinetics; Q/F, apparent intercompartmental clearance; SD, standard abbreviation; T_{max}, time to maximum concentration; VC/F, apparent volume of distribution for central compartment; VP, apparent volume of distr bution for peripheral compartment

Table 84. Summary Statistics of Model-Predicted Individual PK Parameters for Subjects in the Phase 2 and Phase 3 Studies After Turning ADA-Positive

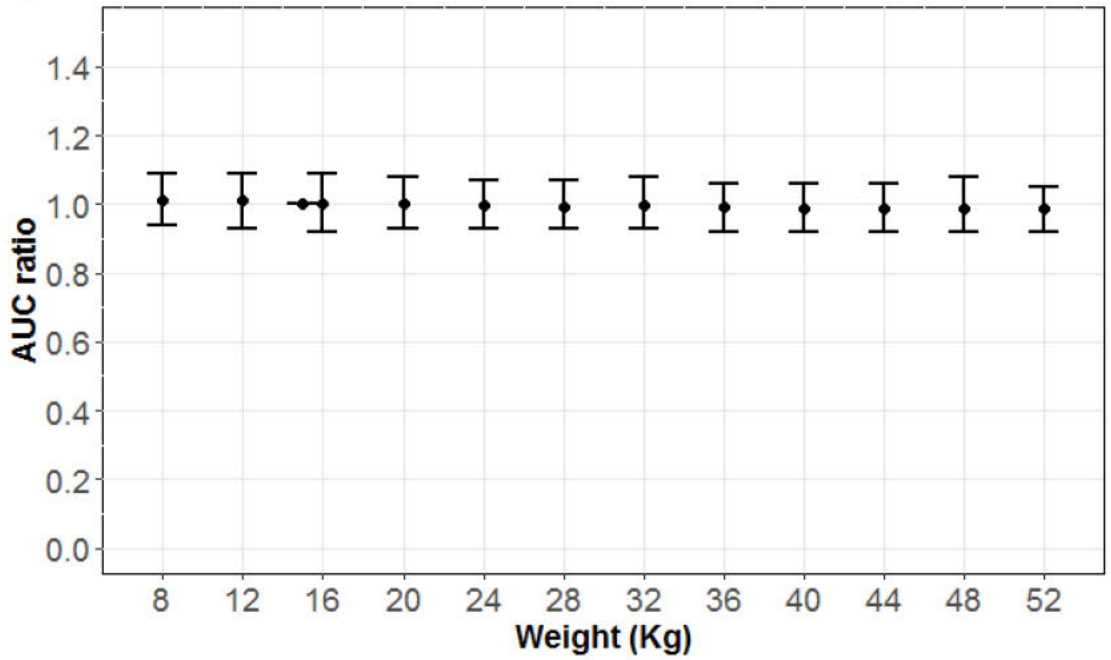
Parameter	ADA	Mean (SD)	Median	Min-Max
CL/F (L/h)	+	0.582 (0.309)	0.552	0.115-1.542
VC/F (L)	+	8.31 (7.748)	6.058	1.478-48.29
Q/F (L/h)	+	0.028 (0.01)	0.026	0.012-0.063
VP (L)	+	14.953 (8.505)	12.829	3.697-51.819
K_a (/h)	+	0.048 (0)	0.048	0.048-0.048
Alpha half-life (h)	+	10.554 (8.696)	6.959	1.707-43.809
Beta half-life (h)	+	369.052 (74.785)	359.974	221.595-595.33
Accumulation factor	+	1.038 (0.019)	1.033	1.012-1.1
Effective half-life (h)	+	34.733 (4.873)	33.736	26.36-48.654
AUC_{ss} (h·mg/L)	+	31.162 (14.498)	26.808	12.504-73.647
C_{max} (mg/L)	+	0.628 (0.184)	0.611	0.171-1.212
T_{max} (h)	+	16.256 (6.214)	14.000	6-33

Source: Reviewer's independent analysis.
Abbreviations: ADA, antidrug antibodies; AUC_{ss}, area under the curve at steady-state; CL/F, clearance after oral administration; C_{max}, maximum concentration; K_a, absorption rate constant; max, maximum; min, minimum; PK, pharmacokinetics; Q/F, apparent intercompartmental clearance; SD, standard abbreviation; T_{max}, time to maximum concentration; VC/F, apparent volume of distribution for central compartment; VP, apparent volume of distribution for peripheral compartment

14.3.1.4.6. Effect of Body Weight on Somatrogon Exposure

The effect of body weight on somatrogon exposure was evaluated through Monte Carlo simulation using the reviewer's final PopPK model. The model had time varying body weight and ADA-titer as the only covariates. Therefore, a virtual sample of pediatric population with uniformly distributed body weight ranging from 8 to 52 kg and with ADA negative status (i.e., ADA titer 0) was created. Stochastic simulation was used to obtain concentrations over the dosing interval at steady state. Noncompartmental analysis was used to obtain predicted AUC. The virtual sample consisted of 1000 subjects on which 200 stochastic simulations were performed. For each simulation, the ratio of mean AUC at each weight to mean AUC at 15 kg was calculated. The median and 95% prediction intervals of these ratios are shown in Figure 41. The figure shows that weight-based dosing provides comparable exposures across body weights despite weight-dependent increase in clearance.

Figure 41. Distribution of AUC Ratios at Different Body Weights to Body Weight of 15 kg



Source: Reviewer's independent analysis.
Abbreviations: AUC, area under the curve

14.3.1.4.7. Impact of Dosing Delay or Dosing Advance on Somatrogon Exposure

The impact of change of day of dosing was evaluated using two dosing scenarios. In the first scenario patients continued to take somatrogon at their usual dosing day of the week. In the second scenario the patients continued to take somatrogon at the new dosing day of the week. Results of these evaluations are given in the two subsections below.

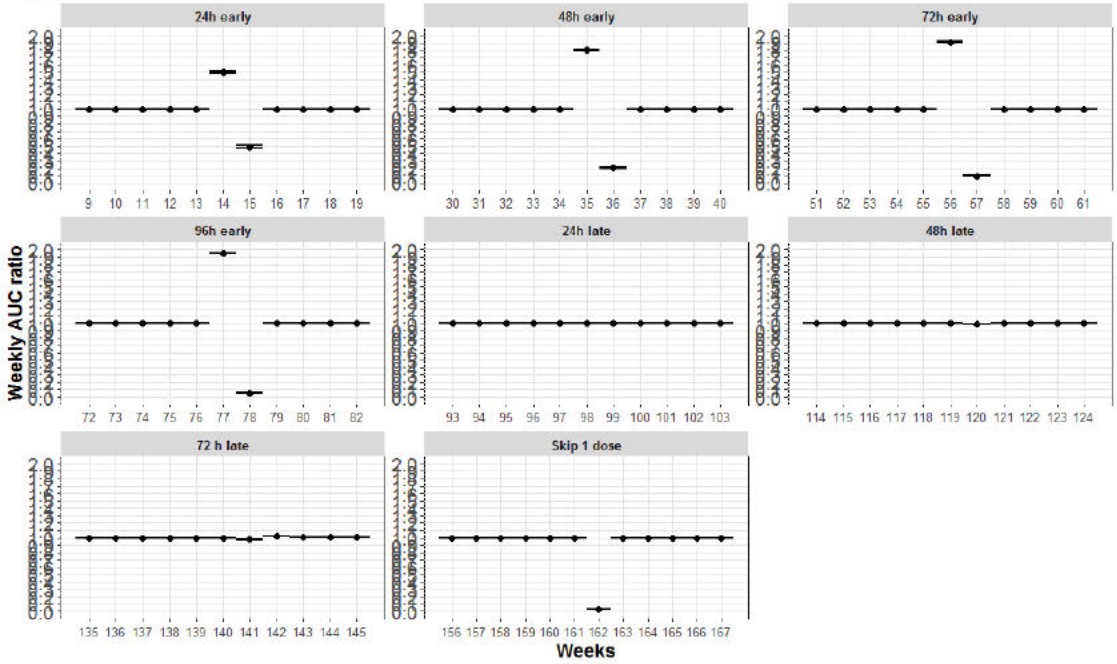
Subjects Return to Their Usual Dosing Day of the Week

The effect of earlier or later dosing of somatrogon on weekly exposure (AUC and C_{max}) was evaluated through stochastic simulations. A virtual population sample (n=200) with weight range between 8 to 46 kg was created by bootstrap resampling of subjects from phase 2 and 3 PKPD dataset. The following dosing design was followed for each virtual subject: Each subject received somatrogon once every 168 hours except at weeks 14, 35, 56, and 77 when the subjects took somatrogon after 144, 120, 96, and 72 hours since the last dose, respectively, and except at weeks 99, 119, 141, and 162 when somatrogon was delayed by 24, 48, and 72 hours and skipped one dose, respectively. At each change scenario, the simulation system was reset to zero for pharmacokinetic compartments and to baseline IGF-1 for the PD compartment. Subjects continued to take somatrogon at their usual dosing-day of the week. The final somatrogon population PKPD model was used to simulate somatrogon and IGF-1 concentration time profiles for 146 weeks. The dosing during the prior 5 weeks before dose-time change was assumed to be at steady state.

The simulated profiles were analyzed in two ways. In the first analysis, weekly AUCs during the prior 5 weeks before dose-time change were the reference AUCs for each subject. Weekly AUC at other weeks were compared to reference AUC (Week 1 of prior 5 weeks) by calculating weekly AUC ratios. For earlier than usual doses, the AUCs account for two doses given within a

span of 168 hours while for late doses the AUCs only account for one dose within the span of 168 hours. Figure 42 shows the results of this analysis. In brief, weekly AUC ratio increased by 1.5-, 1.8-, 1.9-, and 1.95-fold for doses taken 24, 48, 72, and 96 hours earlier, respectively. Late dosing did not affect weekly AUCs, but skipping a dose resulted in an AUC ratio close to zero.

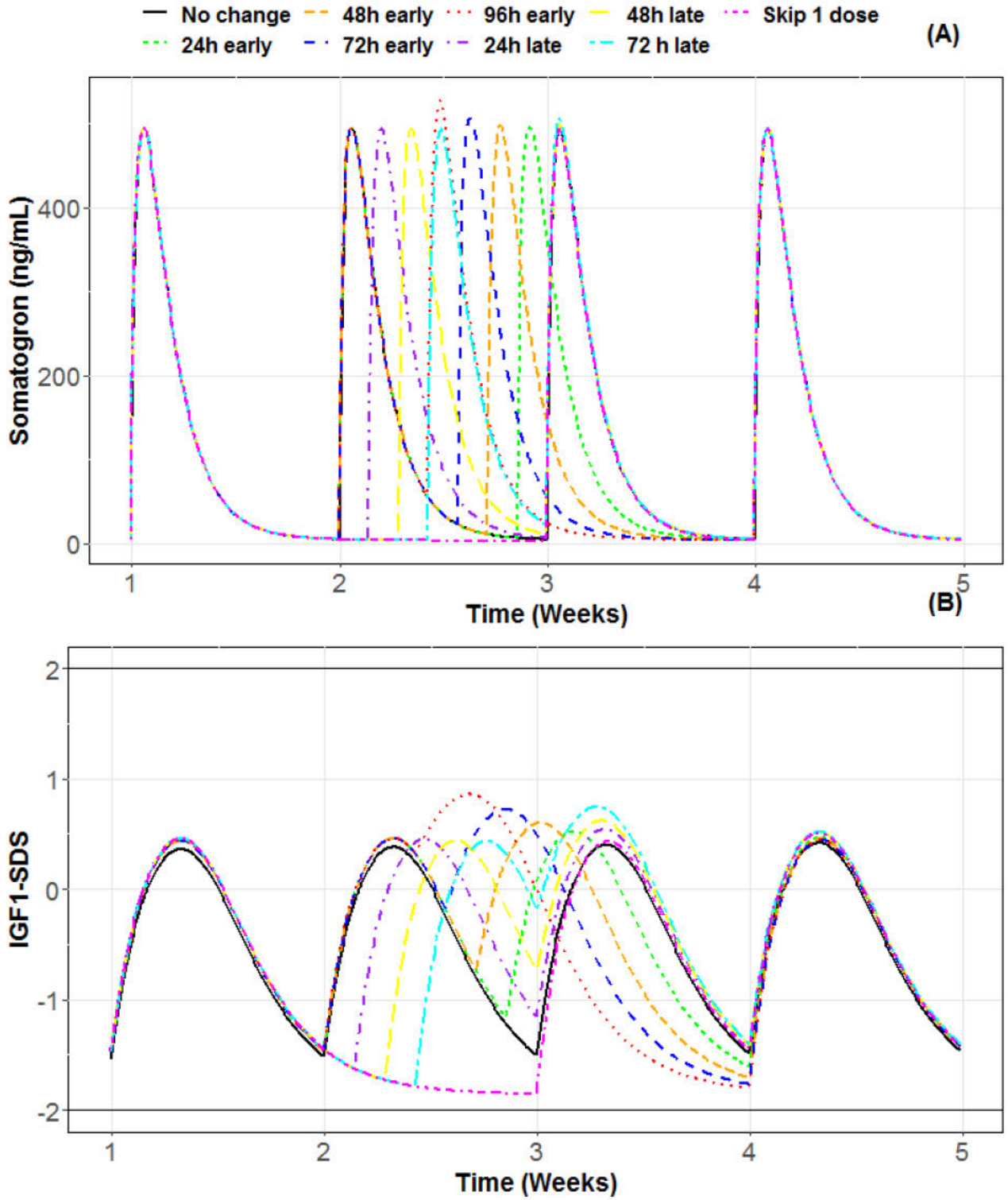
Figure 42. Weekly AUC Ratios at Each Week Since the First Dose



Source: Reviewer's independent analysis.
Abbreviations: AUC, area under the curve

In the second analysis, mean somatrogon and IGF-1 SDS (standard deviation scores) profiles after dose-time change were plotted to observe the impact of dose-time change on the mean of the maximum and the trough concentrations. As shown in Figure 43 advance dosing of up to 4 days have no impact of somatrogon maximum concentrations and IGF-1 SDS. Therefore, although earlier dosing by 96 hours could results in almost 2-fold increase in weekly AUC ratios, the resulting IGF-1 SDS does not exceed the safety threshold of 2.

Figure 43. Somatrogon and IGF-1 SDS Profiles Showing the Impact of Dose-Time Change on Steady State Maximum and Minimum Concentrations



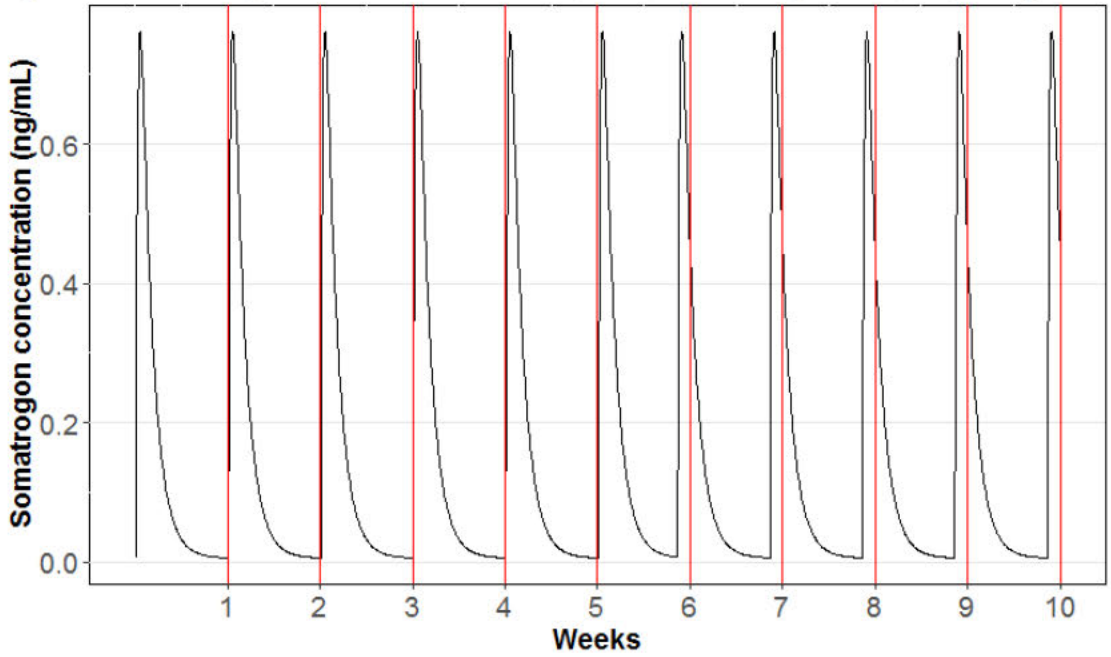
Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

Subjects Continue With the New Dosing Day of the Week

In another analysis, the subjects received somatrogon once every 168 hours except at weeks 6, 17, and 28 when the subjects took somatrogon after 144, 120, and 96 hours since the last dose respectively and also except at weeks 39, 50, and 61 when somatrogon was delayed by 1, 2, and 3 days respectively. The system was not reset after dose-time change. The subjects did not resume their usual dosing schedule but received subsequent doses every 168 hours since the last dose.

The simulated profiles were analyzed by calculating cumulative AUCs since a week of dose-time change up to 5 weeks later. Example, in the first 5 weeks, 5 cumulative AUCs were calculated, i.e., Week1 AUC, Week 1-2 AUC, Week 1-3 AUC, Week 1-4 AUC, and Week 1-5 AUC. Similarly, after dose-time change at week 6, 5 cumulative AUCs were calculated, i.e., Week5-6 AUC, Week 5-7 AUC, Week 5-8 AUC, Week 5-9 AUC, and Week 5-10 AUC. Figure 44 shows time interval used for calculations of cumulative AUC in the first and second five weeks epochs. Similar calculations of cumulative AUC were done after weeks 17, 28, 39, 50, and 61.

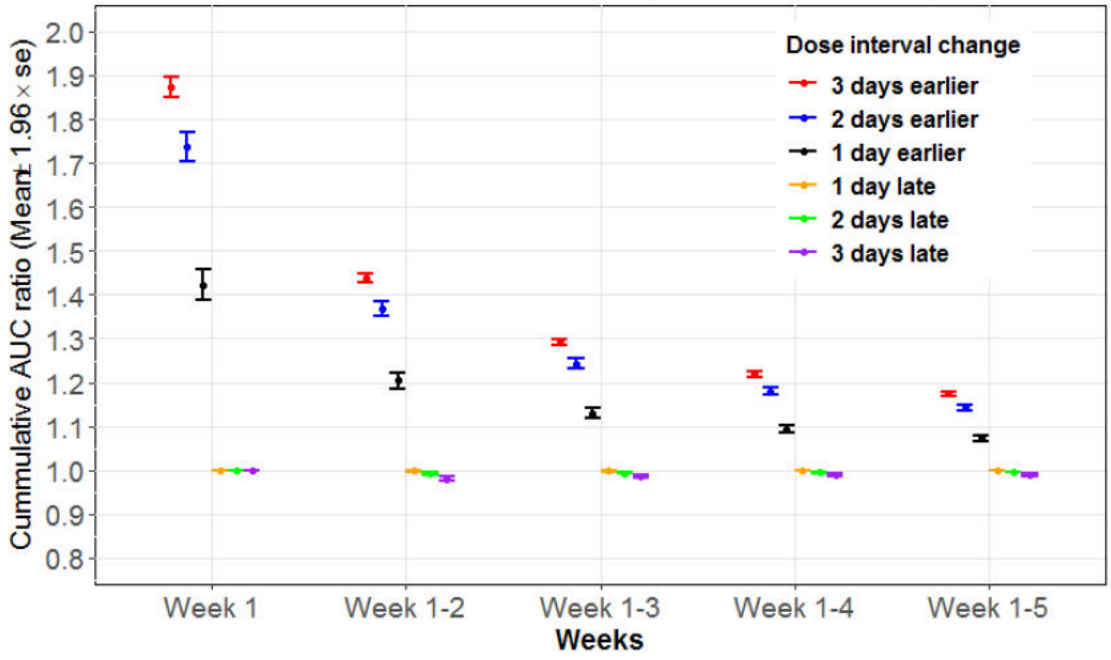
Figure 44. Somatrogon Profiles in the First 10 Weeks of Dosing in a Selected Subject



Source: Reviewer's independent analysis.
The red vertical lines demarcate weekly intervals for calculations of cumulative AUC. Note that the interval between Week 5-6 has two dosing episodes.

Cumulative AUC ratios were calculated by dividing cumulative AUCs in each epoch with corresponding cumulative AUC in the first epoch (first 5 weeks). Figure 45 shows the cumulative AUC ratios in different weeks after change in dose interval stratified by magnitude of deviation. In brief, taking somatrogon 3 days earlier elevates cumulative exposures by 90%, 45%, and 30% at Weeks 1, 2, and 3 after interval change, whereas taking somatrogon 2 days earlier elevates cumulative exposures by 80%, 40%, and 25% and taking somatrogon 1 day earlier elevates the cumulative exposures by about 50%, 25% and 15% at Week 1, 2, and 3 after interval. Delay in dosing is associated with less than 5% change in cumulative exposure even at as much as 3 days delay.

Figure 45. Cumulative AUC Ratios After Stratified by Dose-Interval Changes



Source: Reviewer's independent analysis.
Abbreviations: AUC, area under the curve

14.3.1.4.8. Reviewer's Conclusion

Based on reviewer's final model, somatrogon pharmacokinetics is described by a 2-compartment pharmacokinetic model with first order absorption and no lag-time of absorption from the administration compartment. Somatrogon clearance increases linearly with body weight and decreases as ADA titer increases. Between subject variabilities of clearance (22%) and volume of distribution (67.5%) are medium and large respectively. Goodness of fit plots of the model indicate adequate description of the data and therefore the model is acceptable for exposure-versus-efficacy analyses.

14.3.2. Exposure-Versus-IGF-1 Response

14.3.2.1. Reviewer Summary

- *Using the weight-normalized PopPK model and IGF-1 data the Applicant developed 2 population PKPD models which differ in covariate-parameter relationships. The PKPD models were indirect E_{max} models in which somatrogon plasma concentration stimulated production of IGF-1. In both models, baseline IGF-1 were not used for modeling, but a population average value of baseline IGF-1 was estimated. In the Applicant's first model, age and BMI were covariates for baseline IGF-1. In the Applicant's second model, age was a covariate on baseline IGF-1 and BMI was a covariate on E_{MAX}. Both models assumed no unexplainable between-subject variability (BSV) for baseline IGF-1.*
- *Despite adequate fit of the Applicant models to the observed IGF-1 data, the reviewer determined that the somatrogon PKPD model could be improved to better characterize factors influencing between subject variability in IGF-1 profiles. The Applicant's models could be improved in two ways: Firstly, the reviewer's alternative PopPK model should be used for PKPD modeling as it best characterizes factors*

influencing PK variabilities. Secondly, in both Applicant's models the estimates for baseline IGF1-1 do not represent the true distribution of the observed baseline IGF-1.

- *The reviewer developed an alternative population PKPD model which, like the Applicant's models, was an indirect E_{max} model with somatrogon concentration as the driver of response through stimulation of IGF-1 production. However, in contrast to the Applicant's models, baseline IGF-1 at initiation of treatment was not estimated but fixed to observed values. Furthermore, in the alternative model, baseline IGF-1 could increase linearly as a function of time on treatment. The only identified covariates were sex and baseline IGF1 on E_{max}.*
- *Assessment of impact of patients' characteristics on IGF-1 profiles overtime revealed that ADA positive patients had higher probability of IGF-1 SDS $\geq$ 2 than ADA negative patients. However, there was no association between the probability of IGF-1 SDS $\geq$ 2 and ADA titer levels. In addition, the analysis revealed that female compared to male subjects was associated with higher probability of IGF-1 SDS $\geq$ 2. However, the results should be interpreted with caution due to the small number of subjects assessed.*

14.3.3. Applicant's Exposure-Response Analyses

14.3.3.1. Data

The Applicant developed the PKPD model for somatrogon using IGF-1 responses observed in the phase 3 study. Table 73 provides the description of the phase 3 study, including blood sampling schedules for assessment of PK and PD responses. All samples before the first dose of somatrogon were excluded from the analysis. Dosing history and individual parameter estimates from the Applicant's weight-normalized PopPK model were included in the PKPD dataset to derive plasma somatrogon concentration at the time of IGF-1 observations.

14.3.3.1.1. Base Model

The structural PKPD model was a stimulatory E_{max} model in which somatrogon stimulated IGF-1 production. Parameters of the model were: Baseline IGF-1 (BASEIGF1), to represent IGF-1 values before somatrogon treatment; decay rate of IGF-1 (KOUT); Maximal drug induced increase in EGF-1 (E_{max}); plasma concentration that yield 50% of E_{max} (EC50); and the sigmoidity factor (γ). The initial state of rate of IGF-1 production (KIN_0) was derived as the product of KOUT and Baseline IGF-1. Equation (2.1) describes the rate of change in IGF-1 levels during different states of somatrogon treatment.

$$\frac{\delta IGF_1}{\delta t} = KIN - IGF_1 \times KOUT$$

$$\begin{aligned} &Whereby: \\ KIN &= BASEIGF1 \times KOUT \quad (before\ somatrogon\ treatment) \\ KIN &= KIN_0 \times DRUGEFFECT \quad (After\ somatrogon\ treatment) \\ DRUGEFFECT &= 1 + \frac{Emax \times CP^{\gamma}}{EC50^{\gamma} + CP^{\gamma}} \\ &CP\ is\ plasma\ concentration \end{aligned} \qquad (2.1)$$

14.3.3.1.2. Covariate Model

The Applicant's covariate model building was guided by exploratory graphs of ETA versus covariates and plots of weighted residuals versus time. ETA versus covariate plots identified baseline age and BMI as a covariate to EC_{50} whereas residual plots identified age dependent increase in BASEIGF1. The identified covariate-parameter relations were added to the model one at a time in univariate analyses. After each addition graphical exploration were repeated to identify new relations. Stepwise addition of covariates was followed by stepwise deletion of covariates to achieve a final model.

14.3.3.1.3. Final Model

The Applicant selected 2 models with nearly identical objective function values as final PKPD models. Both models incorporated the effect of age on BASEIGF1. In the first model, BMI was a covariate on BASEIGF1, while in the second model BMI was a covariate on E_{max}. Table 86 shows parameter estimates from the model with BMI as a covariate on BASEIGF1. Summary statistics of individual predicted BASEIGF1 and EC_{50} based on this model are given in Table 87.

Table 85. Parameter Estimates for the Pharmacodynamic Optimal Model With Two Covariates: Baseline IGF-1 Increased With Age and BMI

Description	Estimate	Inter-individual Variability*
Decay rate ($hour^{-1}$)	0.0493103	—†
FACT2	1 + 0.13479 • (AGE‡ - 6)	—†
FACT5	1 + 0.06765 • (BMI§ - 15.2)	—†
Baseline IGF-1 (ng/mL)	10.15 • FACT2 • FACT5	—†
Emax	27.547	—†
EC_{50} (ng/mL)	56.6426	1.593
Power term	0.538326	—†

Standard errors were not obtained.

*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.

† Inter-individual variability was not permitted for this term.

‡ AGE is time-varying age in years; 6 is the median value.

§ BMI is time-varying BMI (mg/m^2); 15.2 is the median value.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 7/1938.
Abbreviations: BMI, body mass index; EC_{50}, 50% effective concentration; E_{max}, maximum effect; IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetics/pharmacodynamics

Table 86. Applicant's Final PKPD Model With Age and BMI as Covariates on BASEIGF1

Description	Estimate	Inter-individual Variability*
Decay rate (hour^{-1})	0.0493103	—†
FACT2	1 + 0.13479 • (AGE‡ - 6)	—†
FACT5	1 + 0.06765 • (BMI§ - 15.2)	—†
Baseline IGF-1 (ng/mL)	10.15 • FACT2 • FACT5	—†
Emax	27.547	—†
EC_{50} (ng/mL)	56.6426	1.593
Power term	0.538326	—†

Standard errors were not obtained.

*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.

† Inter-individual variability was not permitted for this term.

‡ AGE is time-varying age in years; 6 is the median value.

§ BMI is time-varying BMI (mg/m^2); 15.2 is the median value.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 7/1938.
Abbreviations: BMI, body mass index; EC_{50}, 50% effective concentration; E_{max}, maximum effect; IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetics/pharmacodynamics

Table 87. Post Hoc Baseline IGF-1 and IC_{50} From the Applicant's Final PKPD Model With Age and BMI as Covariates on BASEIGF1

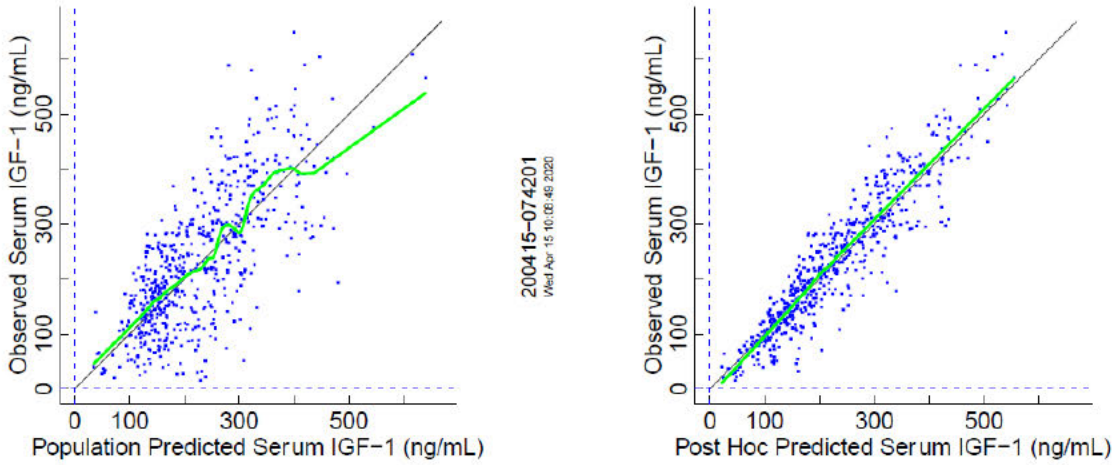
Description	Mean	Standard Deviation	Median	Minimum	Maximum
Baseline IGF-1* (ng/mL)	12.8	4.696	12.5	5.48	31.1
IC50 (ng/mL)	262.9	1081	51.7	3.361	10868

* These values do not reflect the increase in baseline IGF-1 over time.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 43/1938.
Abbreviations: BMI, body mass index; IC_{50}, 50% inhibitory concentration; IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetics/pharmacodynamics

Figure 46 shows the goodness of fit of the model with BMI as covariate on BASEIGF1.

Figure 46. Observed Versus Population Predicted (Left) or Post Hoc Predicted (Right) IGF-1 Values From the Applicant's Final PKPD Model With Age and BMI as Covariate on BASEIGF1



Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 41/1938.
Abbreviations: IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetic/pharmacodynamic; BMI, body mass index; BASEIGF1, baseline IGF-1

Table 88 shows parameter estimates from the model with BMI as covariate on E_{max}. Summary statistics of individual predicted BASEIGF1 and EC50 based on this model are given in Table 89. Figure 47 shows the goodness of fit of the model with BMI as covariate on E_{max}.

Table 88. Applicant's Final PKPD Model With BMI as a Covariate on E_{max}

Description	Estimate	Inter-individual Variability*
Decay rate (hour^{-1})	0.049638	—†
FACT2	1 + 0.13489 • (AGE‡ - 6)	—†
Baseline IGF-1 (ng/mL)	10.15 • FACT2	—†
FACT5	1 + 0. 07155 • (BMI§ - 15.2)	—†
Emax	27.5552 • FACT5	—†
EC_{50} (ng/mL)	56.6832	1.60
Power term	0.536872	—†

Standard errors were not obtained.

*Calculated as sqrt(*omega*^{2}) where *omega*^{2} is the variance of the corresponding *eta* term; 68% of the population lies within this range of the typical value.

† Inter-individual variability was not permitted for this term.

‡ AGE is time-varying age in years; 6 is the median value.

§ BMI is time-varying BMI (mg/m^2); 15.2 is the median value.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 7/1938.
Abbreviations: BMI, body mass index; EC_{50}, 50% effective concentration; E_{max}, maximum effect; IC_{50}, 50% inhibitory concentration; IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetics/pharmacodynamics

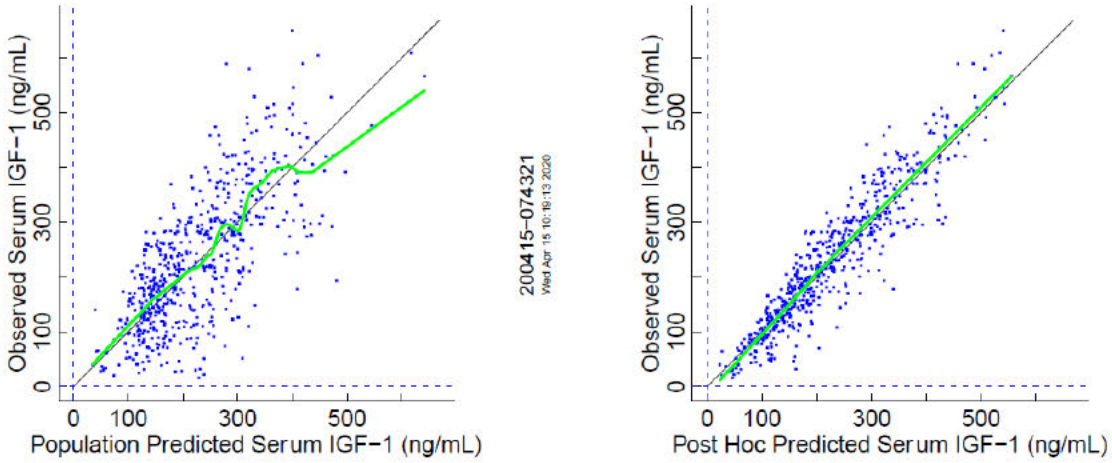
Table 89. Post Hoc Baseline IGF-1 and IC_{50} From the Applicant's Final PKPD Model With BMI as a Covariate on E_{max}

Description	Mean	Standard Deviation	Median	Minimum	Maximum
Baseline IGF-1* (ng/mL)	12.9	3.646	13	6.268	18.6
Emax	27.1	4.378	25.9	20.2	48.1
IC50 (ng/mL)	265.5	1093	51.5	3.436	10984

* These values do not reflect the increase in baseline IGF-1 over time.

Source: Population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 43/1938.
Abbreviations: BMI, body mass index; E_{max}, maximum effect; IC_{50}, 50% inhibitory concentration; IGF-1, insulin-l ke growth factor-1; PKPD, pharmacokinetics/pharmacodynamics

Figure 47. Observed Versus Population Predicted (Left) or Post Hoc Predicted (Right) IGF-1 Values From the Applicant's Final PKPD Model BMI as Covariate on E_{max}



Source: population PK and PKPD report (Report number PMAR-EQDD-C031b-DP4-1121), page 41/1938
Abbreviations: IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetic/pharmacodynamic; BMI, body mass index

– *Reviewer's Comments*

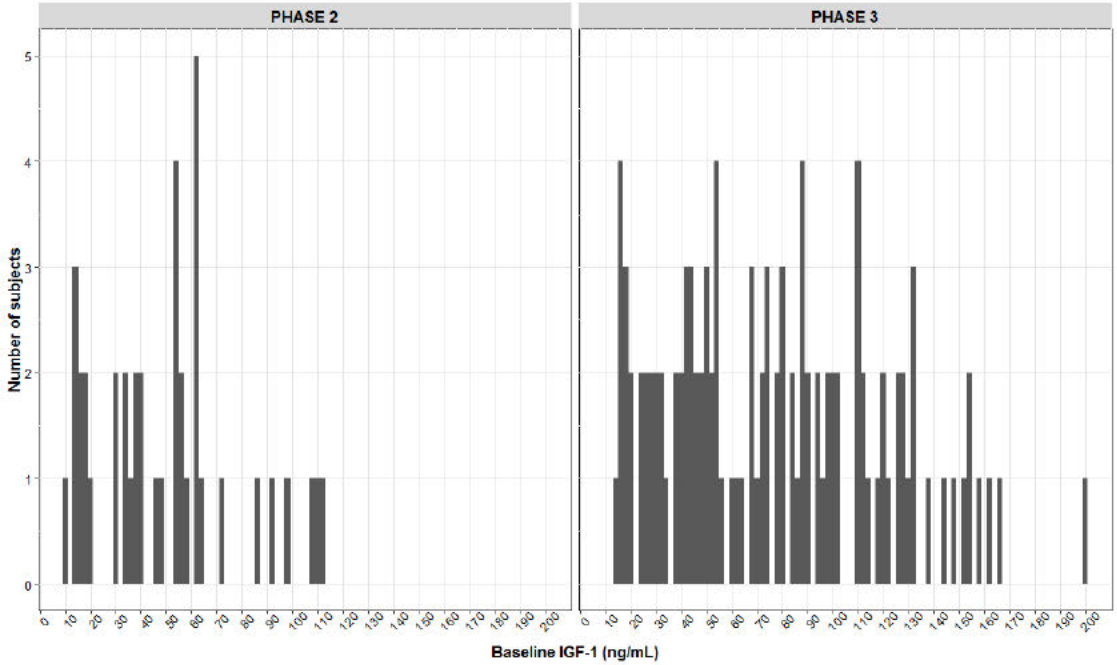
Although the goodness-of-fit plots shows a good description of the observed data, the Applicant's PKPD model could be improved in two ways. Firstly, the reviewer's PopPK model could be used to generate most optimal somatrogon concentration as driver of IGF-1 response.

Secondly, baseline IGF1 were removed from the analyses. This information could have provided relevant estimates of BASEIGF1 that are in the range of the observed baseline IGF-1 values.

- *Figure 48 shows the distribution of baseline IGF-1 in both phase 2 and phase 3 studies. Although the median of the observed baseline IGF-1 are 50 ng/mL and 77 ng/mL for phase 2 and 3 respectively, the Applicant model's estimated typical population value is 10.15 ng/mL and individual estimates ranges between 5.5 ng/mL - 31 ng/mL. This discrepancy indicates that the Applicant's modeling of baseline IGF-1 is mis-specified and may cause underprediction of IGF-1 elevation during somatrogon treatment.*

The reviewer developed an alternative model to correct these two model deficiencies.

Figure 48. Distribution of Baseline IGF-1 Among Patients in Both Phase 2 and Phase 3 Studies



Source: Reviewer's independent analysis.
Abbreviation: IGF-1, insulin-like growth factor-1

14.3.3.2. Reviewer's PKPD Model Development

14.3.3.2.1. Introduction

The deficiencies of the Applicant's final population PKPD models are described in Section I.2.2. The goals of developing an alternative PKPD model were three-fold: First, to provide an adequate description of observed IGF-1 profiles; secondly, to characterize sources of interindividual variability in IGF-1 response, and lastly, to assess the impact of ADA-titer on probability of patients achieving IGF-1 standard deviation score (IGF-1 SDS) >2.

14.3.3.2.2. Data

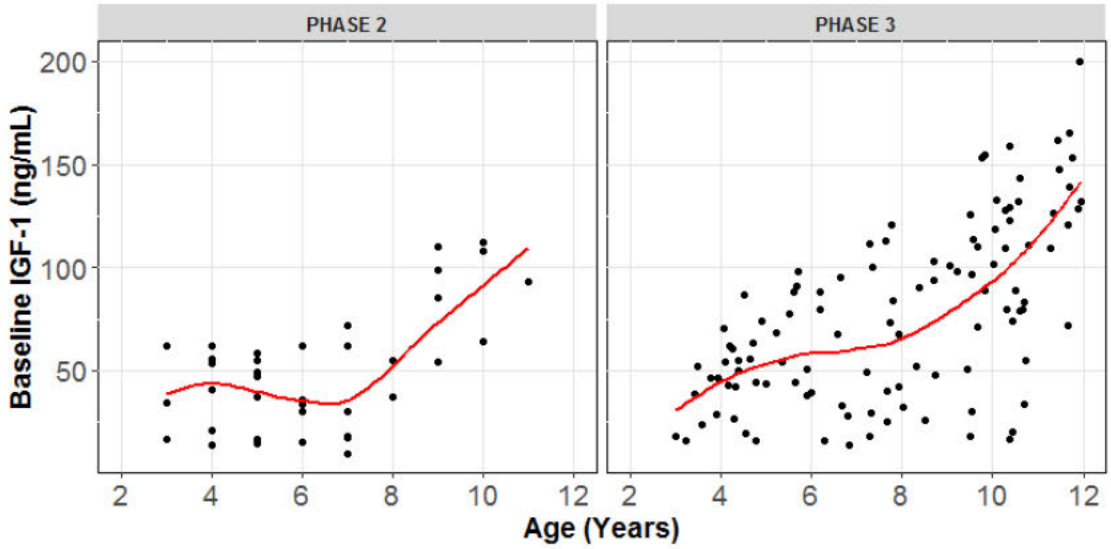
Both IGF-1 data from phase 2 and 3 studies were used for the PKPD model development. The PKPD dataset incorporated individual PK parameters derived from the reviewer's final PopPK model. Summarized descriptions of the phase 2 and 3 studies are given in Table 80 and Table 73, respectively.

14.3.3.2.3. Model Development

The following steps were followed in developing an alternative PKPD model:

- The structural model given in equation (2.1) was used as the base model. However, in contrast to the Applicant's base model, baseline IGF-1 was not estimated, instead for everyone, baseline IGF-1 was the mean of observed IGF-1 values before starting somatrogon treatment. PK fixed effects parameter estimates were fixed to estimated typical values from the PopPK model and the individual PK parameters were derived using the typical values, the time varying covariates and the empirical-bayes estimates for ETA derived from the PopPK model.
- From the base model, the plot of CWRES versus TIME showed increasing trend for CWRES overtime. This indicated that individual predictions (IPRED) plateaued while DV continued to increase overtime. The base model had to be modified for IPRED to continue to increase as DV. In the Applicant's model, baseline IGF-1 increased with age, this is supported by literature. Figure 49 shows that indeed, baseline IGF-1 increased with age in the present cohort.

Figure 49. Baseline IGF-1 Versus Age Among Patients in Both Phase 2 and Phase 3 Studies



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1

The age-dependent IGF-1 increase implies that, even without somatrogon treatment, IGF-1 would increase overtime. This phenomenon was implemented in the model as given in equation (2.2).

$$BASEIGF1_t = BASEIGF1 + TSLP \times TIME$$

$$\begin{aligned} &Whereby: \\ BASEIGF1 &= is\ mean\ of\ observed\ IGF_1\ before\ somatrogon\ treatment \\ TSLP &= is\ slope\ for\ treatment\ independent\ linear\ increase\ in\ IGF_1 \\ TIME &= time\ after\ initiation\ of\ somatrogon\ treatment \end{aligned} \qquad (2.2)$$

- Alternative approaches for handling baseline responses as recommended by Dansirikul (Dansirikul et al. 2008) were tested but did not improve model fit to the data.

- Graphical explorations of ETA versus covariates plot were used to identify potential covariates. This was repeated after each univariate addition of covariate into the model. Finally, after forward inclusion of covariates, covariances among between subject variance parameters were tested.

14.3.3.2.4. Final PKPD Model

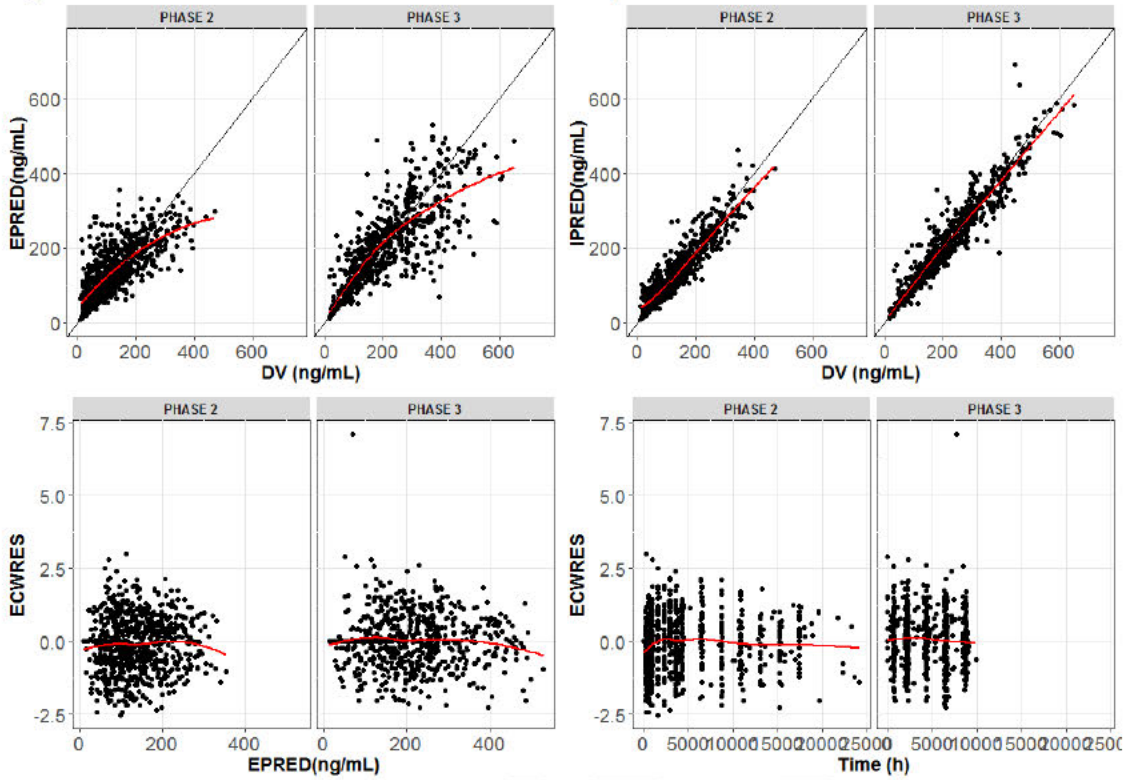
The final PKPD model included time and somatrogon dependent increase in IGF-1 overtime. Parameter estimates of the final model are given in Table 90. Eta shrinkage for E_{max}, EC50, ETSLP were 29.1 %, 25.7 %, and 36.2 %, respectively. Goodness-of-fit plots for the final model are given in Figure 50. The final model conditional number was 23.48 and no model parameter estimates had large correlation (i.e., coefficient of correlation >0.9). Sex and baseline IGF-1 were the only covariates on E_{max}. No other covariate-parameter relations were identified.

Table 90. Parameter Estimates of the Reviewer's Final Population PKPD Model

Parameter	Description	Estimate (RSE)
OFV	Objective function value	11774.851
KOUT	Rate constant of IGF-1 loss (1/h)	0.0261 (7%)
E_{MAX}	Maximum somatrogon effect	2.569 (7%)
EC_{50}	Somatrogon concentration producing half of E_{MAX} (ng/mL)	50.29 (13%)
POWER	Sigmoidity parameter	2.747 (19%)
TSLP	Slope for time-dependent IGF-1 increase	0.001797 (10%)
PROPERR	Typical (population average) proportional residual error	0.188 (5%)
SEXEMAX	Fold increase in E_{MAX} for female compared to male	1.327 (10%)
BIGFEMAX	Exponent for effect of baseline IGF-1 on E_{MAX}	-0.3377 (19%)
EEMAX	Between subject variability for E_{MAX}	0.4033 (12%)
EEMAX_cor_EEC_{50}	Correlation between EE_{MAX} and EEC_{50}	0.2876 (71%)
EEC_{50}	Between-subject variability for EC_{50}	0.9759 (11%)
ETSLP	Between-subject variability for TSLP	0.6878 (13%)
EPROP	Between-subject variability for PROPERR	0.4398 (16%)

Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; PKPD, pharmacokinetics/pharmacodynamics; RSE, relative standard error

Figure 50. GOF Plots of the Reviewer's Final Pop PKPD Model

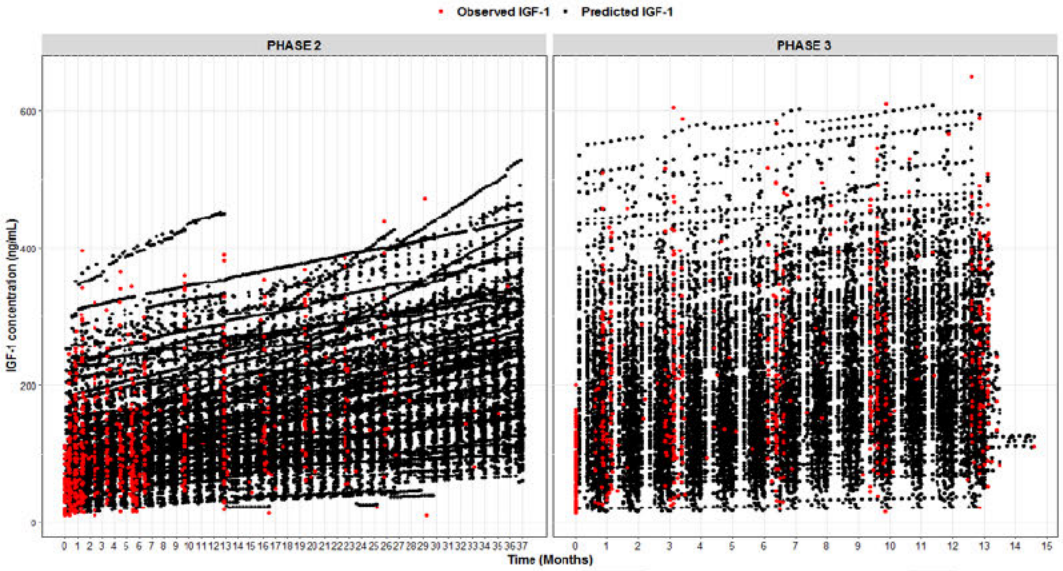


Source: Reviewer's independent analysis
Abbreviations: GOF, goodness-of-fit; Pop PKPD, population pharmacokinetic/pharmacodynamic

14.3.3.2.5. Assessment of Factors Associated With IGF-1 SDS ≥2 Over Time

Factors associated with IGF-1 SDS ≥2 were assessed using the individual predicted IGF-1 data for patients in both phase 2 and 3 studies. The good agreement between observed and predicted trough IGF-1 concentration over time (Figure 51) justifies the use of the predicted IGF-1 for assessment of factors associated with SDS ≥2.

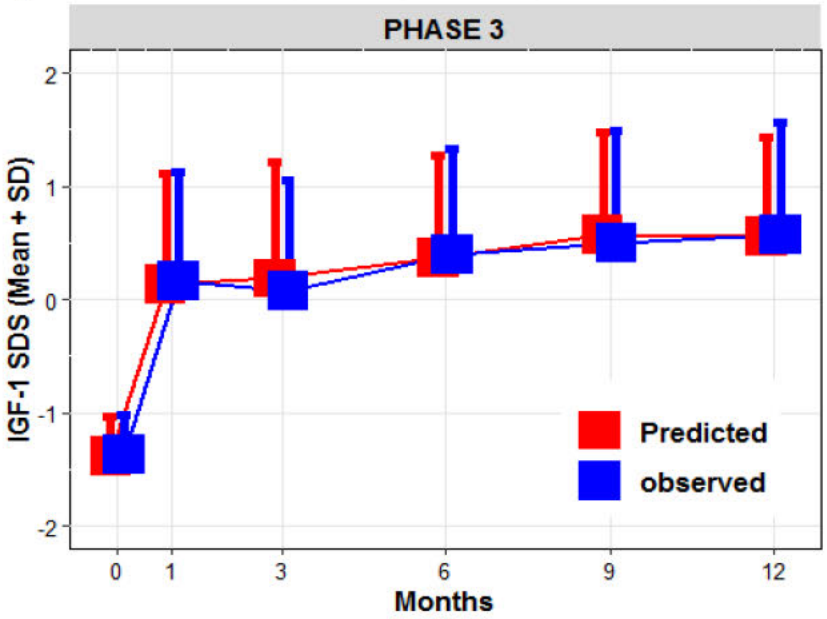
Figure 51. Observed and Predicted Trough IGF-1 Over Time in Phase 2 and 3 Studies



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1

Figure 52 compares observed versus predicted IGF1-SDS at overtime. The figure shows that the model adequately predicts IGF-1 SDS scores overtime. It can be seen from the figure that IGF-1 SDS increases rapidly within 1 month of treatment and then continue to increase gradually to Month 6 and remains stable for the rest of the treatment.

Figure 52. Observed and Predicted IGF-1 SDS Over Time in the Phase 3 Study

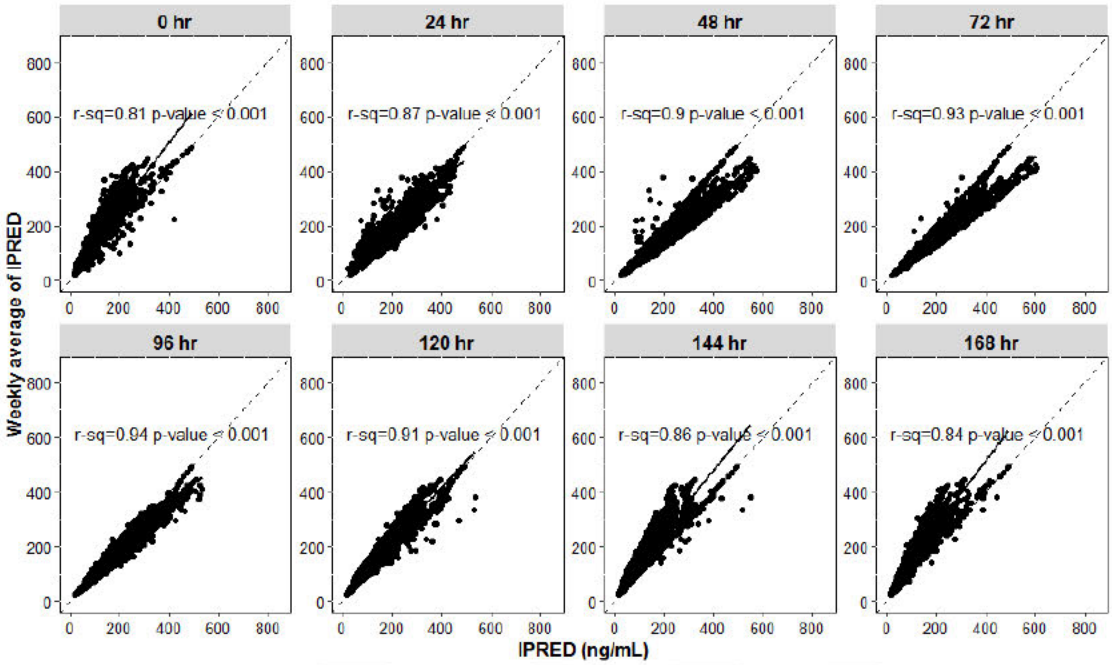


Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

As a first step in assessment of factors associated with IGF-1 SDS ≥ 2, the predicted data were used to determine the sampling time point at which IGF-1 concentration would be most correlated with the average weekly exposure. The average of the individual predicted IGF-1 at the last week of a month was calculated as: $Weekly\ average\ IGF_1 = AUC_\tau/168h$. Pearson-correlations between the individual predicted concentrations (IPRED) at different times in the

dosing-interval and the weekly average IGF-1 were estimated. As shown in Figure 53, predicted IGF-1 concentrations at 96 hours postdose (day 4) had the highest correlation (r^2=0.94) with the weekly average of IGF-1 concentration.

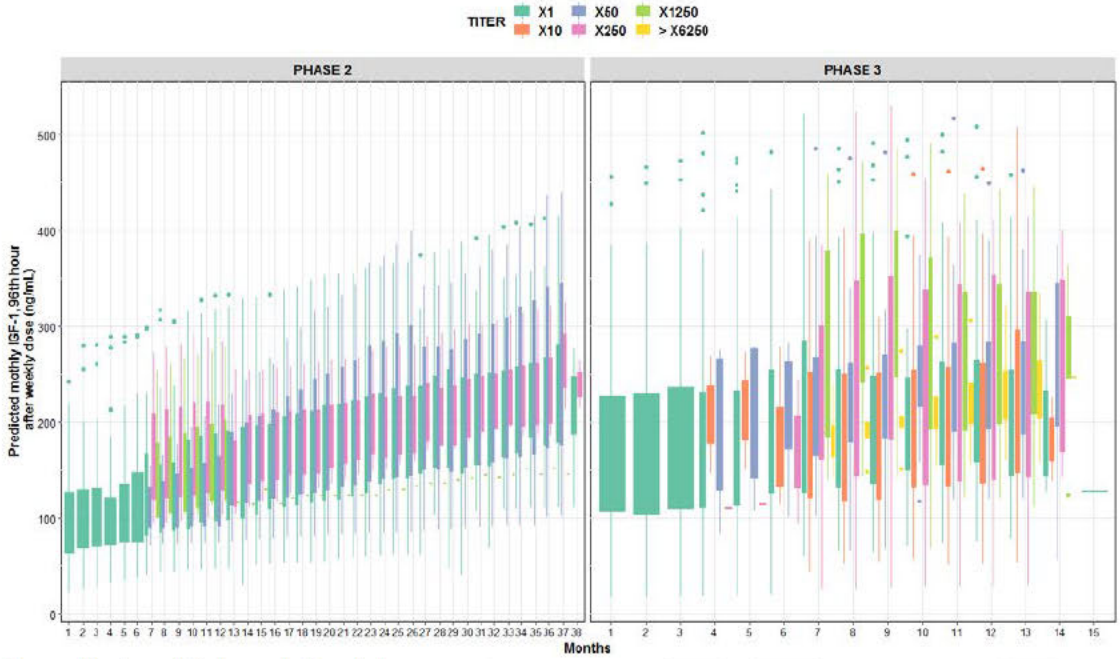
Figure 53. Individual Predicted Weekly Average IGF-1 Concentration Versus Individual Predicted Concentrations at Different Time Points



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1

Based on the correlation results, predicted IGF-1 concentrations on day 4 of the last week of a month were used to determine factors associated with IGF-1 SDS ≥ 2. Firstly, the predicted day-4 IGF-1 versus time profiles were plotted (Figure 54). As the figure shows, subjects with higher ADA-titers have correspondingly higher day-4 IGF1 over time. Although the figure shows a trend of association between ADA titer and IGF-1, this does not translate to clinically meaningful difference in proportions of subjects with IGF-1 SDS > 2 among different ADA titer values (see figure 36).

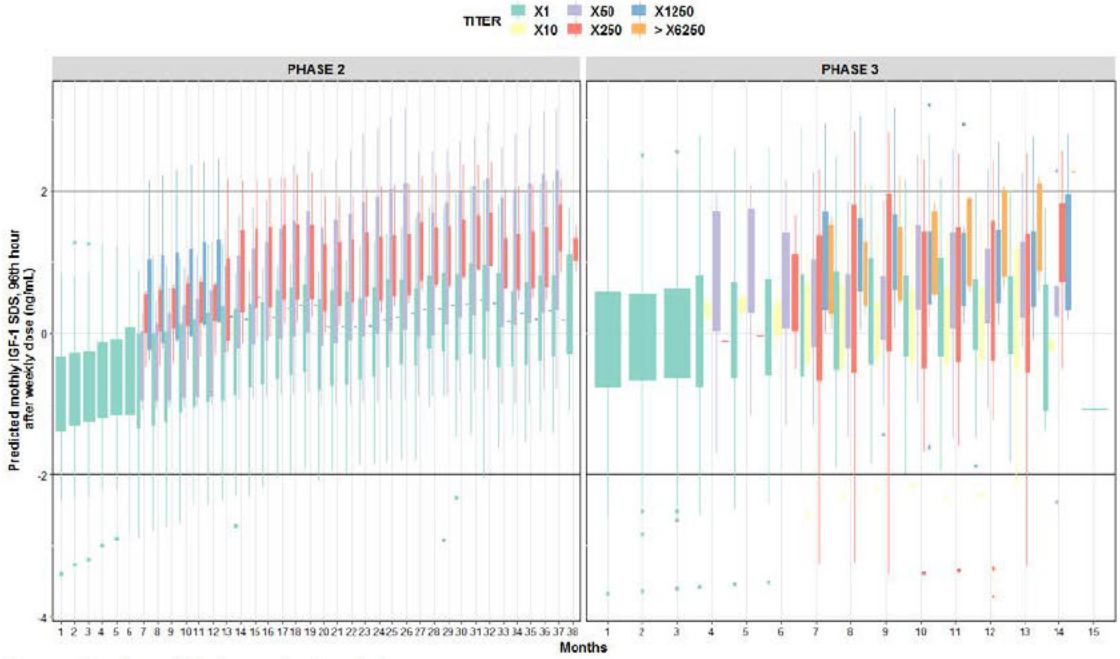
Figure 54. Predicted Day 4 IGF-1 Profiles



Source: Reviewer's independent analysis
Abbreviations: IGF-1, insulin-like growth factor-1

Secondly, predicted IGF1-SDS were calculated and plotted as shown in Figure 55.

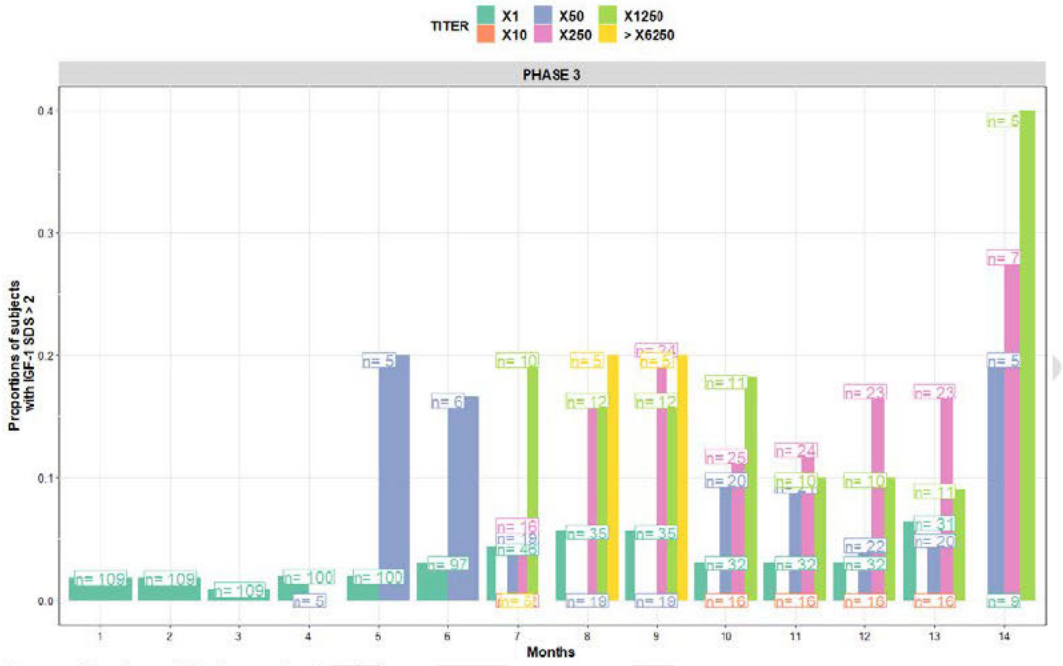
Figure 55. Predicted Day 4 IGF-1 SDS Profiles



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score

Lastly, proportions of subjects with IGF-1 SDS ≥ 2 were calculated overtime based on their ADA-titer values, sex, and baseline IGF-1. Figure 56 shows the monthly proportions of subjects with IGF-1 SDS ≥ 2 the phase 3 study. As the figure shows the proportions of subjects with IGF-SDS ≥ 2 was higher in subjects tested positive for ADA (titer ≥10) than those tested negative for ADA (titer=1). However, there does not appear to be a trend between proportion of subjects with IGF-1 SDS≥ 2 and ADA titer level in ADA positive subjects.

Figure 56. Predicted Proportions of Subjects With IGF-1 SDS ≥2 Over Time Stratified by ADA Titer. The numbers indicate the total number of subjects with a particular ADA titer at a particular time point



Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; n, number of subjects at the visit with a given titer; SDS, standard deviation score; ADA, antidrug ant bodies

Figure 57 shows the monthly proportions of subjects with IGF-1 SDS ≥ 2 the phase 3 study stratified by sex. The figure shows higher proportions with IGF-1 SDS ≥ 2 in female than among male. However, the results should be interpreted with caution due to the smaller number of subjects assessed (n = 6-8 for each ADA titer level).

Figure 57. Predicted Proportions of Subjects With IGF-1 SDS ≥2 Over Time Stratified by Sex and ADA Titer

Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score; ADA, antidrug ant bodies

Figure 58 shows the monthly proportions of subjects with IGF-1 SDS ≥ 2 the phase 3 study stratified by baseline IGF-1 concentration quartiles. The figure shows no clear relationship between baseline IGF-1 and probability of IGF-1 SDS ≥ 2. However, the results should be interpreted with caution due to the smaller number of subjects assessed after 6th month in the lowest and third quartiles of the baseline IGF-1.

Figure 58. Predicted Proportions of Subjects With IGF-1 SDS ≥2 Over Time Stratified by Baseline IGF-1 and ADA-Titer

Source: Reviewer's independent analysis.
Abbreviations: IGF-1, insulin-like growth factor-1; SDS, standard deviation score; ADA, antidrug ant bodies

14.4. Bioanalytical Methods Validation and Performance

Bioanalytical Methods for Somatrogon in Plasma

Over the duration of the somatrogon clinical development program, three bioanalytical assays were used to measure serum concentration of somatrogon. The initial somatrogon ELISA (enzyme-linked immunosorbent assay) was developed and validated at (b) (4) (b) (4) To improve assay sensitivity, an ECL (electro-chemiluminescence) assay was developed and validated by the same company. Later this ECL assay was transferred to a different company and therefore called the ECL (b) (4) assay. The ECL (b) (4) assay was established and validated at (b) (4) and is identical to the PK ECL assay validated at (b) (4) A comparability/cross validation (OX-19-512-015, (b) (4)) was successfully completed confirming the equivalency of the two methods ((b) (4) IC-P-0954 and (b) (4) BALAR 19/014).

The samples were assayed in the first study (CP-4-001) using the ELISA method validated at (b) (4) All subsequent studies used the ECL method with samples from Studies CP-4-003, CP-4-004, CP-4-005, CP-4-007 and CP-4-011 assayed at (b) (4) and the samples collected in CP-4-006 analyzed at (b) (4)

The validation parameters and performance of the two plasma vosoritide PK assays are summarized in Table 91.

Table 91. Assay Validation and Performance for Somatrogon in Human Plasma Samples

Validation Parameter	PK ELISA	PK ECL Assay (b) (4)	PK ECL Assay (b) (4)
Range of quantitation	2000 to 100,000 pg/mL	150 pg/mL to 36,000 pg/mL (Original, Addenda 1-3). 156.25 pg/mL to 40,000 pg/mL (Addenda 4-5). 1.0 ng/mL to 128 ng/mL (Addenda 6-7).	156.25 to 40,000 pg/mL
Minimum required dilution	1:10	1:5	1:5
Intraassay precision and accuracy	|%RE|: ≤24.3* (QC), ≤37* (LLOQ), ≤19.1 (ULOQ), %CV: ≤12.3 (QC), ≤14.2 (LLOQ), ≤24.2 (ULOQ).	|%RE|: ≤26.2# (QC), ≤28.3# (LLOQ), ≤17.2 (ULOQ), %CV: ≤41.2# (QC), ≤20.1 (LLOQ), ≤12.3 (ULOQ).	|%RE|: ≤5.0 across all QCs. %CV: ≤7.2 across all QCs.
Interassay precision and accuracy	|%RE|: ≤2.5 (QC),=0.9 (LLOQ), =0.8 (ULOQ), %CV: ≤11.3 (QC)=20.4 (LLOQ),=9.9 (ULOQ).	|%RE|: ≤5.7 (QC),=13.5 (LLOQ), =5.3 (ULOQ), %CV: ≤11.1 (QC),=7.6 (LLOQ),=8.8 (ULOQ).	|%RE|: ≤6.5 across all QCs. %CV: ≤9.4 across all QCs.
Dilution linearity	No hook effect was seen from 156.3 to 10,000 pg/mL. Percent accuracy was within 77.7-91.8% for all concentrations that fell within the quantitation limits.	No hook effect was seen from 9.77 to 5000 pg/mL. Percent accuracy was within 81-107% for all concentrations that fell within the quantitation limits.	No hook effect as mean measured concentration of first 6 spiked samples was above the ULOQ in all instances tested.
Selectivity	100% of unspiked samples were BLQ.	100% of unspiked samples were BLQ.	100% of unspiked pediatric (age 3-13 years) growth hormone-deficient human serum samples were below BLQ.
Stability	24 hours in human serum at ambient temperature, 5 freeze-thaw cycles at -70°C; 6 months at -70°C.	24 hours in human serum at ambient temperature, 7 freeze-thaw cycles at -70°C; 40 months at -20°C and -70°C	Not assessed, same as ECL (b) (4)

Validation Parameter	PK ELISA	PK ECL Assay (b) (4)	PK ECL Assay (b) (4)
Incurred sample reanalysis	Study 001: Performed in ~8% (28/336) of study samples. Of 28 samples reanalyzed, 25 (89%) met the prespecified criteria.	Study 003: Not performed. Study 004 (main study): Performed in ~10% (59/605) of study samples. Of 59 samples reanalyzed, 54 (92%) were within ±30% difference. Study 004 (OLE Years 1&2): Not performed. Study 004 (OLE years 3&4): performed in ~49% (78/159) of study samples. Of 78 samples reanalyzed, 63 (80%) were within ±30% difference. Study 004 (PEN): Performed in ~10% (23/227) of study samples. Of 23 samples reanalyzed, 23 (100%) were within ±30% difference. Study 005: Performed in ~8.5% (258/3021) of study samples. Of 258 samples reanalyzed, 212 (82%) were within ±30% difference. Study 007: Not performed. Study 011: Performed in ~12% (121/1025) of study samples. Of 121 samples reanalyzed, 101 (83%) were within ±30% difference.	Study 006: Not performed.

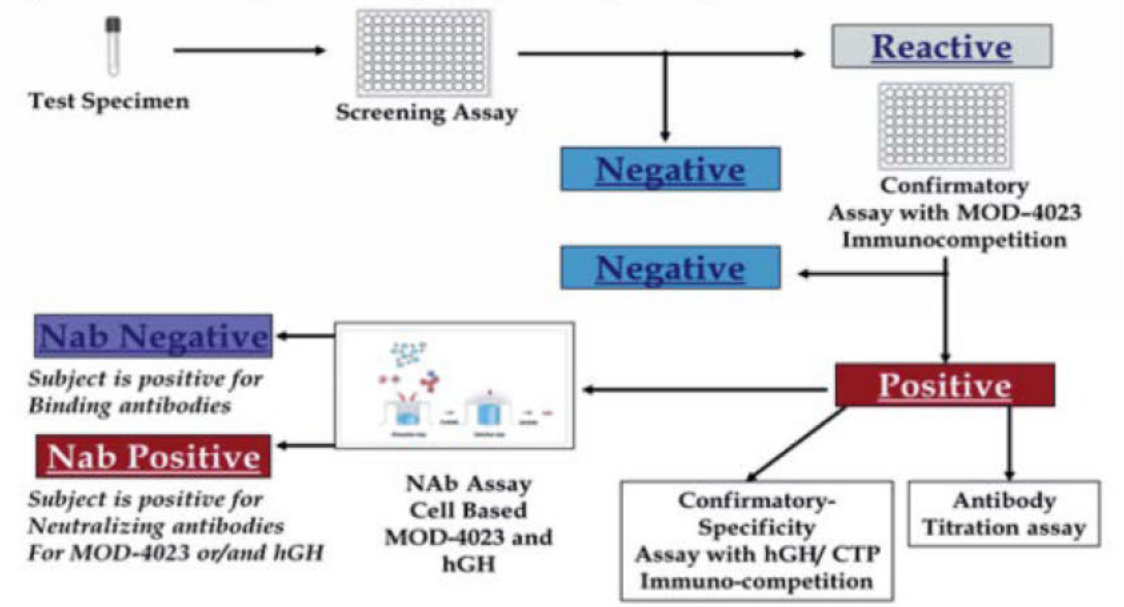
Source: Tables 17-19 of Summary of Biopharmaceutical and Associated Analytical Methods.
* In 2 of 7 runs for PK ELISA and # in 2 of 10 runs for PK ECL assay (b) (4) |%RE| and %CV for some QCs were outside the prespecified range. But for all the validation runs, ≥67% of QCs were ±20% of the nominal values, and ≥50% of QCs per level were within ±20% of their nominal concentrations, in accordance with the FDA guidance.
Abbreviations: BLQ, below limit of quantitation; CV, coefficient of variation; ECL, enhanced chemiluminescence; ELISA, enzyme-linked immunosorbent assay; LLOQ, lower limit of quantitation; OLE, open-label extension; PK, pharmacokinetics; QC, quality control; RE, relative error; ULOQ, upper limit of quantitation

Both ELISA and ECLA PK assays were validated for storage stability. The Long-Term Stability quality control samples were stable for 40 months (1,217 days) at -70°C±10°C and at -20°C±5°C. The long-term storage stability covered corresponding sample storage periods.

Bioanalytical Methods for Immunogenicity

Immunogenicity samples were assessed using a tiered approach. For subjects receiving somatrogon, samples were first screened for anti-somatrogon binding antibodies (ADA). Those tested positive for anti-somatrogon ADA were then tested using competitive confirmatory assay with somatrogon. Confirmed anti-somatrogon ADA-positive samples were assessed for specificity using hGH and CTP, followed by titer and assessed for neutralizing (NAb) to both somatrogon and hGH (Figure 59). For subjects randomized to Genotropin treatment group, samples screened positive for anti-hGH ADA were then tested using confirmatory assay with hGH. Confirmed anti-hGH ADA-positive samples were followed by titer and assessed for NAb only to hGH.

Figure 59. Somatrogon Immunogenicity Testing Paradigm



Source: Figure 1 of Module 2.7.1 Summary-biopharm.pdf.
Abbreviations: CTP, c-terminal peptide; hGH, human growth hormone; MOD-4023, somatrogon; NAb, neutralizing antibody

Per reviewers from Office of Biotechnology Products (OBP), immunogenicity assays were validated for semiquantitative measurement of antidrug binding antibodies (ADA) and neutralizing antibodies (NAb), including assays for anti-somatrogon binding antibodies, anti-somatrogon NAb, anti-hGH binding antibodies and anti-hGH NAb. Qualitative assays were validated for detection of ADA cross-reactivity with endogenous hGH/CTP as part of tier immunogenicity testing strategy.

Anti-somatrogon and anti-hGH ADA assays had reasonable drug tolerance levels. In the presence of 1000 ng/mL somatrogon (i.e., close to the maximum concentration observed after 0.66 mg/kg weekly dosing in Study 006), anti-somatrogon and anti-hGH ADAs can be detected. Anti-somatrogon and anti-hGH NAb assay also had reasonable drug tolerance levels.

Bioanalytical Methods for Pharmacodynamics

Samples to measure insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) were measured in each of the individual studies.

The samples for IGF-1 and IGFBP-3 collected in the studies of healthy volunteers (CP-4-001, CP-4-007 and CP-4-011) were analyzed using Immulite® 2000 kits (Siemens Healthcare Diagnostics) for the respective analytes. The Immulite 2000 IGF-1 and IGFBP-3 are solid-phase enzyme-labeled chemiluminescent immunometric assay.

The samples for IGF-1 and IGFBP-3 collected in studies of patients with GHD (CP-4-003, CP-4-004 and OLE, CP-4-005 and OLE and CP-4-006 and OLE) were analyzed using IDS-iSYS kits (Immunodiagnostic Systems Holdings PLC) for the respective analytes. The IDS-iSYS assay for IGF-1 is a more recently developed monoclonal antibody-based IGF-1 assay, calibrated against the recommended National Institute for Biological Standards and Control standard (02/254).

The IGF-1 and IGFBP-3 biomarker assays are in vitro diagnostics assays intended as aids in the evaluation of patients with growth disorders that are routinely used in clinical practice in laboratories with CAP/CLIA or equivalent regulatory certification for patient management.

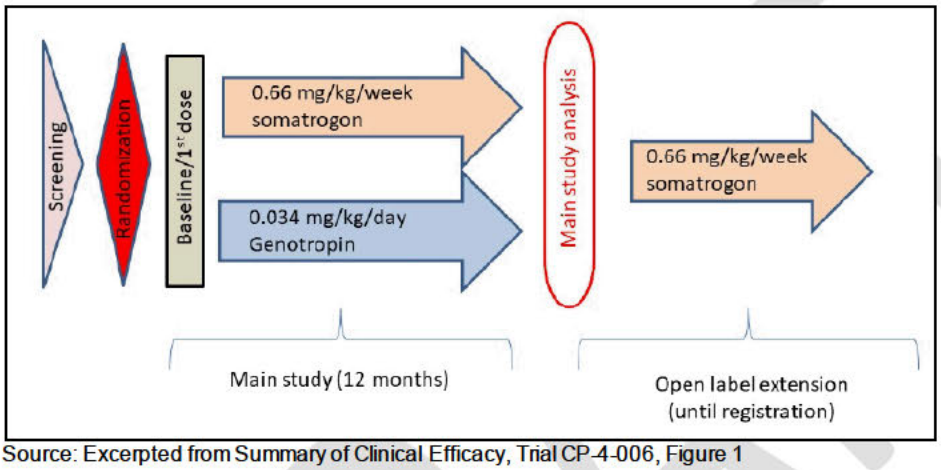
15. Trial Design: Additional Information and Assessment

15.1. Trial CP-4-006

15.1.1. Study Design

The schematic representation of study design for Trial CP-4-006 (main study and OLE study) is shown in Figure 60.

Figure 60. Schematic Representation of Study Design, Trial CP-4-006



Source: Excerpted from Summary of Clinical Efficacy, Trial CP-4-006, Figure 1

15.1.2. Endpoints

In addition to the endpoints listed in Section 6.2.1.1 of this review, other secondary endpoints were:

- Proportion of successful single injections out of total number of single injections using the somatrogon prefilled pen in U.S. subjects at Weeks 1, 2, 3, 4, 5, and 6, based on the Participant Assessment Tool
- Proportion of successful single injections out of total number of single injections using the somatrogon prefilled pen in US subjects at Week 1, based on the Observer Assessment Tool
- Comments on the Participant Assessment Tool related to successful or unsuccessful injection attempts
- Comments on the Observer Assessment Tool related to successful or unsuccessful injection attempts
- Information gained by inspection of returned devices
- Quality of Life core total score as measured by the quality of life in short stature youth (QoLISSY) questionnaire at baseline and Month 12 in specific countries.

Key safety endpoints included assessment of incidence of anti-somatrogon antibodies, local injection site reactions, serum IGF-1 and IGF-1 SDS values, parameters of glucose metabolism (fasting glucose, fasting insulin, and HbA1c), thyroid function tests, fundoscopy, and ECG.

15.1.3. Eligibility Criteria

Key Inclusion Criteria

- Children aged 3 to 10 years (girls) and 3 to 11 years (boys)
- Confirmed diagnosis of GHD (by 2 separate GH provocative tests)
- Bone age (BA) is not older than chronological age (CA); BA <10 for females and <11 for males
- Naïve-to-treatment for GHD
- Impaired growth, defined as:
  - Height velocity (HV) <25th percentile for CA (AHV <-0.7 SDS) and gender
  - The interval between 2 height (HT) measurements should be between 6 and 18 months prior to inclusion
- Baseline IGF-1 value at least 1 standard deviation (SD) below the mean IGF-1 for age and gender
- Normal calculated glomerular filtration rate (eGFR) based on updated "bedside" Schwartz formula for pediatric patients.
- Children with multiple hormonal deficiencies must be on stable replacement therapy for other hypothalamic pituitary organ axes for at least 3 months prior to signing informed consent

Key Exclusion Criteria

- History of cancer
- History of radiation therapy or chemotherapy
- Children with psychosocial dwarfism and small for gestational age
- Presence of anti-hGH antibody at screening
- Diabetic patients who are not receiving standard of care treatment or are noncompliant with treatment or are in poor metabolic control.
- Chromosomal abnormalities
- Concomitant medications including anabolic steroids, or sex steroids, except for attention deficit/hyperactive disorder (ADHD) drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin)
- Children requiring chronic administration of glucocorticoid (e.g., for asthma) at a dose >400 mcg/day of inhaled budesonide or equivalent
- More than 1 closed epiphyses
- Other causes of short stature, e.g., celiac disease, uncontrolled primary hypothyroidism, and rickets, and malnourishment (body mass index <-2 SDS, for age and gender)

15.1.4. Trial CP-4-006 Noninferiority Margin Justification

The Applicant's justification for the noninferiority (NI) margin in Study 006 is as follows:

- From historical data, HV response for the first year of daily GH ranged from 10.2 cm/year, SD=2.5 (Wilton and Gunnarsson 1988) to 11.4 cm/year, SD=2.5 (MacGillivray et al. 1996). Using the standard deviation (SD) of 2.5 from these references, a noninferiority margin of -

1.8 cm/year is well within 1 SD of the expected results, and approximately 23% of the reference treatment response distribution would be below this value.

- Assuming the HV response for daily GH treatment is 11.5 cm/year in the first year, a margin of -1.8 cm/year would show that 84% of the growth rate from the reference daily GH treatment effect on the approved active control is retained.
- Other studies of long-acting GH compared to daily GH have used noninferiority margins of -1.8 to -2.0 cm/year. as used in the recent phase 3 Ascendis Pharma heiGHt pivotal trial (NCT02781727, https://ascendispharma.gcs-web.com/static-files/692edb83-40e9-449a-866c-2368e0898ae9). The use of -1.8 cm/year is the more conservative value based on the precedent set with these other studies.

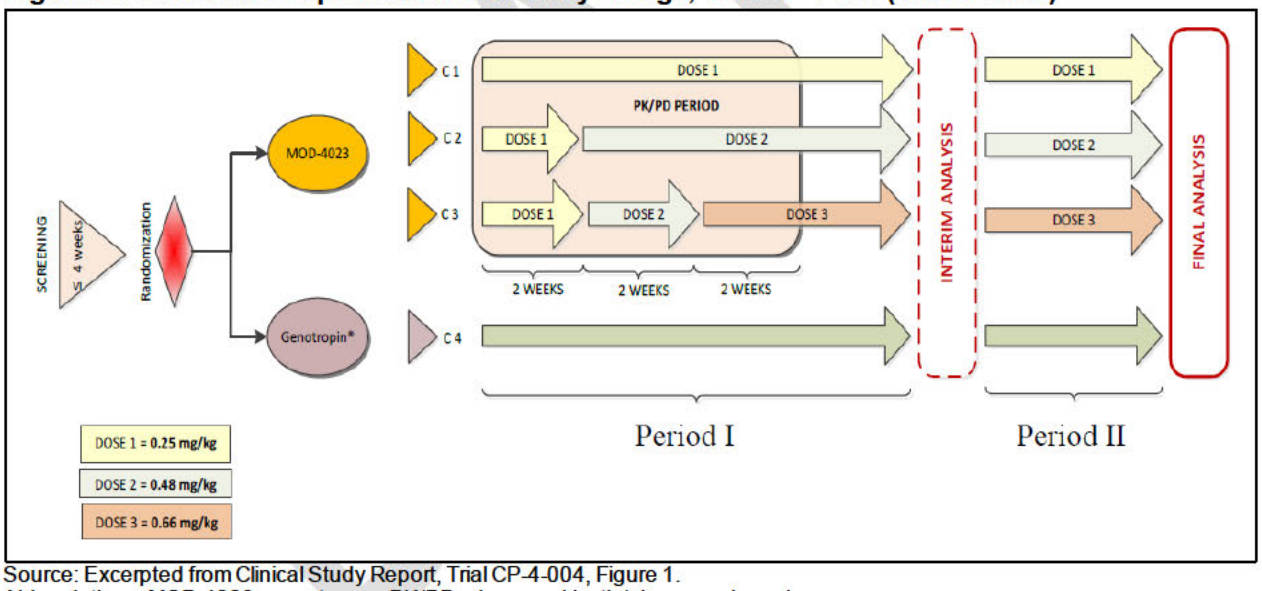
15.1.5. Trial CP-4-006 Protocol Deviations

The majority of the protocol deviations were minor. There were 6 (5.5%) subjects with major deviations in the somatrogon group (4 missing doses and 2 stadiometer calibration) and 5 (4.3%) subjects in the Genotropin group (3 missing doses and 2 stadiometer calibration).

15.2. Trial CP-4-004

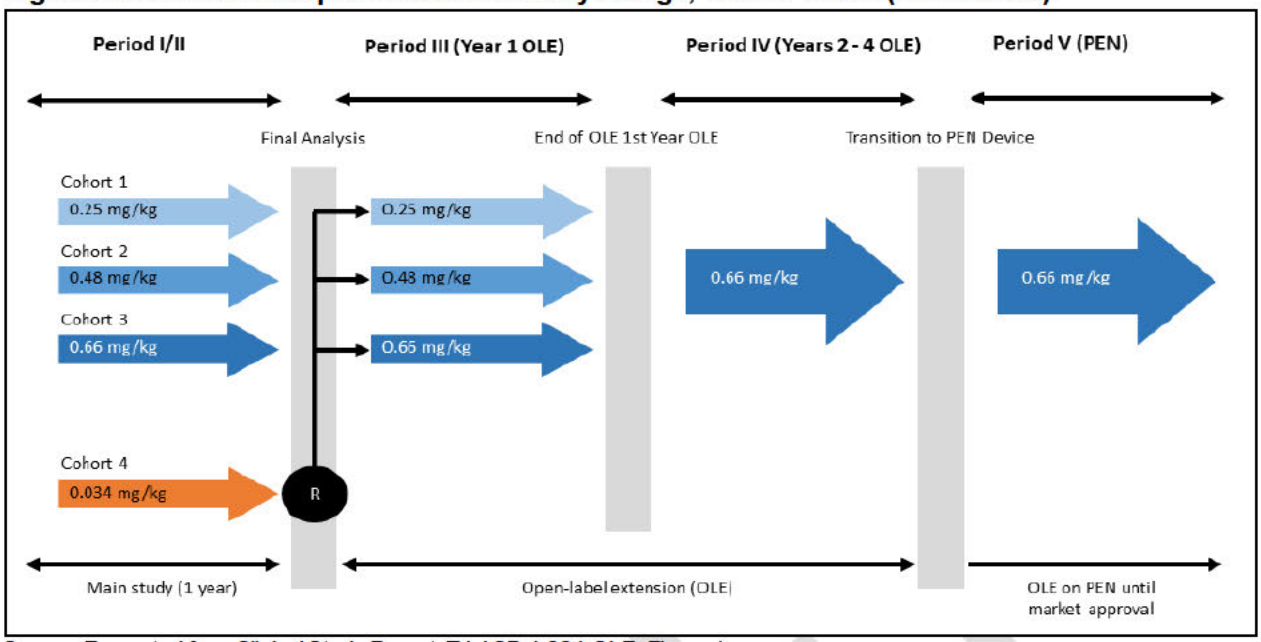
15.2.1. Study Design

Figure 61. Schematic Representation of Study Design, Trial CP-4-004 (Main Period)



Source: Excerpted from Clinical Study Report, Trial CP-4-004, Figure 1.
Abbreviations: MOD-4023, somatrogon; PK/PD, pharmacokinetic/pharmacodynamic

Figure 62. Schematic Representation of Study Design, Trial CP-4-004 (OLE Period)



Source: Excerpted from Clinical Study Report, Trial CP-4-004,OLE, Figure 1.
Abbreviations: OLE, open-label extension

15.2.2. Endpoints

In addition to endpoints listed in Section 6.2.2.1, the following exploratory endpoints were sought:

- Serum levels of insulin growth factor binding protein 3 (IGFBP3)
- Annual evaluation of bone maturation
- Change in predicted adult height from start to 12 months

15.2.3. Eligibility Criteria

Key Inclusion Criteria

- Children aged 3-10 year (girls) and 3-11 years (boys)
- Confirmed diagnosis of GHD (by 2 separate GH provocative tests)
- Bone age (BA) is not older than chronological age (CA); BA <10 for females and <11 for males
- Naïve-to-treatment for GHD
- Impaired growth, defined as:
  - Height velocity (HV) <25th percentile for CA (HV <-0.7 SDS) and gender
  - Height (HT) of at least 2 standard deviation (SDs) below the mean HT for CA and gender. The interval between 2 HT measurements should be 6 to 18 months prior to inclusion
- Baseline IGF-1 value at least 1 standard deviation (SD) below the mean IGF-1 for age and gender
- Normal calculated glomerular filtration rate (eGFR) based on updated "bedside" Schwartz formula for pediatric patients.

- Children with multiple hormonal deficiencies must be on stable replacement therapy for other hypothalamic pituitary organ axes for at least 3 months prior to signing informed consent
- Children with normal fundoscopy at screening

Key Exclusion Criteria

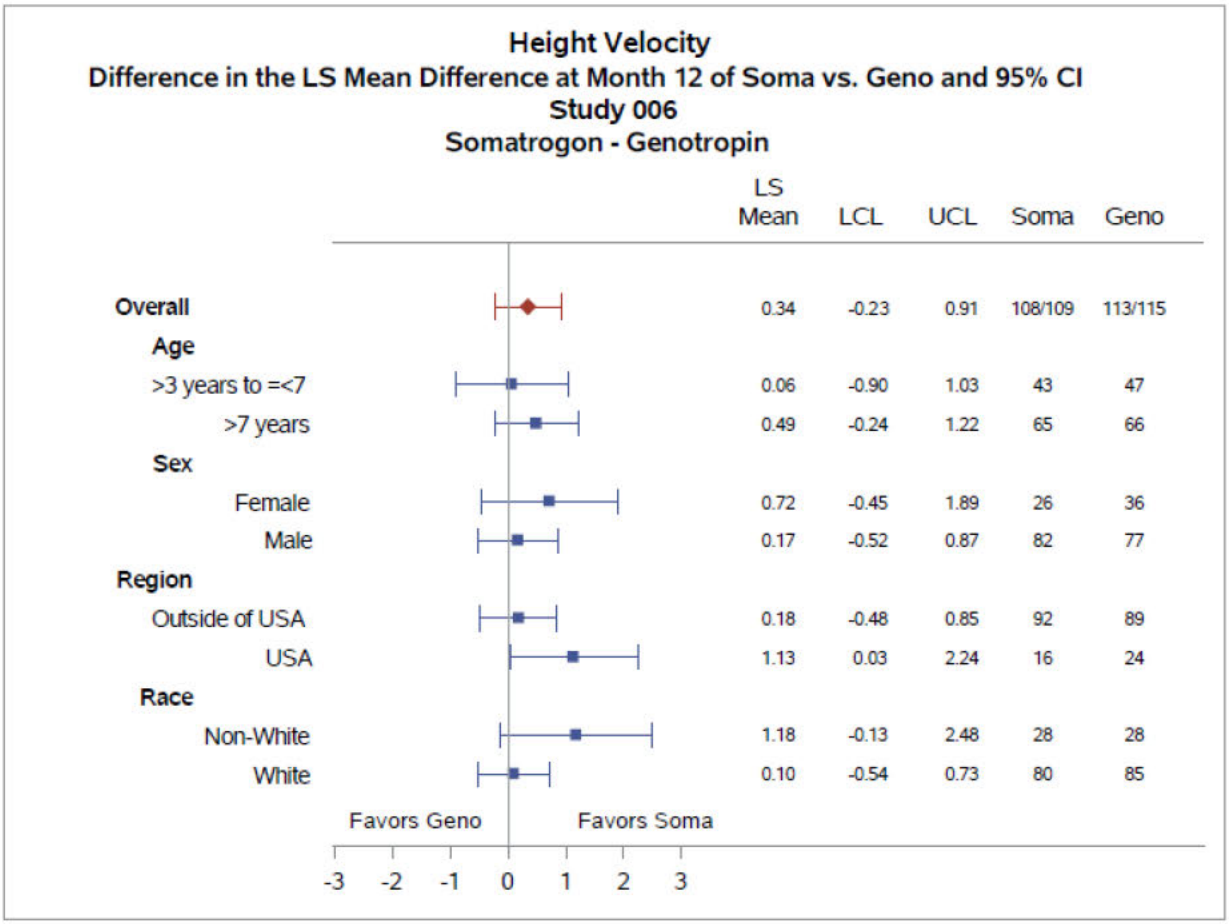
- History of intracranial tumor growth by magnetic resonance imaging
- History of radiation therapy or chemotherapy
- Children with psychosocial dwarfism and small for gestational age
- Presence of anti-hGH antibody at screening
- Patients with diabetes or impaired fasting glucose.
- Chromosomal abnormalities
- Concomitant medications including anabolic steroids and methylphenidate for attention deficit/hyperactive disorder (ADHD) drugs or hormone replacement therapies (thyroxin, hydrocortisone, desmopressin)
- Children requiring chronic administration of glucocorticoid (e.g., for asthma) at a dose >400 mcg/day of inhaled budesonide or equivalent
- Closed epiphyses
- Other causes of short stature, e.g., celiac disease, uncontrolled primary hypothyroidism, and rickets, and malnourishment (body mass index <-2 SDS, for age and gender)

16. Efficacy: Additional Information and Assessment

16.1. Trial CP-4-006 Primary Endpoint Subgroup Analysis

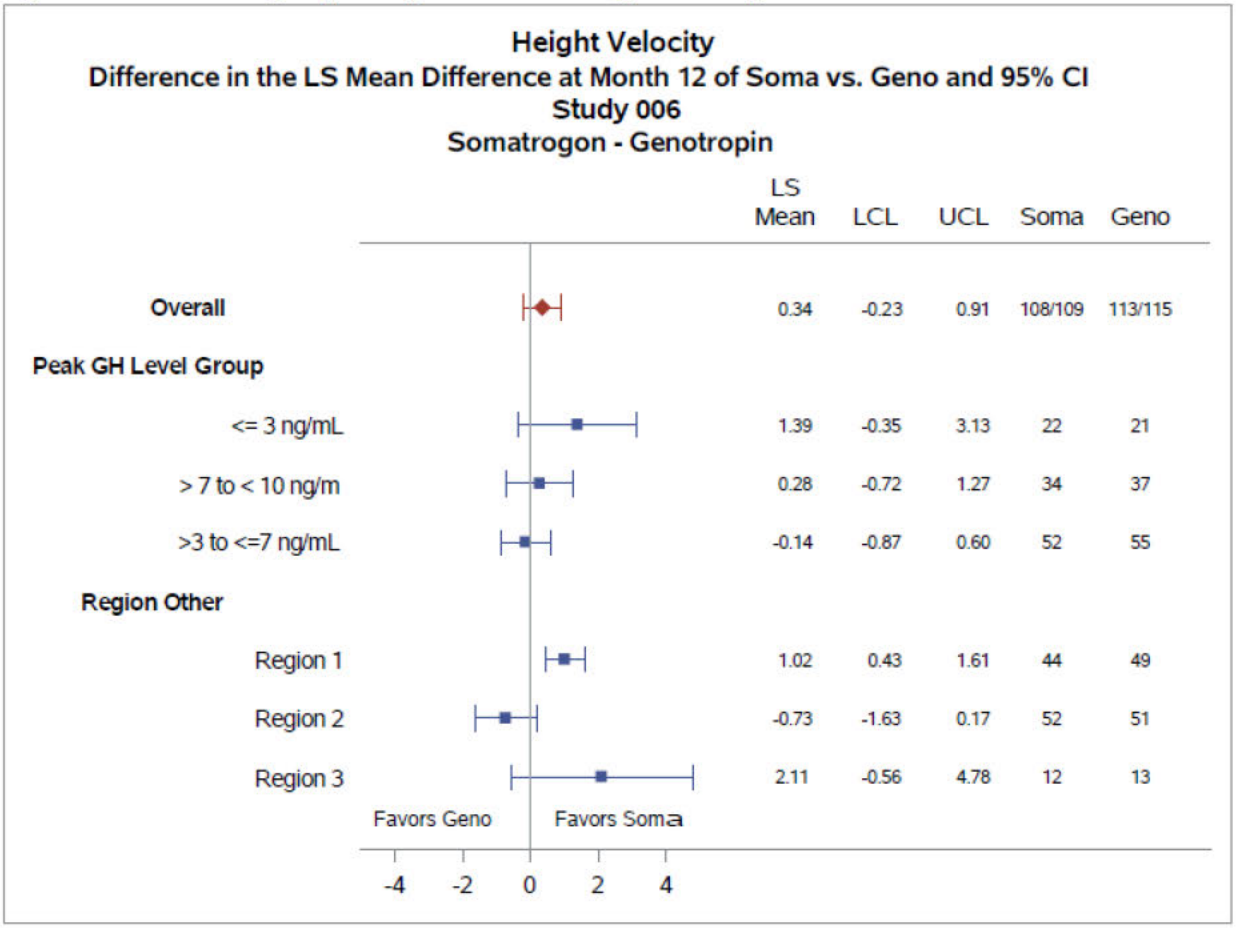
Subgroup analyses were performed on the primary endpoint, annual HV by age group (3-7, >7), sex (Male, Female), region (Outside of USA, USA), and race (White versus Non-White) (see Figure 63). As well as peak GH level group (≤3 ng/mL, >7 to <10 ng/mL, >3 to ≤7 ng/mL) and Region (Region 1: Western Europe, Israel, Greece, Australia, New Zealand, Canada, and USA; Region 2: Central and Eastern Europe, Turkey, Latin America, and Asia, except for India and Vietnam; Region 3: India, Vietnam) (see Figure 64). The subgroup analyses were performed using the FAS population with missing data not imputed. The forest plot combining all results are presented in Figure 63 and Figure 64 for the primary endpoint. Overall, the treatment effects of the subgroups favored somatrogon. The Applicant subgroup analyses did not adjusted for the covariates except for the baseline height. This reviewer's subgroup analyses included all the covariates in the overall primary analysis. In the reviewer analysis of the sex subgroup, both male and female trend in the direction of the overall analysis (favoring somatrogon) after adjusting for the covariates, which differs from the Applicant analysis. Also note, in the reviewer analysis, there is a significant difference in the USA region favoring somatrogon.

Figure 63. Subgroup Analysis: Annual Height Velocity at Month 12



Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; Geno, Genotropin; LCL, lower confidence interval; LS, least squares; Soma, somatrogon; UCL, upper confidence limit

Figure 64. Other Subgroup Analysis: Annual Height Velocity at Month 12



Source: Statistical Reviewer's analysis.
Region 1: Western Europe, Israel, Greece, Australia, New Zealand, Canada, and the United States.
Region 2: Central and Eastern Europe, Turkey, Latin America, and Asia, except for India and Vietnam.
Region 3: India and Vietnam.
Abbreviations: CI, confidence interval; Geno, Genotropin; GH, growth hormone; LCL, lower confidence interval; LS, least squares; Soma, somatrogon; UCL, upper confidence limit

16.2. Trial CP-4-006 Bayesian Shrinkage Analysis

There were likely some random highs and random lows in sample estimates of subgroup treatment effects due to small sample size and large variability for some subgroups. Therefore, we also derive shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. The weights are based on the ratio of the between subgroup variability to the within subgroup variability. The greater that ratio the smaller the weight on the overall estimate (the less the shrinkage). We used the same flat prior to derive shrinkage estimates for all subgroups (age, sex, region, and race). The Bayesian hierarchical model assumptions for annual HV at Month 12 are:

For $i = 1, 2\ldots$ Yi represents the observed sample estimate of treatment effect in a subgroup level i, assume $Yi \sim N(\mu_i, \sigma_i^2)$ where:

- $\sigma i2$ are the observed variance for sample estimates
- $\mu i \sim N(\mu, \tau 2)$
- $\mu \sim N(0, 10)$, $1/\tau 2 \sim Gamma(0.001, 0.001)$

The variance should be selected relative to the residual standard deviation from the primary analysis model. In general, it should be four to ten times of the residual standard deviation. A flat prior with mean 0 and standard deviation of 10 was chosen. This standard deviation is 4 times the residual standard deviation and so this assumption would not be influential. Figure 3 compares the conventional subgroup analysis results of the sample estimate (in blue) and Bayesian shrinkage estimate (in red) for the endpoint of annual HV at Month 12. The overall treatment effect is 0.34 (95% CI: -0.23, 0.91). Subgroup analysis using Bayesian shrinkage estimate exhibits narrower confidence interval, and the shrinkage subgroup estimate is closer to the overall mean.

16.3. Trial CP-4-006

16.3.1. Improvement in AHV and HT SDS in OLE (Second-Year Treatment)

Table 92. AHV and HT SDS in Subjects Who Completed 1 Year, Trial CP-4-006 (OLE (Total 2 Years of Treatment))

Measure	Variable	Originally Randomized to Somatrogon (N=102)	Originally Randomized to Genotropin (N=102)
	N	91	83
AHV (cm/year)	Mean (SD)	9.10 (1.64)	8.98 (1.82)
	Median	8.85	8.88
	Minimum, maximum	5.55, 14.32	5.51, 13.98
HT SDS (cm)	Mean (SD)	-1.49 (0.90)	-1.35 (0.89)
	Median	-1.27	-1.28
	Minimum, maximum	-3.94, 0.76	-5.16, 0.37

Source: Excerpted from Table 3.1 and Table 3.2 provided in response to Information Request dated 10.20 2021.
Abbreviations: AHV, annualized height velocity; HT SDS, height standard deviation score; OLE, open-label extension; SD, standard deviation

16.4. Trial CP-4-004

16.4.1. Growth by Group Across OLE (Year 1 to 4, and PEN Year 1 and 2)

Table 93. AHV and HT SDS, Trial CP-4-004, (Year End in Each OLE Period)

	Year 1		
Variable	**0.25 mg/kg/Week (N=16)**	**0.48 mg/kg/Week (N=17)**	**0.66 mg/kg/Week (N=15)**
AHV (cm/year)			
n	15	17	14
Mean (SD)	7.73 (1.89)	7.54 (1.28)	8.81 (1.12)
Median	7.33	7.22	8.86
Range	5.51, 11.44	5.38, 9.99	7.19, 10.87
HT SDS (cm)			
Mean (SD)	-2.06 (0.77)	-1.92 (0.52)	-2.23 (1.21)
Median	-1.95	-1.79	-1.81
Range	-4.02, -1.26	-3.35, -1.11	-4.51, -0.61
	Year 2 (N=44)	**Year 3 (N=43)**	**Year 4 (N=38)**
AHV (cm/year)			
n	43	38	1
Mean (SD)	7.46 (1.35)	7.12 (1.66)	4.63
Median	7.29	6.99	4.63
Range	4.39, 10.02	4.17, 12.79	-
HT SDS (cm)			
Mean (SD)	-1.59 (0.80)	-1.27 (0.93)	-2.53
Median	-1.39	-1.19	-2.53
Range	-4.06, -0.18	-3.90, 0.27	-
	PEN Year 1 (N=40)	**PEN Year 2 (N=35)**	
AHV (cm/year)			
n	31	30	
Mean (SD)	7.03 (1.85)	6.47 (2.07)	N/A
Median	6.72	6.63	
Range	3.94, 10.93	2.27, 12.36	
HT SDS (cm)			
Mean (SD)	-0.65 (0.89)	-0.43 (0.94)	N/A
Median	-0.57	-0.39	
Range	-2.86, 1.50	-2.49, 1.54	

Source: Excerpted from cp-4-004-ole-report-body, Tables 6, 7, 8, 10, and 11, in addition to Table cp-4-004-table-4-1-annual-height-velocity and Table cp-4-004-table-4-2-height-sds-delta-height provided in response to IR dated October 20, 2021.
Abbreviations: HT SDS, height standard deviation score; N/A, not applicable; OLE, open-label extension; SD, standard deviation

Table 94. Growth Data, Trial CP-4-004 (Main and OLE Studies by Originally Randomized Group)

			Somatrogon Dose or Dose Switch			Genotropin switch to Somatrogon	
Period	Timepoints	Growth Parameter (Statistics)	Group 1: 0.66 mg/kg/wk ($N^{1,4}$=13)	Group 2: 0.25 to 0.66 mg/kg/wk (N^{1}=13)	Group 3: 0.48 to 0.66 mg/kg/wk (N^{1}=15)	Group 4: Switch to 0.66 mg/kg/wk ($N^{1,4}$=3)	Group 5: Switch to 0.25 or 0.48 mg/kg/wk ($N^{1,4}$=7)
Main	6 months	n[2]	13	13	15	3	7
		AHV Mean (SD)	13.54 (5.03)	11.78 (3.58)	12.49 (2.43)	15.07 (2.05)	14.89 (3.49)
		AHV Median (Range)	12.85 (6.73 , 25.10)	12.46 (5.65 , 17.47)	12.32 (7.90 , 16.53)	14.28 (13.53 , 17.40)	15.65 (10.15 , 18.47)
		HT-SDS Median (Range)	-2.75 (-6.52 , -1.83)	-2.97 (-4.71 , -1.90)	-2.96 (-4.80 , -1.78)	-4.41 (-5.63 , -1.98)	-2.56 (-5.70 , -1.97)
		HT-SDS Change [3] Median (Range)	0.84 (0.20 , 1.91)	0.63 (0.11 , 1.33)	0.75 (0.33 , 1.27)	1.07 (0.89 , 1.55)	1.13 (0.49 , 1.45)
		IGF-1-SDS Median (Range)	0.11 (-2.30 , 2.34)	-0.94 (-1.92 , 0.70)	0.09 (-1.37 , 1.27)	0.49 (-1.05 , 0.69)	-0.11 (-1.87 , 0.69)
		IGF-1-SDS Change [3] Median (Range)	1.95 (0.38 , 4.01)	1.28 (0.03 , 1.87)	1.88 (0.83 , 3.26)	2.06 (1.63 , 2.41)	2.05 (0.63 , 2.62)
	12 months	n[2]	13	13	15	3	7
		AHV Mean (SD)	11.93 (3.53)	10.44 (2.62)	10.96 (2.25)	11.97 (1.67)	12.67 (2.54)
		AHV Median (Range)	11.60 (6.35 , 18.27)	10.22 (6.17 , 14.40)	10.48 (6.48 , 14.55)	11.31 (10.74 , 13.87)	12.74 (9.16 , 15.97)
		HT-SDS Median (Range)	-2.44 (-5.38 , -1.47)	-2.46 (-4.18 , -1.65)	-2.21 (-4.82 , -1.46)	-3.77 (-5.24 , -1.71)	-2.11 (-4.83 , -1.55)
		HT-SDS Change [3] Median (Range)	1.40 (0.38 , 2.51)	1.05 (0.32 , 2.16)	1.13 (0.31 , 2.05)	1.46 (1.16 , 2.20)	1.59 (0.82 , 2.30)
		IGF-1-SDS Median (Range)	0.60 (-0.65 , 1.27)	-0.57 (-2.91 , 1.37)	0.13 (-2.64 , 1.54)	0.64 (-0.79 , 0.94)	0.81 (-3.61 , 1.51)
		IGF-1-SDS Change [3] Median (Range)	2.44 (1.25 , 4.07)	1.45 (0.19 , 2.71)	1.90 (-0.24 , 4.35)	2.32 (1.78 , 2.66)	2.14 (-0.17 , 3.54)
OLE - Year 1	6 months	n[2]	12	12	14	3	7
		AHV Mean (SD)	11.04 (2.68)	9.37 (1.86)	10.06 (1.55)	10.78 (1.28)	10.81 (1.72)
		AHV Median (Range)	11.16 (6.77 , 15.25)	9.62 (6.15 , 12.95)	9.47 (7.67 , 12.58)	10.36 (9.77 , 12.22)	10.48 (8.66 , 12.79)
		HT-SDS Median (Range)	-2.23 (-4.87 , -1.04)	-2.02 (-3.89 , -1.32)	-1.87 (-3.23 , -1.29)	-3.29 (-4.87 , -1.43)	-1.94 (-4.25 , -1.47)
		HT-SDS Change [3] Median (Range)	2.02 (0.66 , 3.23)	1.43 (0.46 , 2.78)	1.27 (1.02 , 2.27)	1.83 (1.44 , 2.67)	1.63 (1.13 , 2.68)
		IGF-1-SDS Median (Range)	0.36 (-1.35 , 2.54)	-0.27 (-3.49 , 0.91)	0.38 (-1.23 , 2.25)	0.91 (0.23 , 0.93)	0.98 (-3.25 , 1.58)
		IGF-1-SDS Change [3] Median (Range)	2.46 (0.72 , 4.71)	1.59 (-0.31 , 2.08)	2.06 (0.73 , 4.82)	2.63 (2.07 , 3.34)	2.57 (0.19 , 4.31)
	12 months	n[2]	11	11	14	3	7
		AHV Mean (SD)	10.74 (1.93)	9.00 (1.72)	9.30 (1.49)	10.01 (1.19)	9.85 (1.48)
		AHV Median (Range)	10.88 (7.15 , 13.35)	9.59 (6.38 , 11.90)	9.02 (7.15 , 11.91)	9.37 (9.27 , 11.38)	9.28 (8.21 , 11.97)
		HT-SDS Median (Range)	-1.62 (-4.51 , -0.61)	-1.96 (-3.51 , -1.26)	-1.92 (-3.35 , -1.11)	-3.03 (-4.49 , -1.36)	-1.79 (-4.02 , -1.41)
		HT-SDS Change [3] Median (Range)	2.60 (0.95 , 3.52)	1.83 (0.65 , 3.10)	1.52 (0.90 , 2.63)	2.22 (1.51 , 2.94)	1.62 (1.27 , 3.11)
		IGF-1-SDS Median (Range)	0.49 (-0.83 , 2.41)	0.15 (-1.66 , 1.06)	1.37 (-0.66 , 2.64)	0.85 (0.08 , 1.61)	-0.09 (-0.61 , 2.25)
		IGF-1-SDS Change [3] Median (Range)	2.66 (1.54 , 5.22)	1.65 (1.21 , 2.84)	2.95 (1.69 , 5.21)	2.28 (1.22 , 3.33)	2.32 (0.98 , 4.47)
OLE - Year 2	6 months	n[2]	11	10	14	2	7
		AHV Mean (SD)	9.85 (1.47)	8.33 (1.34)	8.82 (1.36)	8.91 (0.22)	8.92 (1.09)
		AHV Median (Range)	9.88 (7.03 , 12.64)	8.75 (6.44 , 10.57)	8.54 (6.83 , 11.36)	8.91 (8.75 , 9.06)	8.91 (7.60 , 10.52)
		HT-SDS Median (Range)	-1.55 (-4.23 , -0.40)	-1.74 (-3.23 , -0.91)	-1.74 (-3.15 , -0.92)	-2.72 (-4.21 , -1.24)	-1.64 (-4.13 , -1.23)

			Somatrogon Dose or Dose Switch			Genotropin switch to Somatrogon	
Period	Timepoints	Growth Parameter (Statistics)	Group 1: 0.66 mg/kg/wk (N[1,4]=13)	Group 2: 0.25 to 0.66 mg/kg/wk (N[1]=13)	Group 3: 0.48 to 0.66 mg/kg/wk (N[1]=15)	Group 4: Switch to 0.66 mg/kg/wk (N[1,4]=3)	Group 5: Switch to 0.25 or 0.48 mg/kg/wk (N[1,4]=7)
		HT-SDS Change[3] Median (Range)	2.72 (1.08 , 4.15)	1.78 (0.77 , 2.87)	1.61 (1.11 , 2.94)	2.07 (1.64 , 2.49)	1.93 (1.13 , 3.30)
		IGF-1-SDS Median (Range)	1.35 (-0.42 , 2.01)	0.58 (-0.22 , 2.20)	0.86 (-1.85 , 1.52)	0.47 (0.17 , 0.76)	-0.79 (-2.76 , 1.46)
		IGF-1-SDS Change [3] Median (Range)	3.29 (2.07 , 5.19)	2.46 (1.29 , 3.09)	2.09 (-0.42 , 4.46)	1.90 (1.31 , 2.48)	1.02 (0.28 , 3.38)
	12 months	n[2]	11	10	14	2	6
		AHV Mean (SD)	9.55 (1.27)	8.17 (1.34)	8.47 (1.20)	8.74 (0.09)	8.81 (1.16)
		AHV Median (Range)	9.23 (7.54 , 11.85)	8.61 (6.01 , 10.35)	8.19 (6.52 , 10.49)	8.74 (8.67 , 8.80)	8.63 (7.72 , 10.45)
		HT-SDS Median (Range)	-1.28 (-3.82 , -0.18)	-1.54 (-2.85 , -0.49)	-1.52 (-3.26 , -0.83)	-2.49 (-4.06 , -0.92)	-1.26 (-1.70 , -0.96)
		HT-SDS Change[3] Median (Range)	2.83 (1.24 , 4.54)	2.05 (0.81 , 3.29)	1.73 (0.99 , 3.23)	2.30 (1.96 , 2.64)	2.11 (1.40 , 3.80)
		IGF-1-SDS Median (Range)	0.89 (0.17 , 2.69)	0.12 (-1.65 , 1.81)	0.56 (-0.22 , 2.24)	0.47 (0.06 , 0.87)	0.35 (-2.23 , 1.83)
		IGF-1-SDS Change [3] Median (Range)	3.31 (1.80 , 5.72)	1.93 (0.35 , 2.86)	2.72 (1.33 , 5.12)	1.90 (1.78 , 2.01)	2.45 (-0.18 , 4.56)
OLE - Year 3	6 months	n[2]	11	9	13	2	6
		AHV Mean (SD)	9.23 (1.07)	8.11 (1.26)	8.33 (1.18)	8.39 (0.04)	8.72 (1.47)
		AHV Median (Range)	9.33 (7.53 , 11.16)	8.38 (6.10 , 10.29)	8.16 (6.48 , 10.19)	8.39 (8.36 , 8.42)	8.62 (7.18 , 10.39)
		HT-SDS Median (Range)	-1.15 (-3.61 , 0.06)	-1.35 (-2.69 , -0.10)	-1.40 (-2.96 , -0.69)	-2.34 (-3.85 , -0.82)	-1.04 (-1.72 , -0.32)
		HT-SDS Change[3] Median (Range)	3.20 (1.23 , 4.78)	2.26 (0.64 , 3.69)	1.90 (1.29 , 3.39)	2.45 (2.06 , 2.85)	2.42 (1.34 , 4.32)
		IGF-1-SDS Median (Range)	0.63 (-0.46 , 2.24)	0.64 (-1.29 , 2.14)	0.78 (-1.67 , 2.01)	1.07 (0.67 , 1.46)	0.93 (-0.52 , 1.81)
		IGF-1-SDS Change [3] Median (Range)	2.60 (2.02 , 5.42)	2.22 (1.52 , 3.19)	2.24 (-0.24 , 4.84)	2.50 (1.81 , 3.18)	2.63 (1.53 , 4.54)
	12 months	n[2]	11	8	11	2	6
		AHV Mean (SD)	9.03 (0.94)	8.04 (1.21)	8.01 (1.19)	8.10 (0.35)	8.52 (1.54)
		AHV Median (Range)	9.15 (7.80 , 10.66)	8.18 (6.03 , 9.87)	7.85 (5.96 , 9.93)	8.10 (7.85 , 8.35)	8.36 (6.94 , 10.20)
		HT-SDS Median (Range)	-1.03 (-3.20 , 0.27)	-1.41 (-2.50 , 0.06)	-1.25 (-3.03 , -0.55)	-2.24 (-3.90 , -0.57)	-0.75 (-1.79 , 0.09)
		HT-SDS Change[3] Median (Range)	3.32 (1.35 , 4.83)	2.60 (0.66 , 3.85)	2.04 (1.22 , 3.70)	2.55 (2.30 , 2.80)	2.57 (1.39 , 4.62)
		IGF-1-SDS Median (Range)	0.84 (-0.05 , 2.92)	1.17 (-0.96 , 1.76)	1.16 (-0.28 , 2.64)	1.16 (1.10 , 1.21)	1.01 (0.53 , 1.72)
		IGF-1-SDS Change [3] Median (Range)	3.32 (2.03 , 6.10)	2.28 (1.50 , 3.91)	2.82 (1.66 , 5.75)	2.59 (2.24 , 2.93)	2.90 (2.53 , 4.43)
OLE - Year 4	6 months	n[2]	9	6	8	2	2
		AHV Mean (SD)	8.86 (0.82)	7.97 (0.76)	8.04 (1.10)	7.98 (0.33)	8.44 (2.16)
		AHV Median (Range)	8.90 (7.76 , 10.19)	7.94 (6.65 , 8.75)	7.90 (6.46 , 9.84)	7.98 (7.75 , 8.21)	8.44 (6.91 , 9.97)
		HT-SDS Median (Range)	-0.89 (-2.91 , 0.56)	-1.24 (-2.44 , -0.33)	-0.96 (-2.07 , -0.84)	-1.92 (-3.48 , -0.37)	-0.78 (-1.61 , 0.06)
		HT-SDS Change[3] Median (Range)	3.38 (2.14 , 4.95)	2.83 (0.64 , 3.11)	2.41 (1.43 , 4.00)	2.87 (2.51 , 3.23)	3.25 (1.56 , 4.94)
		IGF-1-SDS Median (Range)	0.92 (-1.84 , 1.67)	1.21 (-0.77 , 1.77)	0.57 (-0.52 , 1.95)	0.89 (0.44 , 1.33)	0.32 (-1.18 , 1.81)
		IGF-1-SDS Change [3] Median (Range)	2.91 (1.74 , 4.52)	2.90 (2.51 , 3.47)	3.04 (1.93 , 4.01)	2.32 (1.58 , 3.05)	2.48 (0.41 , 4.54)
	12 months	n[2]	1	0	0	0	0
		AHV Mean (SD)	7.59 (-)				
		AHV Median (Range)	7.59 (7.59 , 7.59)				
		HT-SDS Median (Range)	-2.53 (-2.53 , -2.53)				
		HT-SDS Change[3] Median (Range)	3.14 (3.14 , 3.14)				
		IGF-1-SDS Median (Range)	0.29 (0.29 , 0.29)				
		IGF-1-SDS Change [3] Median (Range)	3.30 (3.30 , 3.30)				

			Somatrogon Dose or Dose Switch			Genotropin switch to Somatrogon	
Period	Timepoints	Growth Parameter (Statistics)	Group 1: 0.66 mg/kg/wk (N[1,4]=13)	Group 2: 0.25 to 0.66 mg/kg/wk (N[1]=13)	Group 3: 0.48 to 0.66 mg/kg/wk (N[1]=15)	Group 4: Switch to 0.66 mg/kg/wk (N[1,4]=3)	Group 5: Switch to 0.25 or 0.48 mg/kg/wk (N[1,4]=7)
Year 1 PEN	6 months	n[2]	11	9	12	1	6
		AHV Mean (SD)	8.56 (0.77)	8.04 (1.11)	8.13 (1.11)	7.77 (-)	8.37 (1.40)
		AHV Median (Range)	8.39 (7.55 , 9.79)	8.25 (6.36 , 10.11)	8.35 (5.97 , 9.58)	7.77 (7.77 , 7.77)	8.30 (7.04 , 9.89)
		HT-SDS Median (Range)	-0.78 (-2.96 , 0.86)	-0.63 (-1.82 , 1.13)	-0.63 (-2.78 , -0.35)	-0.26 (-0.26 , -0.26)	-0.26 (-1.55 , 0.54)
		HT-SDS Change[3] Median (Range)	3.45 (1.38 , 4.95)	3.14 (0.88 , 4.91)	2.58 (1.48 , 4.29)	2.61 (2.61 , 2.61)	2.99 (1.86 , 5.22)
		IGF-1-SDS Median (Range)	0.72 (0.21 , 1.81)	1.79 (1.06 , 2.84)	0.69 (-0.05 , 1.80)	1.43 (1.43 , 1.43)	0.80 (-1.01 , 1.45)
		IGF-1-SDS Change[3] Median (Range)	3.47 (1.84 , 4.66)	3.30 (2.27 , 4.56)	2.52 (1.56 , 4.54)	2.57 (2.57 , 2.57)	2.90 (0.58 , 3.72)
	12 months	n[2]	9	7	12	1	6
		AHV Mean (SD)	8.30 (0.80)	7.93 (1.15)	7.93 (1.02)	7.66 (-)	8.18 (1.43)
		AHV Median (Range)	8.12 (7.27 , 9.33)	7.67 (6.76 , 10.19)	8.06 (6.10 , 9.52)	7.66 (7.66 , 7.66)	8.12 (6.86 , 9.81)
		HT-SDS Median (Range)	-0.80 (-2.86 , 0.51)	-0.49 (-1.27 , 1.50)	-0.55 (-2.44 , -0.10)	-0.14 (-0.14 , -0.14)	-0.20 (-1.75 , 0.85)
		HT-SDS Change[3] Median (Range)	3.55 (1.48 , 5.00)	2.86 (1.12 , 5.28)	2.61 (1.82 , 4.40)	2.74 (2.74 , 2.74)	3.04 (1.66 , 5.19)
		IGF-1-SDS Median (Range)	0.89 (0.00 , 2.52)	2.27 (1.26 , 2.71)	0.89 (-0.01 , 2.55)	0.51 (0.51 , 0.51)	1.46 (-0.34 , 2.07)
		IGF-1-SDS Change[3] Median (Range)	3.54 (2.21 , 5.70)	3.43 (2.25 , 4.43)	2.94 (1.39 , 5.07)	1.65 (1.65 , 1.65)	3.38 (1.25 , 4.80)
Year 2 PEN	6 months	n[2]	8	7	12	1	6
		AHV Mean (SD)	8.14 (0.87)	7.95 (1.11)	7.76 (0.97)	7.52 (-)	8.11 (1.44)
		AHV Median (Range)	8.27 (6.87 , 9.27)	7.51 (6.85 , 10.03)	7.83 (5.94 , 9.29)	7.52 (7.52 , 7.52)	8.30 (6.54 , 9.68)
		HT-SDS Median (Range)	-1.04 (-2.52 , 0.66)	-0.33 (-1.00 , 1.67)	-0.53 (-2.45 , 0.09)	-0.09 (-0.09 , -0.09)	0.13 (-2.03 , 1.12)
		HT-SDS Change[3] Median (Range)	3.95 (1.47 , 5.04)	2.94 (1.28 , 5.45)	2.77 (1.80 , 4.40)	2.79 (2.79 , 2.79)	3.36 (1.38 , 5.36)
		IGF-1-SDS Median (Range)	0.59 (-0.32 , 2.01)	2.07 (0.88 , 2.59)	0.73 (-0.27 , 2.66)	0.76 (0.76 , 0.76)	1.27 (-1.60 , 2.60)
		IGF-1-SDS Change[3] Median (Range)	3.28 (2.03 , 4.87)	3.14 (2.13 , 3.94)	2.87 (0.91 , 5.24)	1.90 (1.90 , 1.90)	3.40 (-0.01 , 4.41)
	12 months	n[2]	7	6	11	1	5
		AHV Mean (SD)	8.07 (0.83)	7.83 (1.20)	7.64 (0.98)	7.27 (-)	8.28 (1.26)
		AHV Median (Range)	8.22 (6.57 , 8.90)	7.25 (6.73 , 9.70)	7.52 (6.02 , 9.31)	7.27 (7.27 , 7.27)	8.90 (6.41 , 9.51)
		HT-SDS Median (Range)	-0.91 (-2.49 , 0.46)	-0.22 (-0.92 , 1.54)	-0.45 (-2.41 , 0.14)	-0.19 (-0.19 , -0.19)	0.47 (-2.15 , 1.31)
		HT-SDS Change[3] Median (Range)	4.35 (1.63 , 5.23)	2.78 (1.35 , 5.32)	3.17 (1.84 , 4.57)	2.68 (2.68 , 2.68)	4.11 (1.26 , 5.35)
		IGF-1-SDS Median (Range)	0.77 (-0.23 , 1.48)	1.64 (0.22 , 2.35)	0.68 (-0.82 , 2.19)	1.01 (1.01 , 1.01)	1.70 (-2.74 , 2.84)
		IGF-1-SDS Change[3] Median (Range)	2.92 (1.82 , 4.66)	3.02 (1.21 , 3.89)	3.08 (0.61 , 5.62)	2.15 (2.15 , 2.15)	2.90 (0.26 , 5.08)
Year 3 PEN	6 months	n[2]	4	3	8	1	3
		AHV Mean (SD)	7.50 (1.06)	7.00 (0.15)	7.74 (0.83)	7.13 (-)	8.67 (0.79)
		AHV Median (Range)	7.54 (6.20 , 8.73)	7.00 (6.85 , 7.16)	7.42 (6.84 , 9.16)	7.13 (7.13 , 7.13)	8.98 (7.77 , 9.25)
		HT-SDS Median (Range)	-0.48 (-1.32 , 0.45)	-0.16 (-0.60 , -0.11)	-0.31 (-0.77 , 0.24)	-0.26 (-0.26 , -0.26)	0.80 (0.29 , 1.28)
		HT-SDS Change[3] Median (Range)	2.79 (1.63 , 4.42)	2.72 (2.12 , 2.99)	2.99 (2.48 , 4.59)	2.62 (2.62 , 2.62)	4.86 (2.99 , 5.69)
		IGF-1-SDS Median (Range)	1.15 (0.51 , 1.91)	1.36 (0.83 , 2.39)	0.90 (-0.66 , 2.71)	0.87 (0.87 , 0.87)	2.03 (1.59 , 2.36)
		IGF-1-SDS Change[3] Median (Range)	2.87 (2.51 , 3.08)	2.35 (1.72 , 4.11)	2.53 (0.95 , 5.74)	2.01 (2.01 , 2.01)	4.17 (2.79 , 4.76)

1. N: number of patients randomized at the beginning of the main period after excluding the 2 subjects (footnote 4) from the corresponding groups.
2. n: number of patients followed upon each visit(timepoint).The n for patients being measured for height or tested for IGF-1 may be equal to or less than n at each visit.
3. Baseline is defined as the beginning of the main period (week 1).
4. Subject exclusion: Subject 08-003 with psychosocial dwarfism was excluded from Group 1 (somatrogon 0.66 mg/kg/wk);
Subject 08-004 who randomized to Genotropin but didn't continue into OLE part of study was not included in Groups 4 and 5.
PFIZER CONFIDENTIAL Source Data: irr_2021_oct_05 Table Generation: 06OCT2021 (17:41)
Output File: /BLA_Submission/CP-4-004_IRR_20211001/excel_dataout

Source: Excerpted from the response provided on October 15, 2021 to an Information Request (dated October 1, 2021), Table-2-cp-4-004-ole.
Abbreviations: AHV, annualized height velocity; HT, height; IGF-1, insulin-like growth factor-1; OLE, open-label extension; SD, standard deviation; SDS, height standard deviation score

16.5. ADA Titers in Trial CP-006, Main Study and OLE

Table 95. ADA Titers, Trial CP-4-006 (Main Study, Safety Analysis Set)

ADA Titer by Time Point	Somatrogon N=109	Genotropin N=115
Month 3		
N	8	12
Median	50	10
Range (minimum, maximum)	(10, 250)	(10, 250)
Month 6		
N	73	12
Median	250	10
Range (minimum, maximum)	(10, 6250)	(10, 1250)
Month 9		
N	47	8
Median	50	10
Range (minimum, maximum)	(10, 6250)	(10, 250)
Month 12		
N	83	7
Median	50	10
Range (minimum, maximum)	(10, 6250)	(10, 250)

Source: Prepared by Medical Reviewer with data from the Integrated Summary of Immunogenicity, Table 15.
* ADA testing is anti-somatrogon for subjects assigned to somatrogon treatment and anti-rhGH for subjects assigned to Genotropin.
For titer values, 6250 was the highest dilution possible and was used to represent values >6250.
Abbreviations: ADA, antidrug antibodies; rhGH, recombinant human growth hormone

Table 96. Summary of ADA Titers, Trial CP-4-006 (OLE Period, Safety Analysis Set)

ADA Titer by Time Point	Originally Randomized to Somatrogon N=104	Originally Randomized to Genotropin N=108
Month 3		
N	1	1
Median	50	250
Range (minimum, maximum)	-	-
Month 6		
N	67	21
Median	250	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)
Month 9		
N	0	1
Median		1250
Range (minimum, maximum		-
Month 12		
N	56	24
Median	250	50
Range (minimum, maximum)	(10, 6250)	(10, 6250)

Source: Prepared by Medical Reviewer with data from the Integrated Summary of Immunogenicity-Supplement, Table 9.
For titer values, 6250 was the highest dilution possible and was used to represent values >6250.
Abbreviations: ADA, antidrug antibodies; rhGH, recombinant human growth hormone

Table 97. Presence and Titer of ADA, Trial CP-4-004 (Main Study Period)

	Somatrogon			Genotropin
	0.25 mg/kg/wk (N=13)	0.48 mg/kg/wk (N=15)	0.66 mg/kg/wk (N=14)	0.034 mg/kg/day (N=11)
Subjects treated	13	15	14	11
ADA incidence, n (%)				
Visit 10/Week 26	0/13 (0)	5/15 (33.3)	5/14 (35.7)	2/11 (18.2)
Visit 12/Week 52	0/13 (0)	3/15 (20.0)	2/14 (14.3)	1/11 (9.1)
Somatrogon ADA titers				
Visit 10/Week 26 Mean (SD) Median (Range)	0	n=5 330.0 (521.5) 50.0 (50.0, 1250.0)	n=5 610.0 (589.9) 250.0 (50.0, 1250.0)	
Visit 12/Week 52 Mean (SD) Median (Range)	0	n=3 516.7 (642.9) 250.0 (50.0, 1250.0)	n=2 250.0 (0.0) 250.0 (25.0, 250.0)	
Somatrogon ADA – hGH specificity test, n (%)				
Visit 10/Week 26 Negative Positive	n=13 13 (100.0) 0	n=15 10 (66.7) 5 (33.3)	n=14 9 (64.3) 5 (35.7)	
Visit 12/Week 52 Negative Positive	n=13 13 (100.0) 0	n=15 12 (80.0) 3 (20.0)	n=14 12 (85.7) 2 (14.3)	
Anti-somatrogon NAb				
Visit 10/Week 26	All samples tested were negative			
Visit 12/Week 52				
Anti-hGH NAb				
Visit 10/Week 26	All samples tested were negative			All samples tested were negative
Visit 12/Week 52				

Source: Excerpted from the Integrated Summary of Immunogenicity, Table 12.
Abbreviations: ADA, antidrug antibodies; hGH, human growth hormone; SD, standard deviation

Table 98. Summary of ADA Titers Overall and by Year, Trial CP-4-004 (OLE Period)

Number Subjects Positive/Titer	Overall (N=48)	Year 1 (N=48)	Year 2 (N=44)	Year 3 (N=43)	Year 4 (N=38)	PEN Y1 (N=40)	PEN Y2 (N=35)
Median	250.0	50.0	250.0	250.0	130.0	250.0	50.0
Min	10	10	50	50	10	10	10
Max	6250	1250	1250	6250	250	6250	1250
Anti-Somatrogon Neutralizing Antibody, n (%) Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-hGH Antibody, n (%) Positive	16 (33.3)	11 (22.9)	11 (25.0)	10 (23.3)	2 (5.3)	13 (32.5)	6 (17.1)
Anti-CTP Antibody, n (%) Positive	4 (8.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.5)	2 (5.7)

Source: Excerpted from Integrated Summary of Immunogenicity-Supplement, Table 6.
Abbreviations: ADA, antidrug antibodies; CTP, c-terminal peptide; hGH, human growth hormone; OLE, open-label extension

Antidrug Antibodies Persistence

The Applicant defined persistent and transient antibodies for the analysis of ADA-positive subjects in Trial CP-4-006, main period as follows (excerpted from the Integrated Summary of Immunogenicity, pages 37 to 38):

Persistent

- Treatment-induced ADA detected at ≥2 sampling time points during treatment including any follow-up period, where the first and last ADA-positive samples are separated by a period of ≥16 weeks (irrespective of any ADA-negative samples in between); or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point <16 weeks before an ADA-negative last sample.

Transient

- Treatment-induced ADA detected only at 1 sampling time point during treatment for follow-up periods (excluding the last time point, which is considered persistent, unless shown to be undetectable at a later time point; or
- Treatment-induced ADA detected at ≥2 sampling time points during treatment including any follow-up period, where the first and last ADA-positive samples are separated by a period of <16 weeks (irrespective of any ADA-negative samples in between) and the subject's last sampling time point is ADA-negative.

Table 99. AHV by ADA Status, Trial CP-4-006 (Main Period, Somatrogon Group)

Time Point Statistics	ADA+ (N=84)	ADA- (N=25)	Difference
Visit 5 (Month 3)			
N	84	25	
Mean (SD)	11.90 (4.16)	10.44 (3.94)	
Median	11.41	10.44	
Range (min, max)	(0.23, 24.09)	(2.13, 17.74)	
LSM[a]	12.17	10.99	1.18
95% CI			-0.63, 2.99
Visit 6 (Month 6)			
N	84	24	
Mean (SD)	10.96 (2.94)	10.48 (2.28)	
Median	10.37	10.09	
Range (min, max)	(1.03, 20.06)	(6.05, 16.42)	
LSM[a]	11.30	11.17	0.13
95% CI			-1.03, 1.29
Visit 7 (Month 9)			
N	84	24	
Mean (SD)	10.34 (2.62)	10.35 (2.38)	
Median	9.74	10.20	
Range (min, max)	(3.31, 18.10)	(5.48, 15.97)	
LSM[a]	10.82	11.19	-0.37
95% CI			-1.41, 0.68
Visit 8 (Month 12)			
N	84	24	
Mean (SD)	10.21 (2.45)	10.07 (2.35)	
Median	9.58	9.99	
Range (min, max)	(4.57, 17.80)	(5.31, 17.37)	
LSM[a]	10.69	10.93	-0.24
95% CI			-1.22, 0.74

Source: Excerpted from Integrated Summary of Immunogenicity, Table 22.
Abbreviations: ADA, antidrug antibodies; AHV, annualized height velocity; CI, confidence interval; LSM, least-squares mean; SD, standard deviation

Table 100. AHV by ADA Status, Trial CP-4-006 (Main Period, Genotropin Group)

Time Point Statistics	ADA+ (N=18)	ADA- (N=97)	Difference
Visit 5 (Month 3)			
N	18	96	
Mean (SD)	13.65 (6.12)	9.99 (3.73)	
Median	11.47	9.35	
Range (min, max)	(7.19, 28.69)	(0.00, 25.82)	
LSM[a]	12.54	9.35	3.19
95% CI			1.21, 5.18
Visit 6 (Month 6)			
N	18	96	
Mean (SD)	11.37 (3.87)	9.88 (2.81)	
Median	10.17	9.34	
Range (min, max)	(5.75, 21.96)	(3.97, 20.93)	
LSM[a]	10.66	9.77	0.90
95% CI			-0.51, 2.30
Visit 7 (Month 9)			
N	18	96	
Mean (SD)	10.87 (3.44)	9.73 (2.49)	
Median	9.36	9.29	
Range (min, max)	(5.86, 17.34)	(5.32, 18.45)	
LSM[a]	10.39	9.75	0.64
95% CI			-0.63, 1.91
Visit 8 (Month 12)			
N	18	95	
Mean (SD)	10.54 (2.85)	9.52 (2.35)	

Time Point Statistics	ADA+ (N=18)	ADA- (N=97)	Difference
Median	9.41	9.15	
Range (min, max)	(6.93, 16.38)	(4.90, 17.60)	
LSM[a]	10.17	9.66	0.51
95% CI			-0.65, 1.68

Baseline is defined as the last non-missing measurement prior to the start of study drug.
[a] Results based on an analysis of covariance (ANCOVA) model with classification terms for ADA status, age group, gender, peak GH levels, and region.
The mean difference will be calculated between ADA+ and ADA- groups within each treatment arm.

Source: Excerpted from Integrated Summary of Immunogenicity, Table 23.
Abbreviations: ADA, antidrug antibodies; AHV, annualized height velocity; CI, confidence interval; LSM, least-squares mean; SD, standard deviation

Table 101. AHV and Change in Height SDS by ADA Status, Trial CP-4-004 (Main Study, Full Analysis Set)

Parameter Statistics	0.25 mg/kg/wk Somatrogon (N=13)		0.48 mg/kg/wk Somatrogon (N=15)		0.66 mg/kg/wk Somatrogon (N=14)		Total (N=42)	
	ADA Status		ADA Status		ADA Status		ADA Status	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	0	13	5	10	5	9	10	32
Height Velocity (cm/year)								
Mean (SD)		10.4 (2.6)	12.5 (2.4)	10.2 (1.8)	10.9 (3.1)	11.7 (4.4)	11.7 (2.7)	10.7 (3.0)
95% CI of Mean		8.9, 12.0	9.6, 15.4	8.9, 11.5	7.1, 14.7	8.3, 15.1	9.8, 13.7	9.6, 11.8
Lower Quartile		8.6	11.4	9.4	9.9	9.7	9.9	8.9
Median		10.2	13.6	10.4	10.8	11.6	12.5	10.4
Upper Quartile		12.3	14.1	10.7	13.6	14.9	13.9	12.3
Range		6.2, 14.4	8.9, 14.5	6.5, 13.8	6.4, 13.9	5.0, 18.3	6.4, 14.5	5.0, 18.3
Height SDS Change								
Mean (SD)		1.09 (0.53)	1.60 (0.51)	0.98 (0.34)	1.41 (0.64)	1.31 (0.75)	1.51 (0.56)	1.12 (0.55)
Lower Quartile		0.70	1.21	0.88	1.09	0.96	1.09	0.70
Median		1.07	1.87	0.98	1.49	1.19	1.67	1.04
Upper Quartile		1.47	1.98	1.22	1.85	1.69	1.98	1.45
Range		0.32, 2.15	0.92, 2.05	0.28, 1.56	0.48, 2.12	0.06, 2.47	0.48, 2.12	0.06, 2.47

Source: Excerpted from the Integrated Summary of Immunogenicity, Table 18.
Abbreviations: ADA, antidrug antibodies; AHV, annualized height velocity; OLE, open-label extension; SD, standard deviation, SDS, standard deviation score

Table 102. Summary of AHV at the End of OLE Years 1-4 and PEN Year 1 and 2, by ADA Status, Trial CP-4-004 (OLE, Full Analysis Set)

	Year 1 (N=48)		Year 2 (N=44)		Year 3 (N=43)		Year 4 (N=38)	
Height Velocity at End of Year (cm/year)	ADA Status		ADA Status		ADA Status		ADA Status	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
N	11	35	14	29	14	24	1	0
Mean (SD)	8.43 (1.02)	7.85 (1.66)	7.17 (1.31)	7.19 (1.25)	6.71 (1.19)	7.36 (1.86)	4.63 (-)	
Median	7.99	7.27	7.29	6.72	6.67	7.20	4.63	
Minimum, Maximum	7.19, 10.17	5.38, 11.44	4.15, 9.25	5.29, 9.76	4.92, 8.64	4.17, 12.79	4.63, 4.63	

	PEN Year 1 (N=40)		PEN Year 2 (N=35)	
Height Velocity at End of Year (cm/year)	ADA Status		ADA Status	
	Positive	Negative	Positive	Negative
N	15	20	15	15
Mean (SD)	6.31 (1.40)	7.48 (2.08)	6.47 (1.69)	6.48 (2.46)
Median	6.49	7.06	6.31	6.67
Minimum, Maximum	3.94, 8.49	3.55, 10.93	4.03, 11.02	2.27, 12.36

Source: Excerpted from Integrated Summary of Immunogenicity – Supplement, Table 10.
A subject is counted in the positive column beginning in the year that he/she has a positive status, and in every year thereafter.
Abbreviations: ADA, antidrug antibodies; AHV, annualized height velocity; OLE, open-label extension; SD, standard deviation

Height velocity at the end of each year used the measure at the Month 12 visit in each year with the measure at the Month 12 visit of the prior year as the reference. In cases where there was a gap in treatment between years, the measure at the restart of treatment (if available) was used as the reference.

17. Clinical Safety: Additional Information and Assessment

17.1. Duration of Exposure

Table 103. Duration of Exposure, Trial CP-4-006 (Main and OLE Periods Combined)

Subjects Treated by Duration, n (%)	Originally Randomized to Somatrogon N=109	Originally Randomized to Genotropin N=108	Total N=217
Completed 6 months	108 (99.08)	103 (95.37)	211 (97.24)
Completed 12 months	104 (95.41)	100 (92.59)	204 (94.01)
Completed 24 months	99 (90.83)	15 (13.89)	114 (52.53)
Completed 36 months	13 (11.93)		13 (5.99)
Duration (months)			
Mean (SD)	29.8 (6.06)	18.4 (5.23)	24.1 (8.05)
Median (min, max)	30.3 (2.1, 38.6)	18.4 (2.5, 30.5)	24.3 (2.1, 38.6)

Source: Excerpted from Applicant's response to an Information Request dated October 14, 2021, Table 1.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OLE, open-label extension; SD, standard deviation

Table 104. Duration of Exposure, Safety Population, Trial CP-4-004 (Main Period)

Variable	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Duration of treatment (weeks)					
Mean (SD)	51.3 (0.4)	51.1 (0.4)	51.1 (0.0)	51.2 (0.3)	52.3 (0.4)
Median (min, max)	51.1 (51.1, 52.1)	51.1 (50.1, 52.1)	51.1 (51.1, 51.1)	51.1 (50.1, 52.1)	52.1 (52.0, 53.3)
Subjects treated, by duration, n (%)					
<12 weeks	0	0	0	0	0
≥12 to <52 weeks	10 (76.9)	14 (93.3)	14 (100.0)	38 (90.5)	0
≥52 weeks	3 (23.1)	1 (6.7)	0	4 (9.5)	11 (100.0)

Source: adex.xpt; software, Python.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

Exposure data from Trial CP-4-004, OLE period submitted in the original application (data lock date of November 1, 2019) is shown in Table 105.

The Major Amendment submitted on September 15, 2021 (data lock date of December 21, 2020) provided new data for Period V (subjects originally randomized to 0.66 mg/kg/wk who were transferred from vial to pen injector).

Table 105. Summary of Exposure in Cohort Originally Randomized to 0.66 mg/kg/Week, Trial CP-4-004 (Main and OLE Periods)

Study Phase	Vial Main (N=14)	Vial OLE + PEN OLE (N=12)	Vial (Main+OLE) (N=14)	PEN OLE (N=11)
Visit	n (%)	n (%)	n (%)	n (%)
[≥Month 6, <Month 12]	14 (100)	12 (100)	14 (100)	11 (100)
[≥Month 12, <Month 24]		11 (91.67)	12 (85.71)	9 (81.82)
[≥Month 24, <Month 36]		11 (91.67)	11 (78.57)	7 (63.64)
[≥Month 36, <Month 48]		11 (91.67)	11 (78.57)	
[≥Month 48, <Month 60]		11 (91.67)	11 (78.57)	
[≥Month 60, <Month 72]		9 (75)	3 (21.43)	
[≥Month 72, <Month 84]		4 (33.33)		
Duration (months)				
Mean (SD)	11.9 (0.00)	64.3 (18.74)	48.4 (18.64)	23.6 (8.38)

Source: Excerpted from Applicant's response to an Information Request (dated October 14, 2021), Table 2.
Abbreviations: OLE, open-label extension; SD, standard deviation

17.2. Treatment-Emergent Adverse Events

Table 106. Overview of Treatment-Emergent Adverse Events, Trial CP-4-006 (OLE Period)

Event Category	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Any AE	72 (69.2)	87 (80.6)	159 (75.0)
Any SAE	7 (6.7)	4 (3.7)	11 (5.2)
SAE with fatal outcome	0	0	0
AE leading to discontinuation of study drug	1 (1.0)	5 (4.6)	6 (2.8)

Source: adae.xpt; software, Python. Data based on response to the Information Request dated October 14, 2021.
Abbreviations: AE, adverse event; OLE, open-label extension; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Table 107. Overview of Adverse Events, Safety Population, Trial CP-4-004 (OLE Period)

Event Category	Period III Somatrogon 0.25 mg/kg/wk N=16 n (%)	Period III Somatrogon 0.48 mg/kg/wk N=17 n (%)	Period III Somatrogon 0.66 mg/kg/wk N=15 n (%)	Period IV Somatrogon 0.66 mg/kg/wk N=44 n (%)	PEN Year 1 Somatrogon 0.66 mg/kg/wk N=40 n (%)	PEN Year 2 Somatrogon 0.66 mg/kg/wk N=35 n (%)
Any AE	12 (75.0)	6 (35.3)	7 (46.7)	32 (72.7)	24 (60.0)	15 (42.9)
Any SAE	0	2 (11.8)	0	2 (4.5)	0	1 (2.9)
SAE with fatal outcome	0	0	0	0	0	0
AE leading to discontinuation of study drug	0	0	0	1 (2.3)	1 (2.5)	1 (2.9)

Source: adae.xpt; software, Python. Data provided in the Major Amendment submitted on September 15, 2021.
Treatment-emergent adverse events defined as any AE with onset post-treatment.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

17.3. Narratives

17.3.1. Serious Adverse Events—Case Narratives (AEs Unrelated to Study Drug)

Trial CP-4-006, OLE Period

Adrenal Insufficiency

Subject (b) (6) was a 7-year-old female who developed adrenal insufficiency in OLE period (Day 386) after 12 months of treatment with somatrogon in main period. This subject had underlying history of secondary AI, neonatal hypoglycemia, septo-optic dysplasia, central hypothyroidism, decreased size of pituitary gland. She developed urinary tract infection with fever and had symptoms suggestive of AI (no cortisol values are provided) and was hospitalized and treated with hydrocortisone. Treatment with somatrogon was continued at the same dose (15 mg/kg/week). All events (adrenal insufficiency and urinary infection) resolved. This SAE of adrenal insufficiency was assessed by this medical reviewer as unrelated to the study drug (due to long duration of treatment and no treatment interruption) and most likely related to her underlying medical condition that was precipitated by the acute infection.

Trial CP-4-004, OLE Period

Gastric Disorder

Subject (b) (6) was a 7-year-old male who was originally randomized and treated with somatrogon in main period for 12 months (dose 0.48 mg/kg/week) and experienced severe gastrointestinal symptoms on Day 604. His medical history was significant for optic nerve hypoplasia, septo-optical dysplasia, pituitary hypoplasia, and hypothalamic-pituitary disorder. Concomitant medication included: levothyroxine for hypothyroidism and hydrocortisone for secondary hypocortisolism. The subject was hospitalized due to multiple bouts of vomiting, fever, abdominal pain, and weakness. Treatment included hydrocortisone, dexamethasone, diphenhydramine, metamizole sodium, arginine glutamate, silicon dioxide, and pancreatin. The event resolved the same day without study drug interruption.

- ***Medical Officer's Comment***
- *It is not clear whether this event of vomiting and diarrhea was suggestive of adrenal insufficiency (precipitated by fever) or vomiting and diarrhea were due to the acute gastrointestinal infection. Without cortisol levels at time of the event no firm conclusion can be made whether this event can be defined as adrenal insufficiency event. More important that in any case, the event of vomiting was unrelated to the study drug and most likely related to the infection (that is not uncommon in this age group) or to adrenal insufficiency that was precipitated by the acute infection and/or inability to take oral hydrocortisone.*

Thyroid Gland Abscess

Subject (b) (6) was a 5-year-old male who experienced two episodes of thyroid gland abscess. His medical history included hypothyroidism. Concomitant medication included Euthyrox

(levothyroxine). He completed the main study at 0.48 mg/kg somatrogon dose and immediately after he entered the OLE phase (Day 353) and continued at 0.48 mg/kg dose. On Day 418, the subject was hospitalized with the diagnosis of thyroid abscess. The event was considered resolved on Day 431 and the medication was resumed. On Day 806, a second occurrence of thyroid abscess (on the same side of the first event) was diagnosed. In both episodes, the subject was treated by abscess drainage and antibiotics. The second occurrence of thyroid abscess was considered resolved on Day 820 and there was no change in the study drug regimen.

Schwannoma

Subject ID# (b) (6) was a 12.7-year-old male who experienced an SAE of schwannoma on Day 2255 of treatment (OLE period). Medical history included anterior chamber cleavage syndrome and visual pathway disorder. The subject started the main phase of Trial CP-4-004 in the Genotropin arm and continued the study in the OLE period, receiving the first dose of somatrogon (5 mg/week) on Day 366. The somatrogon dose was increased to 10.59 mg/week on Day 1374 and to 24 mg/week on Day 1577. At the time of the event, the subject was receiving somatrogon 31 mg/week. On Day 2255, the subject was hospitalized due to difficult breathing and hoarse voice and was subsequently treated in outpatient care. Endoscopic and imaging exams (one month later) showed a neoplasm of an approximate diameter of 1 cm in the lumen of larynx and no enlarge lymph nodes were noted. The study drug was permanently discontinued. The tumor was surgically removed, and the diagnosis of schwannoma was confirmed by an oncologist. The SAE of schwannoma was considered resolved with sequelae (voice did not improve).

AEs Leading to Discontinuation

Anxiety

Subject (ID # (b) (6)) had a nonserious AE coded by the PT of anxiety that led to discontinuation during the OLE period of Trial CP-4-006. This subject was a 10-year-old male who was originally randomized to Genotropin. In the OLE period, the subject experienced moderate anxiety that was reported from Day 339 to Day 649, which was considered resolved on Day 649. No related AE was observed. Other events reported included hypothyroidism (Day 477), injection site pruritus and erythema (Day 540 to 649, assessed as resolved). The cause of anxiety was not available in the narrative. This Medical Reviewer concurs with the Investigator/Applicant's assessment of this nonserious AE as unrelated to study drug.

Irritability

This subject (ID# (b) (6)) was a 3-year-old male, originally randomized to somatrogon who experienced several intermittent mild events of irritable mood that started at Day 1 of treatment and persisted throughout the main and OLE periods. Most events had a duration of 2 days. The subject was discontinued on Day 928 (OLE period). Relevant medical history included glucose-6-phosphate dehydrogenase deficiency, thalassemia minor, and nuclear resonance imaging brain abnormal. The reported concomitant medications at the time of the AE of irritability included pain medication, antibiotic, antihistaminic, and anthelmintic used for few days. This subject tested positive for ADA at Month 9 of the main period and persisted ADA-positive throughout the OLE period. Neutralizing antibody was negative. Other AEs reported included several events of injection site reactions during the main and OLE periods. While it is possible that the events

of irritability were in part associated with the events of injection site reactions, that association was not clear through the data provided in the narrative.

17.4. Treatment-Emergent Adverse Events

Table 108. Adverse Events by FDA Medical Query (Narrow), Safety Population, Trial CP-4-006 (Main Study)

FDA Medical Query (Narrow)	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Local administration reactions	47 (43.1)	29 (25.2)	17.9 (5.7, 30.1)
Erythema	10 (9.2)	3 (2.6)	6.6 (0.4, 12.8)
Hemorrhage	7 (6.4)	1 (0.9)	5.5 (0.6, 10.4)
Nasopharyngitis	36 (33.0)	33 (28.7)	4.3 (-7.8, 16.4)
Pruritus	7 (6.4)	4 (3.5)	2.9 (-2.8, 8.6)
Nausea	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Bronchospasm	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Paranesthesia	2 (1.8)	0	1.8 (-0.7, 4.3)
Pyrexia	18 (16.5)	17 (14.8)	1.7 (-7.8, 11.2)
Fatigue	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
Arthritis	1 (0.9)	0	0.9 (-0.9, 2.7)
Somnolence	1 (0.9)	0	0.9 (-0.9, 2.7)
Syncope	1 (0.9)	0	0.9 (-0.9, 2.7)
Anxiety	1 (0.9)	0	0.9 (-0.9, 2.7)
Irritability	1 (0.9)	0	0.9 (-0.9, 2.7)
Alopecia	1 (0.9)	0	0.9 (-0.9, 2.7)
Anemia	10 (9.2)	10 (8.7)	0.5 (-7.0, 8.0)
Cough	9 (8.3)	9 (7.8)	0.5 (-6.6, 7.6)
Urticaria	2 (1.8)	2 (1.7)	0.1 (-3.4, 3.6)
Hypoglycemia	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Hepatic injury	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Pneumonia	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Parasomnia	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)

FDA Medical Query (Narrow)	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Vomiting	8 (7.3)	9 (7.8)	-0.5 (-7.4, 6.4)
Abdominal pain	7 (6.4)	8 (7.0)	-0.6 (-7.1, 5.9)
Rash	6 (5.5)	7 (6.1)	-0.6 (-6.7, 5.5)
Diarrhea	3 (2.8)	4 (3.5)	-0.7 (-5.2, 3.8)
Dizziness	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Peripheral edema	0	1 (0.9)	-0.9 (-2.6, 0.8)
Back pain	0	1 (0.9)	-0.9 (-2.6, 0.8)
Gynecomastia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Constipation	2 (1.8)	4 (3.5)	-1.7 (-5.9, 2.5)
Insomnia	1 (0.9)	3 (2.6)	-1.7 (-5.1, 1.7)
Myalgia	0	2 (1.7)	-1.7 (-4.1, 0.7)
Leukopenia	0	3 (2.6)	-2.6 (-5.5, 0.3)
Thrombocytopenia	0	3 (2.6)	-2.6 (-5.5, 0.3)
Dyspepsia	2 (1.8)	6 (5.2)	-3.4 (-8.2, 1.4)
Headache	18 (16.5)	25 (21.7)	-5.2 (-15.5, 5.1)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 109. Adverse Events by Preferred Term (PT), Safety Population, Trial CP-4-006 (Main Study)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Any AE	95 (87.2)	97 (84.3)	2.9 (-6.2, 12.0)
Injection site pain	43 (39.4)	29 (25.2)	14.2 (2.1, 26.3)
Injection site erythema	9 (8.3)	0	8.3 (3.1, 13.5)
Injection site pruritus	6 (5.5)	0	5.5 (1.2, 9.8)
Arthropod bite	6 (5.5)	1 (0.9)	4.6 (-0.0, 9.2)
Rhinitis	6 (5.5)	1 (0.9)	4.6 (-0.0, 9.2)
Injection site swelling	5 (4.6)	0	4.6 (0.7, 8.5)
Hypothyroidism	7 (6.4)	3 (2.6)	3.8 (-1.6, 9.2)
Free fatty acids increased	5 (4.6)	1 (0.9)	3.7 (-0.6, 8.0)
Injection site induration	4 (3.7)	1 (0.9)	2.8 (-1.1, 6.7)
Conjunctivitis allergic	3 (2.8)	0	2.8 (-0.3, 5.9)
Hypertriglyceridemia	3 (2.8)	0	2.8 (-0.3, 5.9)
Molluscum contagiosum	3 (2.8)	0	2.8 (-0.3, 5.9)
Pyrexia	18 (16.5)	16 (13.9)	2.6 (-6.8, 12.0)
Pharyngitis	7 (6.4)	5 (4.3)	2.1 (-3.8, 8.0)
Oropharyngeal pain	6 (5.5)	4 (3.5)	2.0 (-3.4, 7.4)
Influenza	5 (4.6)	3 (2.6)	2.0 (-2.9, 6.9)
Abdominal pain	4 (3.7)	2 (1.7)	2.0 (-2.3, 6.3)
Enterobiasis	4 (3.7)	2 (1.7)	2.0 (-2.3, 6.3)
Nausea	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Rhinitis allergic	3 (2.8)	1 (0.9)	1.9 (-1.6, 5.4)
Aphthous ulcer	2 (1.8)	0	1.8 (-0.7, 4.3)
Attention deficit/hyperactivity disorder	2 (1.8)	0	1.8 (-0.7, 4.3)
Enteritis	2 (1.8)	0	1.8 (-0.7, 4.3)
Hordeolum	2 (1.8)	0	1.8 (-0.7, 4.3)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Hypoesthesia	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site hemorrhage	2 (1.8)	0	1.8 (-0.7, 4.3)
Injection site warmth	2 (1.8)	0	1.8 (-0.7, 4.3)
Muscle spasms	2 (1.8)	0	1.8 (-0.7, 4.3)
Pharyngitis streptococcal	2 (1.8)	0	1.8 (-0.7, 4.3)
Gastroenteritis	4 (3.7)	3 (2.6)	1.1 (-3.5, 5.7)
Hyperinsulinemia	4 (3.7)	3 (2.6)	1.1 (-3.5, 5.7)
Iron deficiency anemia	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
Rash generalized	3 (2.8)	2 (1.7)	1.1 (-2.8, 5.0)
Fatigue	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Increased appetite	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Injection site bruising	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Sinusitis	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Thyroxine free decreased	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Viral pharyngitis	2 (1.8)	1 (0.9)	0.9 (-2.1, 3.9)
Abdominal lymphadenopathy	1 (0.9)	0	0.9 (-0.9, 2.7)
Abdominal pain lower	1 (0.9)	0	0.9 (-0.9, 2.7)
Alopecia	1 (0.9)	0	0.9 (-0.9, 2.7)
Asthma	1 (0.9)	0	0.9 (-0.9, 2.7)
Astigmatism	1 (0.9)	0	0.9 (-0.9, 2.7)
Bacterial test positive	1 (0.9)	0	0.9 (-0.9, 2.7)
Blepharospasm	1 (0.9)	0	0.9 (-0.9, 2.7)
Blood cholesterol increased	1 (0.9)	0	0.9 (-0.9, 2.7)
Blood iron decreased	1 (0.9)	0	0.9 (-0.9, 2.7)
Blood triglycerides increased	1 (0.9)	0	0.9 (-0.9, 2.7)
Bronchial obstruction	1 (0.9)	0	0.9 (-0.9, 2.7)
Bronchospasm	1 (0.9)	0	0.9 (-0.9, 2.7)
Chronic tonsillitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Congenital hypothyroidism	1 (0.9)	0	0.9 (-0.9, 2.7)
Contusion	1 (0.9)	0	0.9 (-0.9, 2.7)
Dermatitis allergic	1 (0.9)	0	0.9 (-0.9, 2.7)
Diabetes insipidus	1 (0.9)	0	0.9 (-0.9, 2.7)
Discomfort	1 (0.9)	0	0.9 (-0.9, 2.7)
Dry skin	1 (0.9)	0	0.9 (-0.9, 2.7)
Enuresis	1 (0.9)	0	0.9 (-0.9, 2.7)
Epistaxis	1 (0.9)	0	0.9 (-0.9, 2.7)
Excessive eye blinking	1 (0.9)	0	0.9 (-0.9, 2.7)
Eye pain	1 (0.9)	0	0.9 (-0.9, 2.7)
Eyelid oedema	1 (0.9)	0	0.9 (-0.9, 2.7)
Fear of injection	1 (0.9)	0	0.9 (-0.9, 2.7)
Gastritis	1 (0.9)	0	0.9 (-0.9, 2.7)
Hand-foot-and-mouth disease	1 (0.9)	0	0.9 (-0.9, 2.7)
Henoch-Schonlein purpura	1 (0.9)	0	0.9 (-0.9, 2.7)
Hepatosplenomegaly	1 (0.9)	0	0.9 (-0.9, 2.7)
Hypersensitivity	1 (0.9)	0	0.9 (-0.9, 2.7)
Hypocholesterolemia	1 (0.9)	0	0.9 (-0.9, 2.7)
Hypoglycemia	1 (0.9)	0	0.9 (-0.9, 2.7)
Infected bite	1 (0.9)	0	0.9 (-0.9, 2.7)
Initial insomnia	1 (0.9)	0	0.9 (-0.9, 2.7)
Injection site hypertrophy	1 (0.9)	0	0.9 (-0.9, 2.7)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Injection site inflammation	1 (0.9)	0	0.9 (-0.9, 2.7)
Irritability	1 (0.9)	0	0.9 (-0.9, 2.7)
Lethargy	1 (0.9)	0	0.9 (-0.9, 2.7)
Low density lipoprotein decreased	1 (0.9)	0	0.9 (-0.9, 2.7)
Lyme disease	1 (0.9)	0	0.9 (-0.9, 2.7)
Melanocytic naevus	1 (0.9)	0	0.9 (-0.9, 2.7)
Mite allergy	1 (0.9)	0	0.9 (-0.9, 2.7)
Myringitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Nail bed inflammation	1 (0.9)	0	0.9 (-0.9, 2.7)
Non-scarring alopecia	1 (0.9)	0	0.9 (-0.9, 2.7)
Oral herpes	1 (0.9)	0	0.9 (-0.9, 2.7)
Oral pain	1 (0.9)	0	0.9 (-0.9, 2.7)
Overweight	1 (0.9)	0	0.9 (-0.9, 2.7)
Paronychia	1 (0.9)	0	0.9 (-0.9, 2.7)
Pfapa syndrome	1 (0.9)	0	0.9 (-0.9, 2.7)
Phonophobia	1 (0.9)	0	0.9 (-0.9, 2.7)
Photophobia	1 (0.9)	0	0.9 (-0.9, 2.7)
Polyuria	1 (0.9)	0	0.9 (-0.9, 2.7)
Respiratory disorder	1 (0.9)	0	0.9 (-0.9, 2.7)
Scratch	1 (0.9)	0	0.9 (-0.9, 2.7)
Skin injury	1 (0.9)	0	0.9 (-0.9, 2.7)
Sleep terror	1 (0.9)	0	0.9 (-0.9, 2.7)
Sphincter of Oddi dysfunction	1 (0.9)	0	0.9 (-0.9, 2.7)
Stomatitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Supernumerary teeth	1 (0.9)	0	0.9 (-0.9, 2.7)
Swelling face	1 (0.9)	0	0.9 (-0.9, 2.7)
Swelling of eyelid	1 (0.9)	0	0.9 (-0.9, 2.7)
Syncope	1 (0.9)	0	0.9 (-0.9, 2.7)
Synovitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Tonsillar hypertrophy	1 (0.9)	0	0.9 (-0.9, 2.7)
Tooth abscess	1 (0.9)	0	0.9 (-0.9, 2.7)
Tooth infection	1 (0.9)	0	0.9 (-0.9, 2.7)
Tracheitis	1 (0.9)	0	0.9 (-0.9, 2.7)
Traumatic hematoma	1 (0.9)	0	0.9 (-0.9, 2.7)
Upper limb fracture	1 (0.9)	0	0.9 (-0.9, 2.7)
Urinary incontinence	1 (0.9)	0	0.9 (-0.9, 2.7)
White blood cells urine positive	1 (0.9)	0	0.9 (-0.9, 2.7)
Cough	9 (8.3)	9 (7.8)	0.5 (-6.6, 7.6)
Anemia	7 (6.4)	7 (6.1)	0.3 (-6.0, 6.6)
Pain in extremity	5 (4.6)	5 (4.3)	0.3 (-5.1, 5.7)
Otitis externa	4 (3.7)	4 (3.5)	0.2 (-4.7, 5.1)
Conjunctivitis	3 (2.8)	3 (2.6)	0.2 (-4.0, 4.4)
Viral upper respiratory tract infection	2 (1.8)	2 (1.7)	0.1 (-3.4, 3.6)
Bronchial hyperreactivity	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Dermatitis atopic	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Dizziness	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Idiopathic urticaria	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Ligament sprain	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Malaise	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Parasitic gastroenteritis	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Pneumonia	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Pruritus generalized	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Skin abrasion	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Skin laceration	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Toothache	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Torticollis	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Upper respiratory tract infection	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Urinary tract infection	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Viral infection	1 (0.9)	1 (0.9)	0.0 (-2.5, 2.5)
Vomiting	8 (7.3)	9 (7.8)	-0.5 (-7.4, 6.4)
Tonsillitis	5 (4.6)	6 (5.2)	-0.6 (-6.3, 5.1)
Diarrhea	3 (2.8)	4 (3.5)	-0.7 (-5.2, 3.8)
Rhinorrhea	3 (2.8)	4 (3.5)	-0.7 (-5.2, 3.8)
Rash	2 (1.8)	3 (2.6)	-0.8 (-4.7, 3.1)
Dental caries	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Eosinophilia	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Fall	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Pain	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Skin papilloma	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Traumatic fracture	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Urticaria	1 (0.9)	2 (1.7)	-0.8 (-3.8, 2.2)
Abdominal distension	0	1 (0.9)	-0.9 (-2.6, 0.8)
Adenoidal hypertrophy	0	1 (0.9)	-0.9 (-2.6, 0.8)
Adenoiditis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Adrenocortical insufficiency acute	0	1 (0.9)	-0.9 (-2.6, 0.8)
Aggression	0	1 (0.9)	-0.9 (-2.6, 0.8)
Alanine aminotransferase increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Anal pruritus	0	1 (0.9)	-0.9 (-2.6, 0.8)
Application site irritation	0	1 (0.9)	-0.9 (-2.6, 0.8)
Aspartate aminotransferase increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Back pain	0	1 (0.9)	-0.9 (-2.6, 0.8)
Blood alkaline phosphatase increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Blood glucose decreased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Blood lactate dehydrogenase increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Chalazion	0	1 (0.9)	-0.9 (-2.6, 0.8)
Conductive deafness	0	1 (0.9)	-0.9 (-2.6, 0.8)
Cortisol decreased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Croup infectious	0	1 (0.9)	-0.9 (-2.6, 0.8)
Dyspepsia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Dyssomnia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Eosinophil count increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Epiphyseal fracture	0	1 (0.9)	-0.9 (-2.6, 0.8)
Erythema infectiosum	0	1 (0.9)	-0.9 (-2.6, 0.8)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Flatulence	0	1 (0.9)	-0.9 (-2.6, 0.8)
Gastroesophageal reflux disease	0	1 (0.9)	-0.9 (-2.6, 0.8)
Growing pains	0	1 (0.9)	-0.9 (-2.6, 0.8)
Gynecomastia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Hemoglobin decreased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Head injury	0	1 (0.9)	-0.9 (-2.6, 0.8)
Heat exhaustion	0	1 (0.9)	-0.9 (-2.6, 0.8)
Heat stroke	0	1 (0.9)	-0.9 (-2.6, 0.8)
Hepatic enzyme increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Herpes virus infection	0	1 (0.9)	-0.9 (-2.6, 0.8)
Herpes zoster	0	1 (0.9)	-0.9 (-2.6, 0.8)
Hyperphosphatasemia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Impaired fasting glucose	0	1 (0.9)	-0.9 (-2.6, 0.8)
Keratosis pilaris	0	1 (0.9)	-0.9 (-2.6, 0.8)
Labyrinthitis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Limb injury	0	1 (0.9)	-0.9 (-2.6, 0.8)
Lymphadenitis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Lymphocyte count increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Lymphocyte morphology abnormal	0	1 (0.9)	-0.9 (-2.6, 0.8)
Measles	0	1 (0.9)	-0.9 (-2.6, 0.8)
Miliaria	0	1 (0.9)	-0.9 (-2.6, 0.8)
Mitral valve disease	0	1 (0.9)	-0.9 (-2.6, 0.8)
Monocyte count increased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Monocytopenia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Neutropenia	0	1 (0.9)	-0.9 (-2.6, 0.8)
Neutrophil count decreased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Oedema peripheral	0	1 (0.9)	-0.9 (-2.6, 0.8)
Otosalpingitis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Primary hypothyroidism	0	1 (0.9)	-0.9 (-2.6, 0.8)
Pulpitis dental	0	1 (0.9)	-0.9 (-2.6, 0.8)
Road traffic accident	0	1 (0.9)	-0.9 (-2.6, 0.8)
Skin infection	0	1 (0.9)	-0.9 (-2.6, 0.8)
Skin lesion	0	1 (0.9)	-0.9 (-2.6, 0.8)
Skin swelling	0	1 (0.9)	-0.9 (-2.6, 0.8)
Somnambulism	0	1 (0.9)	-0.9 (-2.6, 0.8)
Speech disorder developmental	0	1 (0.9)	-0.9 (-2.6, 0.8)
Temperature regulation disorder	0	1 (0.9)	-0.9 (-2.6, 0.8)
Thyroid disorder	0	1 (0.9)	-0.9 (-2.6, 0.8)
Tympanic membrane disorder	0	1 (0.9)	-0.9 (-2.6, 0.8)
Ureterolithiasis	0	1 (0.9)	-0.9 (-2.6, 0.8)
Wheezing	0	1 (0.9)	-0.9 (-2.6, 0.8)
White blood cell count decreased	0	1 (0.9)	-0.9 (-2.6, 0.8)
Constipation	2 (1.8)	4 (3.5)	-1.7 (-5.9, 2.5)
Erythema	1 (0.9)	3 (2.6)	-1.7 (-5.1, 1.7)
Iron deficiency	1 (0.9)	3 (2.6)	-1.7 (-5.1, 1.7)

Preferred Term	Somatrogon N=109 n (%)	Genotropin N=115 n (%)	Risk Difference (95% CI)[1]
Nasal congestion	1 (0.9)	3 (2.6)	-1.7 (-5.1, 1.7)
Otitis media acute	1 (0.9)	3 (2.6)	-1.7 (-5.1, 1.7)
Animal bite	0	2 (1.7)	-1.7 (-4.1, 0.7)
Blood glucose increased	0	2 (1.7)	-1.7 (-4.1, 0.7)
Blood thyroid stimulating hormone increased	0	2 (1.7)	-1.7 (-4.1, 0.7)
Body temperature increased	0	2 (1.7)	-1.7 (-4.1, 0.7)
Insomnia	0	2 (1.7)	-1.7 (-4.1, 0.7)
Leukopenia	0	2 (1.7)	-1.7 (-4.1, 0.7)
Myalgia	0	2 (1.7)	-1.7 (-4.1, 0.7)
Neck pain	0	2 (1.7)	-1.7 (-4.1, 0.7)
Pruritus	0	2 (1.7)	-1.7 (-4.1, 0.7)
Seasonal allergy	0	2 (1.7)	-1.7 (-4.1, 0.7)
Tonsillitis streptococcal	0	2 (1.7)	-1.7 (-4.1, 0.7)
Varicella	0	2 (1.7)	-1.7 (-4.1, 0.7)
Viral tonsillitis	0	2 (1.7)	-1.7 (-4.1, 0.7)
Nasopharyngitis	25 (22.9)	29 (25.2)	-2.3 (-13.5, 8.9)
Arthralgia	5 (4.6)	8 (7.0)	-2.4 (-8.5, 3.7)
Otitis media	4 (3.7)	7 (6.1)	-2.4 (-8.0, 3.2)
Blood thyroid stimulating hormone decreased	0	3 (2.6)	-2.6 (-5.5, 0.3)
Gastroenteritis viral	0	3 (2.6)	-2.6 (-5.5, 0.3)
Thrombocytopenia	0	3 (2.6)	-2.6 (-5.5, 0.3)
Abdominal pain upper	2 (1.8)	6 (5.2)	-3.4 (-8.2, 1.4)
Ear pain	2 (1.8)	7 (6.1)	-4.3 (-9.3, 0.7)
Bronchitis	3 (2.8)	9 (7.8)	-5.0 (-10.8, 0.8)
Headache	18 (16.5)	25 (21.7)	-5.2 (-15.5, 5.1)
Blood creatine phosphokinase increased	2 (1.8)	8 (7.0)	-5.2 (-10.5, 0.1)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 110. Adverse Events by FDA Medical Query (Narrow), Safety Population, Trial CP-4-004 (Main Study)

FDA Medical Query (Narrow)	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Headache	4 (30.8)	1 (6.7)	0	5 (11.9)	1 (9.1)
Anemia	3 (23.1)	2 (13.3)	3 (21.4)	8 (19.0)	1 (9.1)
Nasopharyngitis	3 (23.1)	2 (13.3)	1 (7.1)	6 (14.3)	3 (27.3)
Pyrexia	3 (23.1)	1 (6.7)	0	4 (9.5)	1 (9.1)
Cough	1 (7.7)	1 (6.7)	0	2 (4.8)	0
Hemorrhage	1 (7.7)	0	2 (14.3)	3 (7.1)	0
Erythema	1 (7.7)	0	1 (7.1)	2 (4.8)	0
Local administration reactions	1 (7.7)	0	1 (7.1)	2 (4.8)	0
Fatigue	1 (7.7)	0	0	1 (2.4)	1 (9.1)
Back pain	1 (7.7)	0	0	1 (2.4)	0
Hypoglycemia	1 (7.7)	0	0	1 (2.4)	0
Nausea	1 (7.7)	0	0	1 (2.4)	0
Peripheral edema	1 (7.7)	0	0	1 (2.4)	0
Abdominal pain	0	1 (6.7)	0	1 (2.4)	1 (9.1)
Vomiting	0	1 (6.7)	0	1 (2.4)	1 (9.1)
Pruritus	0	0	1 (7.1)	1 (2.4)	0
Rash	0	0	1 (7.1)	1 (2.4)	0
Urticaria	0	0	1 (7.1)	1 (2.4)	0
Dizziness	0	0	0	0	1 (9.1)
Vertigo	0	0	0	0	1 (9.1)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as any AE onset occurring post-treatment.
For specific preferred terms under each FMQ
Abbreviations: FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 111. Adverse Events by Preferred Term (PT), Safety Population, Trial CP-4-004 (Main Study)

Preferred Term	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Any AE	10 (76.9)	10 (66.7)	10 (71.4)	30 (71.4)	8 (72.7)
Headache	4 (30.8)	1 (6.7)	0	5 (11.9)	1 (9.1)
Bronchitis	3 (23.1)	0	0	3 (7.1)	2 (18.2)
Respiratory tract infection	2 (15.4)	1 (6.7)	2 (14.3)	5 (11.9)	3 (27.3)
Nasopharyngitis	2 (15.4)	1 (6.7)	0	3 (7.1)	2 (18.2)
Pyrexia	2 (15.4)	1 (6.7)	0	3 (7.1)	1 (9.1)
Anemia	1 (7.7)	2 (13.3)	3 (21.4)	6 (14.3)	1 (9.1)
Hypothyroidism	1 (7.7)	1 (6.7)	1 (7.1)	3 (7.1)	1 (9.1)
Cough	1 (7.7)	1 (6.7)	0	2 (4.8)	0
Varicella	1 (7.7)	0	2 (14.3)	3 (7.1)	0
Injection site erythema	1 (7.7)	0	1 (7.1)	2 (4.8)	0
Injection site swelling	1 (7.7)	0	1 (7.1)	2 (4.8)	0
Asthenia	1 (7.7)	0	0	1 (2.4)	1 (9.1)
Nasal congestion	1 (7.7)	0	0	1 (2.4)	1 (9.1)

Preferred Term	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Pain in extremity	1 (7.7)	0	0	1 (2.4)	1 (9.1)
Rhinitis	1 (7.7)	0	0	1 (2.4)	1 (9.1)
Accidental overdose	1 (7.7)	0	0	1 (2.4)	0
Adrenal insufficiency	1 (7.7)	0	0	1 (2.4)	0
Amblyopia	1 (7.7)	0	0	1 (2.4)	0
Arthralgia	1 (7.7)	0	0	1 (2.4)	0
Astigmatism	1 (7.7)	0	0	1 (2.4)	0
Back pain	1 (7.7)	0	0	1 (2.4)	0
Biliary dyskinesia	1 (7.7)	0	0	1 (2.4)	0
Body temperature increased	1 (7.7)	0	0	1 (2.4)	0
Chest pain	1 (7.7)	0	0	1 (2.4)	0
Conjunctivitis	1 (7.7)	0	0	1 (2.4)	0
Connective tissue disorder	1 (7.7)	0	0	1 (2.4)	0
Cystitis	1 (7.7)	0	0	1 (2.4)	0
Dermatitis atopic	1 (7.7)	0	0	1 (2.4)	0
Ear infection	1 (7.7)	0	0	1 (2.4)	0
Enteritis	1 (7.7)	0	0	1 (2.4)	0
Eye inflammation	1 (7.7)	0	0	1 (2.4)	0
Eyelid oedema	1 (7.7)	0	0	1 (2.4)	0
Hemoglobin decreased	1 (7.7)	0	0	1 (2.4)	0
Hypercalcemia	1 (7.7)	0	0	1 (2.4)	0
Hypoglycemia	1 (7.7)	0	0	1 (2.4)	0
Impaired fasting glucose	1 (7.7)	0	0	1 (2.4)	0
Iron deficiency anemia	1 (7.7)	0	0	1 (2.4)	0
Nausea	1 (7.7)	0	0	1 (2.4)	0
Oedema peripheral	1 (7.7)	0	0	1 (2.4)	0
Petechiae	1 (7.7)	0	0	1 (2.4)	0
Skin papilloma	1 (7.7)	0	0	1 (2.4)	0
Snoring	1 (7.7)	0	0	1 (2.4)	0
Sphincter of Oddi dysfunction	1 (7.7)	0	0	1 (2.4)	0
Respiratory tract infection viral	0	2 (13.3)	1 (7.1)	3 (7.1)	1 (9.1)
Rhinitis allergic	0	1 (6.7)	1 (7.1)	2 (4.8)	0
Abdominal pain	0	1 (6.7)	0	1 (2.4)	1 (9.1)
Fungal skin infection	0	1 (6.7)	0	1 (2.4)	0
Secondary adrenocortical insufficiency	0	1 (6.7)	0	1 (2.4)	0
Tracheitis	0	1 (6.7)	0	1 (2.4)	0
Tracheobronchitis	0	1 (6.7)	0	1 (2.4)	0
Viral infection	0	1 (6.7)	0	1 (2.4)	0

Preferred Term	Somatrogon 0.25 mg/kg/wk N=13 n (%)	Somatrogon 0.48 mg/kg/wk N=15 n (%)	Somatrogon 0.66 mg/kg/wk N=14 n (%)	Total Somatrogon N=42 n (%)	Genotropin N=11 n (%)
Vomiting	0	1 (6.7)	0	1 (2.4)	0
Thyroxine decreased	0	0	1 (7.1)	1 (2.4)	1 (9.1)
Toothache	0	0	1 (7.1)	1 (2.4)	1 (9.1)
Dental caries	0	0	1 (7.1)	1 (2.4)	0
Gastroenteritis	0	0	1 (7.1)	1 (2.4)	0
Hematuria	0	0	1 (7.1)	1 (2.4)	0
Helminthic infection	0	0	1 (7.1)	1 (2.4)	0
Injection site hematoma	0	0	1 (7.1)	1 (2.4)	0
Injection site pain	0	0	1 (7.1)	1 (2.4)	0
Injection site pruritus	0	0	1 (7.1)	1 (2.4)	0
Insulin-like growth factor increased	0	0	1 (7.1)	1 (2.4)	0
Meniscus cyst	0	0	1 (7.1)	1 (2.4)	0
Urticaria	0	0	1 (7.1)	1 (2.4)	0
Acetonemic vomiting	0	0	0	0	1 (9.1)
Acute tonsillitis	0	0	0	0	1 (9.1)
Attention deficit/hyperactivity disorder	0	0	0	0	1 (9.1)
Hypermetropia	0	0	0	0	1 (9.1)
Pulpitis dental	0	0	0	0	1 (9.1)
Red blood cell count decreased	0	0	0	0	1 (9.1)
Sinusitis	0	0	0	0	1 (9.1)
Vertigo	0	0	0	0	1 (9.1)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as any AE onset occurring post-treatment.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 112. AE of Anemia/Iron Deficiency/Hemoglobin, Trial CP-4-004 (Main Study), by Individual and by Country

ID	Treatment Group	Site#	Country	Total Number of Randomized Subjects Per Site
(b) (6)	Somatrogon 0.25 mg/kg/wk	16	Ukraine	1 Genotropin, 1 somatrogon
	Somatrogon 0.25 mg/kg/wk	21	Russia	2 Genotropin 2 somatrogon
	Somatrogon 0.25 mg/kg/wk	22	Russia	1 Genotropin 3 somatrogon
	Somatrogon 0.48 mg/kg/wk	11	Ukraine	7 somatrogon
	Somatrogon 0.48 mg/kg/wk	11	Ukraine	
	Somatrogon 0.66 mg/kg/wk	08	Bulgaria	1 Genotropin 3 somatrogon
	Somatrogon 0.66 mg/kg/wk	11	Ukraine	
	Somatrogon 0.66 mg/kg/wk	11	Ukraine	
	Genotropin	14	Ukraine	2 Genotropin

Source: Prepared by review team with information from adae,xpt, adsl,xpt, and CP-4-004-investigators.
Abbreviation: ID, identity

Table 113. Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CP-4-006 (OLE Period)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Any TEAE	72 (69.2)	87 (80.6)	159 (75.0)
Blood and lymphatic system disorders	8 (7.7)	13 (12.0)	21 (9.9)
Eosinophilia	3 (2.9)	3 (2.8)	6 (2.8)
Anemia	2 (1.9)	1 (0.9)	3 (1.4)
Basophilia	2 (1.9)	1 (0.9)	3 (1.4)
Thrombocytosis	2 (1.9)	2 (1.9)	4 (1.9)
Lymphadenitis	1 (1.0)	2 (1.9)	3 (1.4)
Lymphadenopathy	1 (1.0)	1 (0.9)	2 (0.9)
Neutropenia	1 (1.0)	1 (0.9)	2 (0.9)
Iron deficiency anemia	0	1 (0.9)	1 (0.5)
Leukocytosis	0	1 (0.9)	1 (0.5)
Leukopenia	0	1 (0.9)	1 (0.5)
Thrombocytopenia	0	1 (0.9)	1 (0.5)
Cardiac disorders	0	2 (1.9)	2 (0.9)
Palpitations	0	1 (0.9)	1 (0.5)
Tachycardia	0	1 (0.9)	1 (0.5)
Congenital, familial, and genetic disorders	1 (1.0)	1 (0.9)	2 (0.9)
Phimosis	1 (1.0)	0	1 (0.5)
Lysinuric protein intolerance	0	1 (0.9)	1 (0.5)
Ear and labyrinth disorders	2 (1.9)	5 (4.6)	7 (3.3)
Cerumen impaction	1 (1.0)	0	1 (0.5)
Ear pain	1 (1.0)	2 (1.9)	3 (1.4)
Tinnitus	0	1 (0.9)	1 (0.5)
Tympanic membrane perforation	0	1 (0.9)	1 (0.5)
Vertigo	0	1 (0.9)	1 (0.5)
Endocrine disorders	4 (3.8)	6 (5.6)	10 (4.7)
Hypothyroidism	2 (1.9)	2 (1.9)	4 (1.9)
Adrenal insufficiency	1 (1.0)	1 (0.9)	2 (0.9)
Adrenocorticotropic hormone deficiency	1 (1.0)	0	1 (0.5)
Delayed puberty	0	1 (0.9)	1 (0.5)
Secondary adrenocortical insufficiency	0	1 (0.9)	1 (0.5)
Secondary hypothyroidism	0	1 (0.9)	1 (0.5)
Thyroid disorder	0	1 (0.9)	1 (0.5)
Eye disorders	5 (4.8)	4 (3.7)	9 (4.2)
Astigmatism	1 (1.0)	0	1 (0.5)
Conjunctivitis allergic	1 (1.0)	1 (0.9)	2 (0.9)
Excessive eye blinking	1 (1.0)	0	1 (0.5)
Eyelid edema	1 (1.0)	0	1 (0.5)
Hypermetropia	1 (1.0)	1 (0.9)	2 (0.9)
Myopia	1 (1.0)	0	1 (0.5)
Blepharospasm	0	1 (0.9)	1 (0.5)
Eye allergy	0	1 (0.9)	1 (0.5)
Eye pain	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Gastrointestinal disorders	19 (18.3)	23 (21.3)	42 (19.8)
Vomiting	9 (8.7)	9 (8.3)	18 (8.5)
Diarrhea	7 (6.7)	3 (2.8)	10 (4.7)
Abdominal pain upper	2 (1.9)	4 (3.7)	6 (2.8)
Constipation	2 (1.9)	0	2 (0.9)
Toothache	2 (1.9)	2 (1.9)	4 (1.9)
Abdominal pain	1 (1.0)	6 (5.6)	7 (3.3)
Aphthous ulcer	1 (1.0)	1 (0.9)	2 (0.9)
Dental caries	1 (1.0)	1 (0.9)	2 (0.9)
Enteritis	1 (1.0)	0	1 (0.5)
Gastrointestinal disorder	1 (1.0)	0	1 (0.5)
Lip ulceration	1 (1.0)	0	1 (0.5)
Nausea	1 (1.0)	2 (1.9)	3 (1.4)
Odynophagia	1 (1.0)	1 (0.9)	2 (0.9)
Oral pain	1 (1.0)	1 (0.9)	2 (0.9)
Salivary gland mucocele	1 (1.0)	0	1 (0.5)
Abdominal discomfort	0	1 (0.9)	1 (0.5)
Anal incontinence	0	1 (0.9)	1 (0.5)
Glossodynia	0	1 (0.9)	1 (0.5)
Noninfective sialadenitis	0	1 (0.9)	1 (0.5)
Stomatitis	0	1 (0.9)	1 (0.5)
General disorders and administration site conditions	36 (34.6)	57 (52.8)	93 (43.9)
Injection site reaction	23 (22.1)	48 (44.4)	71 (33.5)
Pyrexia	18 (17.3)	11 (10.2)	29 (13.7)
Vaccination site pain	1 (1.0)	0	1 (0.5)
Fatigue	0	2 (1.9)	2 (0.9)
Gait disturbance	0	1 (0.9)	1 (0.5)
Influenza-like illness	0	1 (0.9)	1 (0.5)
Injection site deformation	0	2 (1.9)	2 (0.9)
Medical device pain	0	1 (0.9)	1 (0.5)
Immune system disorders	6 (5.8)	3 (2.8)	9 (4.2)
Seasonal allergy	3 (2.9)	2 (1.9)	5 (2.4)
Allergy to arthropod bite	2 (1.9)	0	2 (0.9)
Allergy to arthropod sting	1 (1.0)	0	1 (0.5)
Mite allergy	1 (1.0)	0	1 (0.5)
Multiple allergies	1 (1.0)	0	1 (0.5)
Smoke sensitivity	1 (1.0)	0	1 (0.5)
Hypersensitivity	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Infections and infestations	49 (47.1)	51 (47.2)	100 (47.2)
Nasopharyngitis	24 (23.1)	22 (20.4)	46 (21.7)
Influenza	6 (5.8)	6 (5.6)	12 (5.7)
Rhinitis	4 (3.8)	4 (3.7)	8 (3.8)
Pneumonia	3 (2.9)	1 (0.9)	4 (1.9)
Tonsillitis	3 (2.9)	1 (0.9)	4 (1.9)
Bronchitis	2 (1.9)	5 (4.6)	7 (3.3)
Enterobiasis	2 (1.9)	1 (0.9)	3 (1.4)
Gastroenteritis	2 (1.9)	2 (1.9)	4 (1.9)
Gastroenteritis viral	2 (1.9)	0	2 (0.9)
Herpes dermatitis	2 (1.9)	0	2 (0.9)
Otitis media	2 (1.9)	2 (1.9)	4 (1.9)
Pharyngitis	2 (1.9)	3 (2.8)	5 (2.4)
Urinary tract infection	2 (1.9)	0	2 (0.9)
Viral infection	2 (1.9)	1 (0.9)	3 (1.4)
Acute sinusitis	1 (1.0)	1 (0.9)	2 (0.9)
Appendicitis	1 (1.0)	2 (1.9)	3 (1.4)
Atypical pneumonia	1 (1.0)	0	1 (0.5)
Conjunctivitis	1 (1.0)	0	1 (0.5)
Cystitis	1 (1.0)	0	1 (0.5)
Dermatophytosis of nail	1 (1.0)	0	1 (0.5)
Diverticulitis	1 (1.0)	0	1 (0.5)
Ear infection	1 (1.0)	1 (0.9)	2 (0.9)
Eye infection	1 (1.0)	0	1 (0.5)
Gastrointestinal infection	1 (1.0)	0	1 (0.5)
Gastrointestinal viral infection	1 (1.0)	0	1 (0.5)
Hordeolum	1 (1.0)	0	1 (0.5)
Otitis externa	1 (1.0)	0	1 (0.5)
Parasitic gastroenteritis	1 (1.0)	0	1 (0.5)
Parotitis	1 (1.0)	1 (0.9)	2 (0.9)
Peritonitis	1 (1.0)	0	1 (0.5)
Pharyngitis streptococcal	1 (1.0)	3 (2.8)	4 (1.9)
Respiratory tract infection viral	1 (1.0)	3 (2.8)	4 (1.9)
Skin infection	1 (1.0)	1 (0.9)	2 (0.9)
Tonsillitis streptococcal	1 (1.0)	0	1 (0.5)
Tooth abscess	1 (1.0)	1 (0.9)	2 (0.9)
Tooth infection	1 (1.0)	0	1 (0.5)
Upper respiratory tract infection bacterial	1 (1.0)	0	1 (0.5)
Viral upper respiratory tract infection	1 (1.0)	1 (0.9)	2 (0.9)
Adenoiditis	0	1 (0.9)	1 (0.5)
Arthropod infestation	0	1 (0.9)	1 (0.5)
Bronchitis viral	0	1 (0.9)	1 (0.5)
Coronavirus infection	0	1 (0.9)	1 (0.5)
Fungal skin infection	0	1 (0.9)	1 (0.5)
Gastroenteritis rotavirus	0	1 (0.9)	1 (0.5)
Gingivitis	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Hepatitis E	0	1 (0.9)	1 (0.5)
Impetigo	0	1 (0.9)	1 (0.5)
Infection	0	1 (0.9)	1 (0.5)
Myringitis	0	1 (0.9)	1 (0.5)
Oral herpes	0	1 (0.9)	1 (0.5)
Otitis media acute	0	2 (1.9)	2 (0.9)
Pulpitis dental	0	1 (0.9)	1 (0.5)
Rhinotracheitis	0	1 (0.9)	1 (0.5)
Sinusitis	0	2 (1.9)	2 (0.9)
Upper respiratory tract infection	0	4 (3.7)	4 (1.9)
Varicella	0	2 (1.9)	2 (0.9)
Viral pharyngitis	0	2 (1.9)	2 (0.9)
Viral tonsillitis	0	1 (0.9)	1 (0.5)
Injury, poisoning and procedural complications	11 (10.6)	12 (11.1)	23 (10.8)
Concussion	2 (1.9)	0	2 (0.9)
Ligament sprain	2 (1.9)	1 (0.9)	3 (1.4)
Accident	1 (1.0)	0	1 (0.5)
Arthropod bite	1 (1.0)	0	1 (0.5)
Arthropod sting	1 (1.0)	1 (0.9)	2 (0.9)
Contusion	1 (1.0)	2 (1.9)	3 (1.4)
Head injury	1 (1.0)	2 (1.9)	3 (1.4)
Heat stroke	1 (1.0)	0	1 (0.5)
Limb injury	1 (1.0)	1 (0.9)	2 (0.9)
Muscle injury	1 (1.0)	0	1 (0.5)
Muscle strain	1 (1.0)	0	1 (0.5)
Post-concussion syndrome	1 (1.0)	0	1 (0.5)
Procedural pain	1 (1.0)	0	1 (0.5)
Skin abrasion	1 (1.0)	2 (1.9)	3 (1.4)
Sunburn	1 (1.0)	1 (0.9)	2 (0.9)
Traumatic fracture	1 (1.0)	2 (1.9)	3 (1.4)
Clavicle fracture	0	1 (0.9)	1 (0.5)
Corneal abrasion	0	1 (0.9)	1 (0.5)
Fall	0	3 (2.8)	3 (1.4)
Foreign body in ear	0	1 (0.9)	1 (0.5)
Humerus fracture	0	1 (0.9)	1 (0.5)
Injury	0	1 (0.9)	1 (0.5)
Joint injury	0	2 (1.9)	2 (0.9)
Skin injury	0	1 (0.9)	1 (0.5)
Thermal burn	0	1 (0.9)	1 (0.5)
Venomous sting	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Investigations	15 (14.4)	14 (13.0)	29 (13.7)
Free fatty acids increased	3 (2.9)	3 (2.8)	6 (2.8)
Blood alkaline phosphatase increased	2 (1.9)	2 (1.9)	4 (1.9)
Low density lipoprotein decreased	2 (1.9)	1 (0.9)	3 (1.4)
Thyroxine free decreased	2 (1.9)	1 (0.9)	3 (1.4)
Weight decreased	2 (1.9)	0	2 (0.9)
White blood cell count decreased	2 (1.9)	0	2 (0.9)
Alanine aminotransferase increased	1 (1.0)	0	1 (0.5)
Blood creatine phosphokinase increased	1 (1.0)	1 (0.9)	2 (0.9)
Blood insulin increased	1 (1.0)	0	1 (0.5)
Blood thyroid stimulating hormone decreased	1 (1.0)	0	1 (0.5)
Blood thyroid stimulating hormone increased	1 (1.0)	0	1 (0.5)
Blood lactate dehydrogenase increased	0	1 (0.9)	1 (0.5)
Body temperature increased	0	1 (0.9)	1 (0.5)
Coronavirus test positive	0	1 (0.9)	1 (0.5)
Crystal urine present	0	1 (0.9)	1 (0.5)
Eosinophil count increased	0	1 (0.9)	1 (0.5)
Insulin-like growth factor increased	0	3 (2.8)	3 (1.4)
Neutrophil count increased	0	1 (0.9)	1 (0.5)
Weight increased	0	1 (0.9)	1 (0.5)
Metabolism and nutrition disorders	7 (6.7)	3 (2.8)	10 (4.7)
Hypoinsulinemia	5 (4.8)	0	5 (2.4)
Hypertriglyceridemia	2 (1.9)	0	2 (0.9)
Hypercholesterolemia	1 (1.0)	0	1 (0.5)
Hyperglycemia	1 (1.0)	0	1 (0.5)
Hyperinsulinemia	1 (1.0)	0	1 (0.5)
Hypocholesterolemia	1 (1.0)	0	1 (0.5)
Abnormal weight gain	0	1 (0.9)	1 (0.5)
Increased appetite	0	1 (0.9)	1 (0.5)
Iron deficiency	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Musculoskeletal and connective tissue disorders	12 (11.5)	11 (10.2)	23 (10.8)
Pain in extremity	4 (3.8)	3 (2.8)	7 (3.3)
Arthralgia	3 (2.9)	4 (3.7)	7 (3.3)
Scoliosis	2 (1.9)	0	2 (0.9)
Growth accelerated	1 (1.0)	0	1 (0.5)
Musculoskeletal stiffness	1 (1.0)	0	1 (0.5)
Myalgia	1 (1.0)	1 (0.9)	2 (0.9)
Neck pain	1 (1.0)	1 (0.9)	2 (0.9)
Pain in jaw	1 (1.0)	0	1 (0.5)
Back pain	0	2 (1.9)	2 (0.9)
Groin pain	0	1 (0.9)	1 (0.5)
Growing pains	0	1 (0.9)	1 (0.5)
Joint swelling	0	1 (0.9)	1 (0.5)
Medial tibial stress syndrome	0	1 (0.9)	1 (0.5)
Muscle fatigue	0	1 (0.9)	1 (0.5)
Muscle spasms	0	1 (0.9)	1 (0.5)
Snapping hip syndrome	0	1 (0.9)	1 (0.5)
Tendon pain	0	2 (1.9)	2 (0.9)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	0	2 (1.9)	2 (0.9)
Skin papilloma	0	2 (1.9)	2 (0.9)
Nervous system disorders	12 (11.5)	15 (13.9)	27 (12.7)
Headache	10 (9.6)	13 (12.0)	23 (10.8)
Psychomotor hyperactivity	1 (1.0)	0	1 (0.5)
Syncope	1 (1.0)	1 (0.9)	2 (0.9)
Autonomic neuropathy	0	1 (0.9)	1 (0.5)
Dizziness	0	1 (0.9)	1 (0.5)
Lethargy	0	1 (0.9)	1 (0.5)
Psychiatric disorders	2 (1.9)	6 (5.6)	8 (3.8)
Enuresis	1 (1.0)	1 (0.9)	2 (0.9)
Irritability	1 (1.0)	0	1 (0.5)
Stereotypy	1 (1.0)	0	1 (0.5)
Affect lability	0	1 (0.9)	1 (0.5)
Anxiety	0	1 (0.9)	1 (0.5)
Attention deficit/hyperactivity disorder	0	1 (0.9)	1 (0.5)
Emotional distress	0	1 (0.9)	1 (0.5)
Neurosis	0	1 (0.9)	1 (0.5)
Renal and urinary disorders	1 (1.0)	1 (0.9)	2 (0.9)
Urinary incontinence	1 (1.0)	0	1 (0.5)
Pollakiuria	0	1 (0.9)	1 (0.5)
Reproductive system and breast disorders	1 (1.0)	2 (1.9)	3 (1.4)
Dysmenorrhea	1 (1.0)	0	1 (0.5)
Dysfunctional uterine bleeding	0	1 (0.9)	1 (0.5)
Gynecomastia	0	1 (0.9)	1 (0.5)

System Organ Class Preferred Term	Originally Randomized to Somatrogon N=104 n (%)	Originally Randomized to Genotropin N=108 n (%)	Total N=212 n (%)
Respiratory, thoracic, and mediastinal disorders	16 (15.4)	19 (17.6)	35 (16.5)
Cough	6 (5.8)	11 (10.2)	17 (8.0)
Oropharyngeal pain	5 (4.8)	3 (2.8)	8 (3.8)
Nasal congestion	3 (2.9)	2 (1.9)	5 (2.4)
Rhinitis allergic	3 (2.9)	1 (0.9)	4 (1.9)
Rhinorrhea	3 (2.9)	4 (3.7)	7 (3.3)
Adenoidal hypertrophy	1 (1.0)	0	1 (0.5)
Bronchial hyperreactivity	1 (1.0)	0	1 (0.5)
Dyspnea	1 (1.0)	1 (0.9)	2 (0.9)
Pharyngeal erosion	1 (1.0)	0	1 (0.5)
Productive cough	1 (1.0)	0	1 (0.5)
Snoring	1 (1.0)	0	1 (0.5)
Tonsillar hypertrophy	1 (1.0)	1 (0.9)	2 (0.9)
Epistaxis	0	2 (1.9)	2 (0.9)
Vasomotor rhinitis	0	1 (0.9)	1 (0.5)
Skin and subcutaneous tissue disorders	11 (10.6)	11 (10.2)	22 (10.4)
Idiopathic urticaria	2 (1.9)	0	2 (0.9)
Urticaria	2 (1.9)	1 (0.9)	3 (1.4)
Acne	1 (1.0)	1 (0.9)	2 (0.9)
Dry skin	1 (1.0)	0	1 (0.5)
Erythema	1 (1.0)	1 (0.9)	2 (0.9)
In-growing nail	1 (1.0)	0	1 (0.5)
Rash	1 (1.0)	1 (0.9)	2 (0.9)
Rash pruritic	1 (1.0)	0	1 (0.5)
Skin hypopigmentation	1 (1.0)	0	1 (0.5)
Dermatitis	0	1 (0.9)	1 (0.5)
Dermatitis atopic	0	1 (0.9)	1 (0.5)
Eczema	0	2 (1.9)	2 (0.9)
Prurigo	0	1 (0.9)	1 (0.5)
Seborrheic dermatitis	0	1 (0.9)	1 (0.5)
Skin swelling	0	1 (0.9)	1 (0.5)
Urticaria physical	0	1 (0.9)	1 (0.5)
Vascular disorders	2 (1.9)	0	2 (0.9)
Hypotension	1 (1.0)	0	1 (0.5)
Kawasaki's disease	1 (1.0)	0	1 (0.5)

Source: adae.xpt; software, R.
Treatment-emergent adverse events defined as if the event started for the first time after the start of treatment or increased in severity if another event also occurred before the start of treatment.
Safety analysis of data provided in Major Amendment (submitted on September 15, 2021).
Abbreviations: N, number of patients in treatment arm; n, number of patients with adverse event; OLE, open-label extension; SOC, system organ class; TEAE, treatment-emergent adverse event

Table 114. Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CP-4-004 (OLE Period), by period

System Organ Class Preferred Term	Period III Somatrogon 0.25 mg/kg/wk N=16 n (%)	Period III Somatrogon 0.48 mg/kg/wk N=17 n (%)	Period III Somatrogon 0.66 mg/kg/wk N=15 n (%)	Period IV Somatrogon 0.66 mg/kg/wk N=44 n (%)	Period V Somatrogon 0.66 mg/kg/wk N=40 n (%)
Infections and infestations (SOC)	11 (68.8)	5 (29.4)	6 (40.0)	27 (61.4)	14 (35.0)
Bronchitis	2 (12.5)	1 (5.9)	0	7 (15.9)	5 (12.5)
Rhinitis	2 (12.5)	1 (5.9)	0	3 (6.8)	2 (5.0)
Viral upper respiratory tract infection	2 (12.5)	1 (5.9)	0	0	0
Viral infection	2 (12.5)	0	1 (6.7)	2 (4.5)	0
Nasopharyngitis	2 (12.5)	0	0	3 (6.8)	2 (5.0)
Upper respiratory tract infection	1 (6.2)	2 (11.8)	2 (13.3)	12 (27.3)	2 (5.0)
Pneumonia	1 (6.2)	0	1 (6.7)	0	1 (2.5)
Respiratory tract infection	1 (6.2)	0	1 (6.7)	0	0
Ear infection	1 (6.2)	0	0	3 (6.8)	0
Pharyngitis	1 (6.2)	0	0	0	1 (2.5)
Ascariasis	1 (6.2)	0	0	0	0
Lower respiratory tract infection	0	1 (5.9)	1 (6.7)	1 (2.3)	0
Hand-foot-and-mouth disease	0	1 (5.9)	0	1 (2.3)	0
Thyroid gland abscess	0	1 (5.9)	0	1 (2.3)	0
Infectious mononucleosis	0	1 (5.9)	0	0	0
Varicella	0	0	1 (6.7)	2 (4.5)	2 (5.0)
Conjunctivitis	0	0	0	2 (4.5)	0
Tonsillitis	0	0	0	1 (2.3)	2 (5.0)
Rotavirus infection	0	0	0	1 (2.3)	1 (2.5)
Gastroenteritis	0	0	0	1 (2.3)	0
Gastrointestinal infection	0	0	0	1 (2.3)	0
Lower respiratory tract infection viral	0	0	0	1 (2.3)	0
Periodontitis	0	0	0	1 (2.3)	0
Tracheitis	0	0	0	1 (2.3)	0
Urinary tract infection	0	0	0	1 (2.3)	0
Varicella zoster virus infection	0	0	0	1 (2.3)	0
Acute sinusitis	0	0	0	0	1 (2.5)
Hordeolum	0	0	0	0	1 (2.5)
Measles	0	0	0	0	1 (2.5)
Otitis externa	0	0	0	0	1 (2.5)
Paronychia	0	0	0	0	1 (2.5)
Urethritis	0	0	0	0	1 (2.5)
Gastrointestinal disorders (SOC)	4 (25.0)	1 (5.9)	1 (6.7)	4 (9.1)	3 (7.5)
Vomiting	2 (12.5)	0	0	0	1 (2.5)

System Organ Class Preferred Term	Period III Somatrogon 0.25 mg/kg/wk N=16 n (%)	Period III Somatrogon 0.48 mg/kg/wk N=17 n (%)	Period III Somatrogon 0.66 mg/kg/wk N=15 n (%)	Period IV Somatrogon 0.66 mg/kg/wk N=44 n (%)	Period V Somatrogon 0.66 mg/kg/wk N=40 n (%)
Abdominal pain	1 (6.2)	0	1 (6.7)	0	0
Dental caries	1 (6.2)	0	0	0	0
Diarrhea	1 (6.2)	0	0	0	0
Duodenitis	1 (6.2)	0	0	0	0
Enteritis	1 (6.2)	0	0	0	0
Gastritis	1 (6.2)	0	0	0	0
Gastric disorder	0	1 (5.9)	0	0	0
Dyspepsia	0	0	0	1 (2.3)	1 (2.5)
Gastroduodenitis	0	0	0	1 (2.3)	0
Gingival hypertrophy	0	0	0	1 (2.3)	0
Toothache	0	0	0	1 (2.3)	0
Erosive esophagitis	0	0	0	0	1 (2.5)
Gastroesophageal reflux disease	0	0	0	0	1 (2.5)
General disorders and administration site conditions (SOC)	3 (18.8)	1 (5.9)	0	2 (4.5)	3 (7.5)
Pyrexia	1 (6.2)	1 (5.9)	0	2 (4.5)	0
Gait disturbance	1 (6.2)	0	0	0	0
Oedema peripheral	1 (6.2)	0	0	0	0
Medical device pain	0	0	0	1 (2.3)	0
Injection site bruising	0	0	0	0	2 (5.0)
Injection site erythema	0	0	0	0	1 (2.5)
Blood and lymphatic system disorders (SOC)	2 (12.5)	2 (11.8)	0	1 (2.3)	1 (2.5)
Iron deficiency anemia	1 (6.2)	0	0	0	1 (2.5)
Anemia	1 (6.2)	0	0	0	0
Neutropenia	1 (6.2)	0	0	0	0
Lymphadenopathy	0	1 (5.9)	0	1 (2.3)	0
Eosinophilia	0	1 (5.9)	0	0	0
Musculoskeletal and connective tissue disorders (SOC)	2 (12.5)	0	0	5 (11.4)	3 (7.5)
Arthralgia	1 (6.2)	0	0	1 (2.3)	1 (2.5)
Connective tissue disorder	1 (6.2)	0	0	0	0
Myalgia	1 (6.2)	0	0	0	0
Osteopenia	1 (6.2)	0	0	0	0
Scoliosis	0	0	0	2 (4.5)	0
Foot deformity	0	0	0	1 (2.3)	0
Keeled chest acquired	0	0	0	1 (2.3)	0
Limb asymmetry	0	0	0	1 (2.3)	0
Pain in extremity	0	0	0	1 (2.3)	0
Pelvic deformity	0	0	0	1 (2.3)	0
Synovial cyst	0	0	0	1 (2.3)	0
Osteochondrosis	0	0	0	0	2 (5.0)
Eye disorders (SOC)	2 (12.5)	0	0	0	1 (2.5)

System Organ Class Preferred Term	Period III Somatrogon 0.25 mg/kg/wk N=16 n (%)	Period III Somatrogon 0.48 mg/kg/wk N=17 n (%)	Period III Somatrogon 0.66 mg/kg/wk N=15 n (%)	Period IV Somatrogon 0.66 mg/kg/wk N=44 n (%)	Period V Somatrogon 0.66 mg/kg/wk N=40 n (%)
Eyelid oedema	1 (6.2)	0	0	0	0
Myopia	1 (6.2)	0	0	0	0
Conjunctivitis allergic	0	0	0	0	1 (2.5)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (6.2)	0	1 (6.7)	3 (6.8)	2 (5.0)
Nasal congestion	1 (6.2)	0	0	0	0
Rhinitis allergic	0	0	1 (6.7)	1 (2.3)	2 (5.0)
Rhinorrhea	0	0	0	1 (2.3)	1 (2.5)
Epistaxis	0	0	0	1 (2.3)	0
Oropharyngeal pain	0	0	0	1 (2.3)	0
Endocrine disorders (SOC)	1 (6.2)	0	0	2 (4.5)	2 (5.0)
Hypothyroidism	1 (6.2)	0	0	0	1 (2.5)
Delayed puberty	0	0	0	1 (2.3)	1 (2.5)
Secondary hypothyroidism	0	0	0	1 (2.3)	0
Injury, poisoning and procedural complications (SOC)	1 (6.2)	0	0	2 (4.5)	0
Arthropod bite	1 (6.2)	0	0	0	0
Clavicle fracture	0	0	0	1 (2.3)	0
Foot fracture	0	0	0	1 (2.3)	0
Hepatobiliary disorders (SOC)	1 (6.2)	0	0	1 (2.3)	1 (2.5)
Biliary dyskinesia	1 (6.2)	0	0	1 (2.3)	0
Sphincter of Oddi dysfunction	0	0	0	0	1 (2.5)
Nervous system disorders (SOC)	0	1 (5.9)	0	2 (4.5)	3 (7.5)
Headache	0	1 (5.9)	0	0	2 (5.0)
Dizziness	0	0	0	1 (2.3)	1 (2.5)
Cognitive disorder	0	0	0	1 (2.3)	0
Intellectual disability	0	0	0	1 (2.3)	0
Cranial nerve disorder	0	0	0	0	1 (2.5)
Investigations (SOC)	0	0	0	2 (4.5)	2 (5.0)
Insulin-like growth factor increased	0	0	0	1 (2.3)	1 (2.5)
Blood pressure increased	0	0	0	1 (2.3)	0
Electrocardiogram abnormal	0	0	0	1 (2.3)	0
Thyroxine free decreased	0	0	0	0	1 (2.5)
Skin and subcutaneous tissue disorders (SOC)	0	0	0	2 (4.5)	0
Dermatitis allergic	0	0	0	1 (2.3)	0
Ingrowing nail	0	0	0	1 (2.3)	0

System Organ Class Preferred Term	Period III Somatrogon 0.25 mg/kg/wk N=16 n (%)	Period III Somatrogon 0.48 mg/kg/wk N=17 n (%)	Period III Somatrogon 0.66 mg/kg/wk N=15 n (%)	Period IV Somatrogon 0.66 mg/kg/wk N=44 n (%)	Period V Somatrogon 0.66 mg/kg/wk N=40 n (%)
Metabolism and nutrition disorders (SOC)	0	0	0	1 (2.3)	1 (2.5)
Obesity	0	0	0	1 (2.3)	0
Hypercholesterolemia	0	0	0	0	1 (2.5)
Reproductive system and breast disorders (SOC)	0	0	0	1 (2.3)	1 (2.5)
Testicular disorder	0	0	0	1 (2.3)	1 (2.5)
Ear and labyrinth disorders (SOC)	0	0	0	1 (2.3)	0
Deafness	0	0	0	1 (2.3)	0
Immune system disorders (SOC)	0	0	0	0	1 (2.5)
Food allergy	0	0	0	0	1 (2.5)
Psychiatric disorders (SOC)	0	0	0	0	1 (2.5)
Autism spectrum disorder	0	0	0	0	1 (2.5)

Source: adae.xpt; software, Python.
Treatment-emergent adverse events defined as any AE onset occurring post-treatment.
Safety analysis of data provided in the original BLA submission (data lock date November 1, 2019)
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; OLE, open-label extension

Table 115. Treatment Emergent Adverse Events by Anti-Drug Antibody Status in PEN Year 1 Group, Trial CP-4-004 (OLE Period)

	PEN Year 1 (N=40)	
System Organ Class Preferred Term	Positive ADA N=15 n (%)	Negative ADA N=25 n (%)
Any TEAE	9 (60.0)	14 (56.0)
Endocrine disorders (SOC)	1 (6.7)	1 (4.0)
Hypothyroidism	1 (6.7)	0
Delayed puberty	0	1 (4.0)
Eye disorders (SOC)	0	1 (4.0)
Conjunctivitis allergic	0	1 (4.0)
Gastrointestinal disorders (SOC)	1 (6.7)	2 (8.0)
Dyspepsia	1 (6.7)	0
Erosive oesophagitis	0	1 (4.0)
Gastrooesophageal reflux disease	0	1 (4.0)
Vomiting	0	1 (4.0)
General disorders and administration site conditions (SOC)	1 (6.7)	2 (8.0)
Injection site reaction	1 (6.7)	2 (8.0)
Hepatobiliary disorders (SOC)	0	1 (4.0)
Sphincter of Oddi dysfunction	0	1 (4.0)
Immune system disorders (SOC)	0	1 (4.0)
Food allergy	0	1 (4.0)
Infections and infestations (SOC)	4 (26.7)	10 (40.0)
Acute sinusitis	1 (6.7)	0

System Organ Class Preferred Term	PEN Year 1 (N=40) Positive ADA N=15 n (%)	 Negative ADA N=25 n (%)
Bronchitis	1 (6.7)	4 (16.0)
Measles	1 (6.7)	0
Nasopharyngitis	1 (6.7)	1 (4.0)
Upper respiratory tract infection	1 (6.7)	1 (4.0)
Varicella	1 (6.7)	1 (4.0)
Hordeolum	0	1 (4.0)
Otitis externa	0	1 (4.0)
Paronychia	0	1 (4.0)
Pharyngitis	0	1 (4.0)
Pneumonia	0	1 (4.0)
Rhinitis	0	2 (8.0)
Rotavirus infection	0	1 (4.0)
Tonsillitis	0	2 (8.0)
Urethritis	0	1 (4.0)
Metabolism and nutrition disorders (SOC)	1 (6.7)	0
Hypercholesterolemia	1 (6.7)	0
Musculoskeletal and connective tissue disorders (SOC)	1 (6.7)	2 (8.0)
Arthralgia	1 (6.7)	0
Osteochondrosis	0	2 (8.0)
Nervous system disorders (SOC)	0	3 (12.0)
Cranial nerve disorder	0	1 (4.0)
Dizziness	0	1 (4.0)
Headache	0	2 (8.0)
Psychiatric disorders (SOC)	1 (6.7)	0
Autism spectrum disorder	1 (6.7)	0
Reproductive system and breast disorders (SOC)	0	1 (4.0)
Testicular disorder	0	1 (4.0)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (6.7)	1 (4.0)
Rhinitis allergic	1 (6.7)	1 (4.0)
Rhinorrhea	1 (6.7)	0

Source: adae.xpt; software, R. Data provided in the Major Amendment submitted on September 15, 2021.
Treatment-emergent adverse events defined as any AE with onset post-treatment.
Abbreviations: ADA, anti-drug antibody, N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class; TEAE, treatment-emergent adverse event.

Table 116. Treatment Emergent Adverse Events by Anti-Drug Antibody Status in PEN Year 2 Group, Trial CP-4-004 (OLE Period)

System Organ Class Preferred Term	PEN Year 2 (N=35) Positive ADA N=12 n (%)	 Negative ADA N=23 n (%)
Any TEAE	6 (50.0)	9 (39.1)
Endocrine disorders	0	2 (8.7)
Autoimmune thyroiditis	0	1 (4.3)
Hypothyroidism	0	1 (4.3)
General disorders and administration site conditions	1 (8.3)	1 (4.3)
Injection site reaction	1 (8.3)	0
Pyrexia	0	1 (4.3)

System Organ Class Preferred Term	PEN Year 2 (N=35) Positive ADA N=12 n (%)	 Negative ADA N=23 n (%)
Immune system disorders	0	1 (4.3)
Food allergy	0	1 (4.3)
Infections and infestations	5 (41.7)	6 (26.1)
Upper respiratory tract infection	2 (16.7)	1 (4.3)
Nasopharyngitis	1 (8.3)	0
Respiratory tract infection viral	1 (8.3)	1 (4.3)
Rhinitis	1 (8.3)	1 (4.3)
Coxsackie viral infection	0	1 (4.3)
Lower respiratory tract infection viral	0	1 (4.3)
Pyoderma streptococcal	0	1 (4.3)
Tonsillitis	0	1 (4.3)
Injury, poisoning and procedural complications	0	1 (4.3)
Clavicle fracture	0	1 (4.3)
Metabolism and nutrition disorders	1 (8.3)	0
Iodine deficiency	1 (8.3)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (8.3)	0
Schwannoma	1 (8.3)	0
Nervous system disorders	0	1 (4.3)
Headache	0	1 (4.3)
Psychiatric disorders	1 (8.3)	0
Anxiety	1 (8.3)	0
Respiratory, thoracic, and mediastinal disorders	1 (8.3)	0
Respiratory failure	1 (8.3)	0

Source: adae.xpt; software, R. Data provided in the Major Amendment submitted on September 15, 2021.
Treatment-emergent adverse events defined as any AE onset occurring post-treatment.
Abbreviations: ADA, antidrug antibody; N, number of patients in treatment arm; n, number of patients with adverse event; OLE, open-label extension; TEAE, treatment-emergent adverse event

17.5. Adverse Events of Special Interest

Table 117. Adverse Events of Special Interest and Respective Defined MedDRA Terms

MedDRA version: 22.0	
Category of Interest	**Criteria/Programming Details**
Glucose metabolism impairment	Hyperglycemia/new onset diabetes mellitus (SMQ) Narrow Scope
Thyroid function impairment	Thyroid dysfunction (SMQ) Broad and Narrow Scope
Cortisol changes	HLT for Adrenal Cortical Hypofunctions
Intracranial hypertension	Increased intracranial pressure and hydrocephalus (HLGT All Paths) and select PT (CSF pressure increased)
Neoplasias	SOC Neoplasms benign, malignant and unspecified (includes cysts and polyps)
Intracranial hemorrhage and intracranial aneurysm	Hemorrhagic central nervous system vascular conditions (SMQ) Narrow Scope, and Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ) Narrow Scope
Immunogenicity	Anti somatrogon Neutralizing Antibody present, Anaphylactic reaction (SMQ) Narrow Scope, Angioedema (SMQ) Narrow Scope, Hypersensitivity (SMQ) Narrow Scope
Injection site reactions (including lipoatrophy/skin dystrophy)	Severe injection site reactions (HLT – All Paths) and select PTs (Lipoatrophy and Skin dystrophy)
'Other' non-serious adverse events of special interest identified during safety review	Arthralgia Musculoskeletal and Connective Tissue Disorders (specifically pain in extremity) Increased Protein Kinase (specifically blood creatine phosphokinase increased) Oedema
Pancreatitis	Acute pancreatitis (SMQ) Broad
Epiphyseal Disorders	Epiphysiolysis (LLT) Slipped Femoral Capital Epiphysis (LLT)

Source: Excerpted from Clinical Study Report, Trial CP-4-006, Table 5.
Abbreviations: CSF, cerebrospinal fluid; HLGT, high-level group term; HLT, high-level term; LLT, lowest-level term; MedDRA, Medical Dictionary for Regulatory Affairs; PT, preferred term; SMQ, Standardized MedDRA Query; SOC, system organ class

17.6. Clinical Laboratory Evaluation

Fasting Glucose Above Normal Values

In Trial CP-4-006, main period, somatrogon group, there were 6 subjects with fasting glucose above the normal limit (i.e., 5.6 mmol/L). The highest value was 6.3 mmol/L observed in 2 subjects (# (b) (6) and # (b) (6)), both at the 6-month timepoint. Subject (b) (6) had 2 other levels above normal (6.0 at baseline and 5.8 at Month 9). In the Genotropin group there were 13 subjects above 5.6 mmol/L and the highest level was 7.2 in subject # (b) (6) at Month 6, who had a value of 5.7 at Month 3 and the other values within normal range; a value of 6.3 was found in 2 subjects (# (b) (6) at Month 3 and # (b) (6) at baseline). In the OLE period, the number of subjects with fasting glucose above normal was lower and balanced between treatment arms (3 in somatrogon and 2 in Genotropin groups).

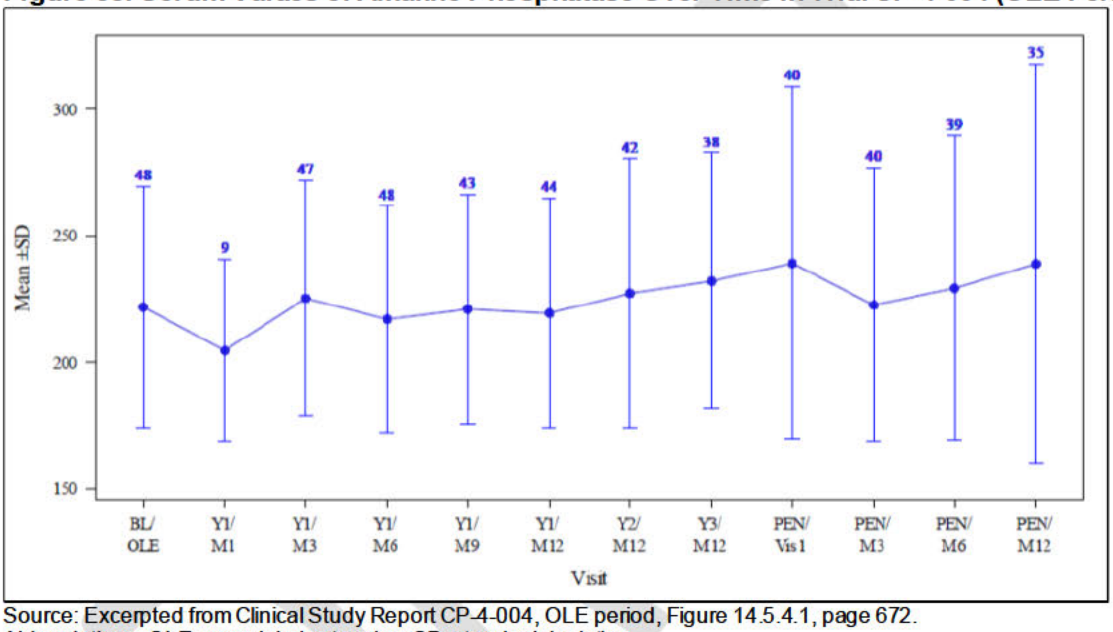
In Trial CP-4-004, all changes in glucose, insulin and HbA1C levels were small and of unknown clinical significance. During the main period, 3 subjects in somatrogon group were reported with fasting glucose levels above normal [subject # (b) (6) 5.9 mmol/L (106 mg/dL) at Week 1 and 6.0 mmol/L (108 mg/dL) at Week 10, subject # (b) (6) 5.7 mmol/L (103 mg/dL) at Week 1, and subject # (b) (6) 5.8 mmol/L (104 mg/dL) at Week14], and 2 subjects in Genotropin group

(subject # (b) (6) 5.9 mmol/L [106 mg/dL] at Week 1, 5.8 mmol/L [104 mg/dL] at Week 10, and 5.6 mmol/L [101 mg/dL] at Week 14, and subject # (b) (6) 5.7 mmol/L [103 mg/dL] at Month 9). All levels normalized without treatment or drug interruption and all patients were asymptomatic. Two subjects in Genotropin group had elevated fasting glucose levels above normal range (up to 106 mg/dL (5.9 mmol/L)). No hyperglycemia-related AEs were reported in the trial. No glucose increases occurred in somatrogon dose cohort of 0.66 mg/kg/week.

Alkaline Phosphatase

The mean values of alkaline phosphatase in Trial CP-4-004, OLE period remained within normal range (normal range varies with gender and age and the reference values provided by the Sponsor have a lower limit of 51 and an upper limit of 385 U/L), as shown in Figure 65.

Figure 65. Serum Values of Alkaline Phosphatase Over Time in Trial CP-4-004 (OLE Period)



Source: Excerpted from Clinical Study Report CP-4-004, OLE period, Figure 14.5.4.1, page 672.
Abbreviations: OLE, open-label extension; SD, standard deviation

ECG

Mean baseline values and mean changes from baseline in ECG parameters were similar in both treatment groups. A total of 4 subjects (two subjects in each group) had QTcF interval above 450 msec at 6 months in the main study period. In somatrogon group, the QTcF interval for one subject was 462 msec (decreased from 480 msec at baseline) and 452 msec for the other; in Genotropin group, the QTcF interval was 454 msec and 550 msec, respectively for each subject. None of the prolonged QTcF interval occurrences were considered clinically significant by the Investigator, thus not further evaluated by a cardiologist. These occurrences were not associated with any AE or changes in study drug dose. There were no subjects with clinically meaningful changes in ECG parameters in Trial CP-4-004 and in any of the OLE periods.

Injection Site Reactions

Injection Site Reaction Grading Scores

Redness

Grade	Description
0 NONE	No visible redness
1 MILD	0 to 2 cm redness
2 MODERATE	2 to 5 cm redness
3 SEVERE	Greater than 5 cm redness

Bruising

Grade	Description
0 NONE	No visible bruising
1 MILD	0 to 2 cm bruising
2 MODERATE	2 to 5 cm bruising
3 SEVERE	Greater than 5 cm bruising

Swelling

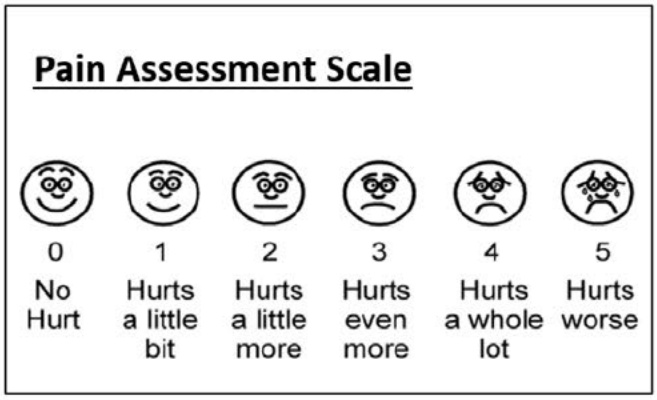
Grade	Description
0 NONE	No swelling detected
1 MILD	Palpable "firmness" only
2 MODERATE	<4 cm swelling
3 SEVERE	>4 cm swelling

Itching

Grade
0 NONE
1 MILD
2 MODERATE
3 SEVERE

Pain Assessment

Figure 66. Pain Assessment Scale



Source: Excerpted from CP-4-006 Protocol (Appendix H).

Table 118. Summary of Subjects With Injection Site Reactions by Most Severe Pain, Redness, Bruising, Swelling and Itching, Safety Population, Trial CP-4-006 (Main Period)

Injection Site Reaction	Most Severe Pain Score	Somatrogon N=97 n (%)	Genotropin N=102 n (%)
Pain score	0	1 (1)	0
	1	17 (17.5)	27 (26.5)
	2	19 (19.6)	32 (31.4)
	3	17 (17.5)	15 (14.7)
	4	14 (14.4)	14 (13.7)
	5	29 (29.9)	14 (13.7)
Bruising	0	73 (75.3)	83 (81.4)
	1	21 (21.6)	18 (17.6)
	2	3 (3.1)	1 (1)
Erythema/redness	0	72 (74.2)	97 (95.1)
	1	15 (15.5)	5 (4.9)
	2	10 (10.3)	0
Induration/swelling	0	83 (85.6)	100 (98)
	1	7 (7.2)	1 (1)
	2	7 (7.2)	1 (1)
Itching	0	83 (85.6)	100 (98)
	1	8 (8.2)	2 (2)
	2	6 (6.2)	0
Tenderness	0	91 (93.8)	98 (96.1)
	1	6 (6.2)	4 (3.9)

Source: adsr.xpt; Software: R
Percentages are based on the number of subjections with an injection site reaction in the treatment group.
A subject who reports more than one injection site reaction will only be counted once at the most severe level of each reaction type.
Abbreviations: N, number of subjects with injection site reaction data in the injection site reaction dataset (adsr.xpt); n, number of subjects with adverse event

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

Information pertaining to the mechanism of action is summarized in Section 5. Refer to this section for details.

19. Other Drug Development Considerations: Additional Information and Assessment

Trial CP-4-006 utilized the following clinical outcome assessments (COAs) as exploratory endpoints to assess the impacts associated with short stature for participants >3 years with growth hormone deficiency:

- Quality of Life in Short Stature Youth (QoLISSY)-Child Version. This is a patient-reported outcome measure completed by participants ≥7 years of age.
- QoLISSY-Parent Version. This is an observer-reported outcome measure completed by caregivers of participants <7 years of age.

The QoLISSY was assessed at Baseline (Visit 2) and end of treatment (Visit 8) in Study CP-4-006.

Each instrument version consists of three core domains: Physical, Social, and Emotional. In addition, there are three mediator domains: Coping, Beliefs, and Treatment. The Parent version also contains two supplementary domains: Future and Effects on parents. Each item in the instruments is rated on a 5-point verbal rating scale ranging from 1 ("not at all/never") to 5 ("extremely/always"). The recall period is the previous 7 days ("the previous week").

The QoLISSY generates domain and core total scores. For Trial CP-4-006, the core total score was used in the exploratory analyses. The core total score is calculated as the sum of the means of these three domains and divided by 3. Scores were transformed from raw scores to 0 to 100 scores, where higher scores represent a higher quality of life.

While the results from Trial CP-4-006 demonstrated numerical increases in QoLISSY core total scores for both treatment groups (somatrogon and Genotropin) at Month 12, the findings are uninterpretable for the following reasons:

- The open-label study design. Patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown. Further, in the absence of evidence regarding the measurement properties, it is also unclear whether the tool is sufficiently sensitive and reliable enough to directly compare the two active treatments.
- The COA research objectives and endpoint definitions are unclear.
- There is insufficient information to determine whether the instrument is fit-for-purpose for the context of this development program (e.g., lack of detail regarding relevancy of concepts to patients, lack of evidence to support patient/caregiver comprehension of measures, lack of evidence on the responsiveness of the measures).
- The threshold(s) for meaningful withing-patient score change is unknown as the Applicant did not utilize anchor-based methods, which are the primary methods used to interpret meaningful within-patient score changes in COA endpoints.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this biologics license application (BLA) consisted of two domestic clinical sites and the co-sponsor (OPKO Health, Inc.) of Study CP-4-006.

The ongoing COVID-19 global pandemic has significantly limited the ability of the Office of Regulatory Affairs (ORA) to conduct onsite foreign good clinical practice (GCP) inspections. As a result, the planned inspection of the sponsor Pfizer Ireland Pharmaceuticals was not conducted. Remote data investigation of source records by ORA was not feasible due to local restriction to obtain remote access of source records.

In general, based on the inspections of the two clinical sites and the co-sponsor, the inspectional findings support validity of data as reported by the sponsor under this BLA.

II. BACKGROUND

Pfizer Ireland Pharmaceuticals has submitted a biologics license application (BLA) for somatrogon, a long-acting recombinant human growth hormone (rhGH) that has been developed for use in the treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD]).

Pfizer Ireland Pharmaceuticals appointed Pfizer Inc. to serve as its authorized representative in connection with BLA 761184. Somatrogon has been granted Orphan Drug Designation (ODD) by the Office of Orphan Drug Products for the treatment of GHD. On September 3, 2020, Pfizer Inc. transferred the ownership and all rights to the ODD to Pfizer Ireland Pharmaceuticals.

The safety and efficacy of somatrogon for the proposed indication is supported by the results of a single pediatric Phase 3 study, a supportive pediatric Phase 2 study, and data from the ongoing open-label extensions (OLEs) of both studies.

The Phase 3 study was managed by OPKO Biologics Ltd. (OBL), a subsidiary of OPKO Health, Inc. (OPKO), the initial sponsor, and conducted by investigators contracted by and under the direction of OPKO. After database lock, OPKO transferred the complete set of data from the database to Pfizer. The data in the clinical study report (CSR) reflect and include the data reported in both the OPKO database (transferred to Pfizer) and the safety database (Pfizer Global Safety database for serious adverse events [SAEs]).

Inspections were requested for the Phase 3 study CP-4-006 entitled "*A Phase 3, Open-label, Randomized, Multicenter, 12 months, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency*."

This 12-month, open-label, multicenter, randomized, active controlled, parallel group study compared the efficacy and safety of weekly somatrogon to daily growth hormone (GH) in prepubertal children with growth hormone disorder (GHD). Prepubertal children (boys 3-11 years, girls 3-10 years) diagnosed with GHD who had no prior exposure to any recombinant human growth hormone (rhGH) therapy, had impaired height and height velocity (HV), and with a baseline insulin-like growth factor-1 (IGF-1) level of at least 1 standard deviation (SD) below the mean IGF-1 level standardized for age and sex were enrolled into the study.

After a screening period of up to 12 weeks, eligible subjects were randomized (stratified by region, GH peak levels at screening, and chronological age) in a 1:1 ratio to weekly subcutaneous (SC) doses of somatrogon or daily SC administration of Genotropin® for 12 months (main study). Somatrogon was provided as a solution for injection containing 20 or 50 mg/mL of somatrogon in a single subject use, multi-dose disposable prefilled pen. Genotropin® was provided in prefilled cartridges for administration with the Genotropin® pen delivery device.

The primary endpoint was annual height velocity (HV) in cm/year after 12 months of treatment. Subjects who successfully completed the 12-month main study could participate in a single-arm long-term open-label extension (LT-OLE) treatment period with somatrogon.

The study began April 19, 2017 and completed August 23, 2019. A total of 84 study sites screened 536 subjects and randomized 228 subjects in this study. Of the 228 subjects who were randomized, 4 subjects (3 in the somatrogon group; 1 in the Genotropin® group) did not receive study drug (3 withdrawn by parent/guardian, 1 lost to follow-up during the screening phase).

Therefore, 224 subjects were randomized and received at least 1 dose of study drug; 2 of these subjects discontinued during the main study. There were 212 subjects who went into the LT-OLE study and 10 subjects did not.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

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   Site: 007

Dates of inspection: March 1– 3, 2021

There were 5 subjects screened and 4 subjects enrolled into the study; 3 subjects completed the study. There were 5 subject records reviewed.

The institutional review board (IRB) of record was (b) (4)

Dr. Flynn is medical director of St. Luke's Children's Endocrinology.

The source documents were organized and the records for each subject were maintained in a separate file. Source documents were attributable, legible, contemporaneous, original, and accurate. Both paper case report forms (CRFs) and electronic CRFs were used for the study. All subject information was initially entered into paper CRFs. The required information was transposed from each subject's paper CRF to the eCRF by the delegated study staff. All data for the subjects recruited for the trial was entered into the eCRFs via an Electronic Data Capture (EDC) system provided by the sponsor.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. **Joel W. Steelman, M.D.**
   Cook Children's Medical Center
   1500 Cooper Street, 2nd Floor
   Fort Worth, TX 76104-2710
   Site: 021

Dates of inspection: January 25 – 27, 2021

There were 7 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study (all rolled into the open-label extension study). There were 7 subject records reviewed.

The IRB of record was Cook Children's Health Care System IRB. Subjects were recruited from patients of Cook Children's Medical Center Endocrinology Dodson Specialty Clinic.

Source records were organized, legible, and available. Paper documents, including the subject diary, for each subject were maintained in a binder; electronic medical records for medical histories were printed and provided within each subject's binder. All records were complete, and deviations were reported as appropriate to the sponsor and IRB. The site initially utilized Inform for the study EDC system, and transitioned to Medidata Rave on approximately September 24, 2018. The site did not receive a formal copy of the eCRFs at the time of inspection. A USB flash drive with the site's data were sent during the inspection.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. OPKO Health, Inc. (with focus on subsidiary OPKO Biologics Ltd.)
4400 Biscayne Blvd.
Miami, FL 33137-3212

**In trying to announce the inspection of the CRO* (b) (4) *it was discovered that* (b) (4) *The study was managed by OPKO Biologics Ltd. (OBL) and they had hired* (b) (4) *for monitoring and regulatory work. OBL informed FDA that* (b) (4) *was not responsible for housing the electronic records or the electronic Trial Master File. Rather, the CP-4-006 study used a cloud-based controlled platform (Veeva) which is accessible under OBL's control/oversight.*

Dates of inspection: February 23 – March 1, 2021

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/CRO, deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

OPKO Health, Inc. (OPKO) was established in 2007. In 2008, company officials made a private investment in a company named Prolor Biotech based in Israel, which was working on technologies that allowed for therapeutic half-life extension. In 2012, OPKO acquired Prolor as a wholly owned subsidiary, which became OPKO Biologics (OBL). Then in 2014, OPKO partnered with Pfizer for the development and marketing of somatrogon. A Joint Development Committee was established. During the study preparation phase, OBL played a larger role but this transitioned to OPKO and Transition Therapeutics (based in Toronto, Canada) around June 2017. (OPKO acquired Transition Therapeutics, which became a subsidiary of OPKO).

A Joint Risk Management Team with OPKO and Pfizer staff met on a quarterly basis to review and discuss safety data with the goal of monitoring the safety risk profile and determining the safety strategy for the study. After completion of the main study and database lock, OPKO transferred the complete set of data from the database to Pfizer according to the OPKO-Pfizer Data Transfer Plan. The database was unlocked and relocked twice after the initial database lock, and the files were transferred from OPKO to Pfizer a total of three times. In each instance, OPKO's Standard Operating Procedure (SOP) for Database Freeze Lock and Unlock and all necessary processes appeared to be followed.

(b) (4) was involved in the site qualification visits for clinical investigator sites. During the lead up to study initiation in October 2016, OPKO discovered that (b) (4) was also providing monitoring services to a competitor and decided to terminate the contract with (b) (4) and switch to (b) (4) for the US, Canada and Spain monitoring. The responsibility for monitoring in Spain was subcontracted by (b) (4) In January 2020, OPKO received notification from a financial entity to make all future payments to them (b) (4) (b) (4) In March 2020, OPKO made the decision to take over management of monitoring of sites that were monitored by (b) (4)

(b) (4) did not possess any study related files as they were all part of the electronic Trial Master File (eTMF) hosted on the cloud based Veeva platform. The sites in the US and Canada transitioned monitoring responsibility to OPKO and OPKO contracted monitoring responsibility directly to (b) (4) This occurred after the completion of the main study, during the LT-OLE, and there was never a lapse in monitoring during the transition from (b) (4) to OPKO monitoring.

No major issues of clinical investigator noncompliance with the investigational plan or FDA regulations were identified that warranted special action by OPKO. No clinical investigators were terminated from the protocol. Monitoring of the sites by the CROs and sponsor oversight appeared to be adequate. After completion of the main study, subject case report forms were provided as PDF zip files to the sites on password protected USBs.

During the main study there were three levels of blinding: fully unblinded personnel (Level 1), fully blinded personnel (Level 3), and partially blinded personnel (Level 2) who had access to all pages and data available except for raw and derived primary endpoint growth data and secondary endpoint bone maturation data. After the completion of the main study and during the ongoing Long-term Open Label Extension of the protocol, all personnel have been unblinded. The inspection did not reveal any accidental unblinding prior to full unblinding of the trial.

As specified in the protocol, sample collection to measure IGF-1 was to be performed on Day 4 (-1). However, it was noted that there were samples collected out-of-window throughout the weekly dosing interval. This issue was discussed in depth during the inspection and there was documentation that OPKO staff made attempts to keep the sites in compliance. When these out of window IGF-1 samples were obtained, the sites were to input a minor protocol deviation according to the Protocol Deviations Plan so that they could be tracked. Monitoring report follow-up letters specifically noted IGF-1 was collected out-of-window and newsletters were sent to clinical investigators during the main study and extension study highlighting the importance of obtaining the IGF-1 levels three to four days post dose as per protocol. The

sponsor took steps to correct the deviations from the approved protocol both through the monitor and directly through emails to the site and updates in the monthly study newsletter.

There was not a finalized Protocol Deviation Plan (PDP) in effect prior to the initiation of the study. Version 1 of the PDP was finalized on September 8, 2017. The study start date was 12/2016 and the first subject visit and screening for the study took place on April 19, 2017. OPKO representatives present during the inspection were unable to account for why the PDP was not finalized prior to the initiation of the study.

(b) (4) was assigned the responsibilities for pharmacovigilance and SAE management, periodic report generation, and reporting of SAEs to the sponsor and CROs. (b) (4) assumed these obligations beginning December 15, 2016 but this was not reported to the FDA as part of an FDA 1571 submission until September 11, 2020. Moreover, the information did not include the actual effective date for the transfer of regulatory obligations. Prior to the closeout of the inspection on March 1, 2021, OPKO voluntarily resubmitted a Form FDA 1571 to the FDA listing the transfer of obligations to (b) (4) and the effective date for the transfer of obligations as December 15, 2016.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

Min Lu, M.D., M.P.H.
Team Leader
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CONCURRENCE:

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation

Office of Scientific Investigations

21. Labeling Summary of Considerations and Key Additional Information

Insert text here.

22. Postmarketing Requirements and Commitments

Deferred at this time because of Complete Response action.

23. Financial Disclosure

The financial disclosure was reviewed, and no issues were identified.

Table 119. Covered Clinical Studies: [CP-4-003, CP-4-004, CP-4-005, CP-4-006, CP-4-007, CP-4-011]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 828		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 11		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: None Significant payments of other sorts: 11 Proprietary interest in the product tested held by investigator: None Significant equity interest held by investigator: 1 Sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): None		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from Applicant)

24. References

Ahangari, G, MR Ostadali, A Rabani, J Rashidian, MH Sanati, and MR Zarindast, 2004, Growth hormone antibodies formation in patients treated with recombinant human growth hormone, Int J Immunopathol Pharmacol, 17(1):33-38.

Binder, G, L Heidenreich, D Schnabel, D Dunstheimer, R Oeverink, W Kiess, A Korner, and J Kratzsch, 2019, Biological Significance of Anti-GH Antibodies in Children Treated with rhGH, Horm Res Paediatr, 91(1):17-24.

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Shankar, G, S Arkin, L Cocea, V Devanarayan, S Kirshner, A Kromminga, V Quarmby, S Richards, CK Schneider, M Subramanyam, S Swanson, D Verthelyi, S Yim, and S American Association of Pharmaceutical, 2014, Assessment and reporting of the clinical immunogenicity of therapeutic proteins and peptides-harmonized terminology and tactical recommendations, AAPS J, 16(4):658-673.

Wilton, P and R Gunnarsson, 1988, Clinical experience with Genotropin in growth hormone deficient children, Acta Paediatr Scand Suppl, 343:95-101.

Wit, JM and B Boersma, 2002, Catch-up growth: definition, mechanisms, and models, J Pediatr Endocrinol Metab, 15 Suppl 5:1229-1241

25. Review Team

Table 120. Reviewers of Integrated Assessment

Role	Names
Regulatory Project Manager	Sejal Kiani
Chief, Project Management Staff	Elisabeth Hanan
Nonclinical Reviewer	Elena Braithwaite
Nonclinical Supervisor	Federica Basso
Office of Clinical Pharmacology Reviewer(s)	Lin Zhou Eliford Kitabi
Office of Clinical Pharmacology Team Leader(s)	Jaya Vaidyanathan Justin Earp
Clinical Reviewer	Sonia Doi
Clinical Team Leader	Marina Zemskova
Statistical Reviewer	Kiya Hamilton
Statistical Team Leader	Feng Li
Cross-Disciplinary Team Leader	Marina Zemskova
Deputy Division Director (clinical)	Naomi Lowy
Office Director (or designated signatory authority)	Lisa Yanoff

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 121. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Susan Kirshner Massod Rahimi Tracy Denison Montserrat Puig Amy Rosenberg James Barlow
Microbiology	Yun Wu Madushini Dharmasena Candace Gomez-Broughton
OPDP	Charuni Shah Melinda Wilson
OSI	Cynthia Kleppinger Min Lu
OSE/DEPI	Po Yin Chang Yandong Qiang
OSE/DMEPA	Melina Fanari Sevan Kolejian Avani Bhalodia Ebony Whaley Murewa Oguntimein Jason Flint
OSE/DRISK	Till Olickal Naomi Boston
OSE/DPV	Amy Chen Ali Niak Christian Cao
DMPP	Sharon Williams Marcia Williams
DPMH	Kristie Baisden Christos Mastroyannis Tamara Johnson
CDRH	Robert Nakielny Rumi Young Suzanne Hudak Janice Ferguson Courtney Evans Joseph Kotarek
DCOA	Yasmin Choudhry Selena Daniels
Clinical Data Scientist	DeAngelo McKinley Alena (Qunshu) Zhang

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Deputy Director	Lisa B. Yanoff, MD	OND/OCHEN	☒ Authored: Section 1 ☒ Approved: All Sections
Signatory Authority	**Signature:** *{See appended electronic signature page}*		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Naomi Lowy, MD	OND/OCHEN/ DGE	☒ Authored: Section 2.2 ☒ Contributed: Sections 2,3,6,7 ☒Approved: All Sections
Deputy Director	**Signature:** Digitally signed by Naomi Lowy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Naomi Lowy -S, 0.9.2342.19200300.100.1.1=2000219474 Date: 2022.01.20 12:09:35 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Marina Zemskova, MD	OND/OCHEN/ DGE	☒ Contributed: Sections 2,3,6,7 ☒ Approved: All Sections
Cross-Disciplinary Team Lead	**Signature:** Marina S. Zemskova -S Digitally signed by Marina S. Zemskova -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011510606, cn=Marina S. Zemskova -S Date: 2022.01.20 09:38:57 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Sonia Doi, MD	OND/OCHEN/ DGE	☒ Authored: Sections 2.2, 3, 4, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 8.3, 10, 11, 17, 21, 22, 23 ☒ Contributed: Sections 6.2, 6.3, 15, 16
Primary Reviewer	**Signature:** Sonia D. Doi -S Digitally signed by Sonia D. Doi -S Date: 2022.01.20 07:29:03 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Mangement	Elisabeth Hanan, MS	OND/ORO/ DROCHEN	☒ Authored: Section 12 ☒ Approved: Section 12
Chief, Project Management Staff	**Signature:** Elisabeth Hanan -S Digitally signed by Elisabeth Hanan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001248286, cn=Elisabeth Hanan -S Date: 2022.01.18 15:40:44 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Regulatory Project Mangement	Sejal Kiani, MS	OND/ORO/ DROCHEN	☒ Authored: Section 12
Regulatory Project Manager	**Signature:** Sejal Kiani -S Digitally signed by Sejal Kiani -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sejal Kiani -S, 0.9.2342.19200300.100.1.1=0014049364 Date: 2022.01.19 13:20:39 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	Calvin Lee Elmore, PhD	OND/OCHEN/ DPTCHEN	☒ Approved: Sections 5.1, 7.1, 8.3, 8.4,13
Deputy Director	**Signature:** Calvin L. Elmore -S Digitally signed by Calvin L. Elmore -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000356615, cn=Calvin L. Elmore -S Date: 2022.01.18 10:14:02 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	Federica Basso, PhD	OND/OCHEN/ DPTCHEN	☒ Approved: Sections 5.1, 7.1, 8.3, 8.4, 13
Supervisor	**Signature:** Federica Basso -S Digitally signed by Federica Basso -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Federica Basso -S, 0.9.2342.19200300.100.1.1=0011076316 Date: 2022.01.18 10:19:52 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/ Toxicology	Elena Braithwaite, PhD	OND/OCHEN/ DPTCHEN	☒ Authored: Sections 5.1, 7.1, 8.3, 8.4, 13
Primary Reviewer	**Signature:** Elena K. Braithwaite -S Digitally signed by Elena K. Braithwaite -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011322183, cn=Elena K. Braithwaite -S Date: 2022.01.18 10:26:56 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Doanh Tran, PhD	OTS/OCP/DCEP	☒ Approved: Sections 5, 6.1, 8.1, 8.2, 14
Deputy Director	**Signature:** Doanh C. Tran -S Digitally signed by Doanh C. Tran -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Doanh C. Tran -S, 0.9.2342.19200300.100.1.1=1300378169 Date: 2022.01.18 10:46:44 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jayabharathi Vaidyanathan, PhD	OTS/OCP/DCEP	☒ Approved: Sections 5, 6.1, 8.1, 8.2, and 14
Team Leader	**Signature:** Jayabharath Vaidyanathan -S Digitally signed by Jayabharath Vaidyanathan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300220018, cn=Jayabharath Vaidyanathan -S Date: 2022.01.18 10:59:14 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Lin Zhou, PhD	OTS/OCP/DCEP	☒ Authored: Sections 6.1, 8.1, 8.2, and 14 ☒ Contributed: Section 5
Primary Reviewer	**Signature:** Lin Zhou -S Digitally signed by Lin Zhou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Lin Zhou -S, 0.9.2342.19200300.100.1.1=2000423233 Date: 2022.01.18 11:26:34 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Justin Earp, PhD	OTS/OCP/DPM	☒ Approved: Section 14.3
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2022.01.18 14:33:20 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Eliford Kitabi, PhD	OTS/OCP/DPM	☒ Authored: Section 14.3
Primary Reviewer	**Signature:** Eliford N. Kitabi -S Digitally signed by Eliford N. Kitabi -S DN: c=US, o=U S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002641767, cn=Eliford N. Kitabi -S Date: 2022.01.18 13:37:15 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Feng Li, PhD	OTS/OB	☒ Approved: Sections 6.2,15, 16.1, 16.2, 16.3, 16.4
Team Leader	**Signature:** Feng Li -S Digitally signed by Feng Li -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Feng Li -S, 0.9.2342.19200300.100.1.1=2000332337 Date: 2022.01.18 13:57:47 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Kiya Hamilton, PhD	OTS/OB	☒ Authored: Sections: 6.2, 16.1, 16.2, 16.3, 16.4 ☒ Contributed: Sections: 6.2, 15, 16
Primary Reviewer	**Signature:** Digitally signed by Kiya Hamilton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kiya Hamilton -S, 0.9.2342.19200300.100.1.1=2000501741 Date: 2022.01.18 15:29:44 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Susan Kirshner, PhD	OPQ/OBP/ DBRRIII	☒ Approved: Sections 3.1.1.1, 6.3.1, 7.6.4, and 9
Review Chief	**Signature:** Susan L. Kirshner -S Digitally signed by Susan L. Kirshner -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300194629, cn=Susan L. Kirshner -S Date: 2022.01.18 16:10:12 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Massod Rahimi, PhD	OPQ/OBP/ DBRRIII	☒ Authored: Section 9
Application Team Lead	**Signature:** Massod Rahimi -S Digitally signed by Massod Rahimi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Massod Rahimi -S, 0.9.2342.19200300.100.1.1=0014424508 Date: 2022.01.18 20:35:36 -05'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Tracy Denison, PhD	OPQ/OBP/ DBRRIII	☒ Contributed: Section 9
Primary Reviewer	**Signature:** Tracy A. Denison -S Digitally signed by Tracy A. Denison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001154781, cn=Tracy A. Denison -S Date: 2022.01.19 09:52:33 -05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Product Quality	Montserrat Puig, PhD	OPQ/OBP/ DBRRIII	☒ Authored: Sections 3.1.1.1, 6.3.1, 7.6.4
Primary Reviewer	**Signature:** Montserrat Puig -S Digitally signed by Montserrat Puig -S DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=1300378642 cn=Montserrat Puig -S Date: 2022 01 19 10:40:19 05'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

MARINA ZEMSKOVA
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NAOMI N LOWY
01/21/2022 10:20:24 AM

LISA B YANOFF
01/21/2022 11:03:38 AM

Clinical Outcome Assessment Review Memorandum

From	Yasmin Choudhry, M.D. Clinical Outcome Assessment (COA) Reviewer Division of Clinical Outcome Assessment (DCOA) Selena Daniels, PharmD, PhD COA Team Leader DCOA Elektra Papadopoulos, M.D., MPH Deputy Director DCOA David Reasner, PhD Director DCOA
To	Division of General Endocrinology
COA tracking number	C2021339
BLA# (Drug Name) / Referenced IND#	761184 / 132494 (Somatrogon)
Drug Sponsor	Pfizer
Indication:	For long-term replacement therapy of pediatric patients with short stature due to growth hormone deficiency in pre-pubertal children. Please check all that apply: ☒ Rare Disease/Orphan Designation ☒ Pediatric (≥3 – 12 years)
Instrument(s) reviewed:	Quality of Life in Short Stature Youth ☒ Patient-reported outcome (PRO) ☒ Observer-reported outcome (ObsRO)

This memo is in response to the clinical outcome assessment (COA) consult request filed in DARRTS by the Division of General Endocrinology (DGE) on August 19, 2021 [DARRTS Reference ID: 4844035] for BLA 761184 regarding somatrogon (MOD-4023) for the use of long-term replacement therapy of pediatric patients with short stature due to growth hormone deficiency (GHD) in pre-pubertal children.

This COA consult response is related to review of the exploratory COA endpoints to help support clinical benefit of the investigational product.

Trial Design and Study Endpoints

Study CP-4-006 was a multicenter, open-label, randomized, active-controlled efficacy and safety study of weekly somatrogon (MOD-4023) compared to daily Genotropin® -therapy in pre-pubertal children aged ≥3 years diagnosed with GHD who had no prior exposure to any

recombinant human growth hormone therapy, had impaired height and height velocity[1], and with a baseline insulin-like growth factor-1 (IGF-1) level of at least 1 standard deviation below the mean IGF-1 level standardized for age and sex (IGF-1 standard deviation score ≤ -1).

This study consisted of a 12-week screening period, a randomization period in which a total of 224 subjects (who received at least 1 dose of study drug) were randomized (stratified by region, growth hormone peak levels at screening, and chronological age) in a 1:1 ratio to weekly subcutaneous (SC) doses of somatrogon (investigational treatment, 0.66 mg/kg/wk) or daily SC administration of Genotropin (0.034 mg/kg/day) for 12 months. The duration of this study was approximately 12 months.

Patients were to enter a long-term open-label extension period to demonstrate continued safety and efficacy of MOD-4023 treatment (all patients) after successful completion of the first 12 months of treatment. The open-label period is to continue until marketing approval.

Study CP-4-006 was a non-inferiority trial.

The study endpoints for Study CP-4-006 are as follows:

Primary Efficacy Endpoint

- The annual height velocity in cm/year after 12 months of treatment.

Exploratory Efficacy COA Endpoint

- Quality of life core total score at baseline and month 12 in specific countries as assessed by Quality of Life in Short Stature Youth (QoLISSY) Core Domain.

Refer to the integrated review for more details on the clinical trial design, eligibility criteria, and statistical analyses.

COA Description

Quality of Life in Short Stature Youth (QoLISSY)

The QoLISSY is a 51-item instrument (three core domains with 22 items plus three mediator domains with 29 items) designed to assess symptoms and impacts in short statured youth.

The following versions were used in Study CP-4-006:

- Self-report: Participants aged 7 years or older were encouraged to complete the child version of the QoLISSY core questionnaire for children and adolescents ("QoLISSY-Child") on their own.
- Parent-report: For participants under 7 years, a QoLISSY core questionnaire for Parents ("QoLISSY-Parent") was to be completed by the parent or caregiver.

Each version consists of three core domains: Physical, Social, and Emotional. There are three mediator domains: Coping, Beliefs, and Treatment. The parent's version contains two

[1] Impaired height velocity (HV) defined as: (1) Annualized HV below the 25th percentile for CA (HV < -0.7 SDS) and gender according to the OPKO HV (Tanner, Prader and Hermanussen) calculator and (2) The interval between 2 height measurements should be at least 6 months, but should not exceed, 18 months prior to inclusion.

supplementary domains: Future and Effects on parents. Each item is rated on a 5-point verbal rating scale ranging from 1 ("not at all/never") to 5 ("extremely/always"). The recall period is "the previous week."

The QoLISSY was assessed at Baseline (Visit 2) and end of treatment (Visit 8).

For copies of the QoLISSY-Child and -Parent versions, see Appendices A and B of this review, respectively.

The three dimensions (physical, social, and emotional) of the QoLISSY questionnaire will be calculated individually and as a combined core total score based on the QoLISSY scoring manual. This core score is calculated as the sum of the means of these three dimensions and divided by 3. All scores were transformed from raw scores to 0 to 100 scores, where higher scores represent a higher health-related quality of life.

Reviewer's comments: *Of note, DCOA was not consulted to review QoLISSY during the IND phase of this drug development program. Based on discussions with DGE Clinical with regard to this BLA, they are interested in any COA-related evidence that may support benefit of this drug. The DCOA is being consulted by DGE to provide a closure in the form of a short, focused review for inclusion in their integrated review.*

This reviewer has conducted a review of the materials submitted in the BLA submission (i.e., the QoLISSY User Manual) to support this instrument.

There is insufficient information to fully assess the content validity[2] of the QoLISSY.

- *The user manual (see Section 16.1.9.7 of the Statistical Analysis Plan, SDN 1) lacks detail regarding the relevancy of concepts. It is unclear whether all concepts included in the adult/child versions of QoLISSY are relevant and important to the target patient population.*

- *In the absence of patient transcripts, it is unclear how the participants (particularly children 8-13 years) defined and understood the concepts/content included in the questionnaires. Additionally, it appears that the discussion guide[3] for the focus groups includes leading questions (e.g., Do you get any comments at home about your height? From brothers/sisters, mother/father, others in family? When did you hear your height might be a problem for the first time (your age)?). This reviewer believes that leading questions (i.e., questions that include or imply the desired answer to the question in the phrasing of the question itself) are problematic because they may result in biased or false/misleading answers (results). They may also lead to a missed opportunity to hear an unexpected insight.*

- *While caregiver input was obtained during the development of the QoLISSY Child and Parent versions, the QoLISSY user manual notes that the QoLISSY Parent version was*

[2] The QoLISSY User Manual includes the methodology and results of the focus groups (86 children 4-7 years; 114 parents).
[3] See Table 5: *List of questions discussed in the focus groups* in Section 5.2.2 of the QoLISSY User Manual.

not cognitively tested in caregivers. Therefore, it is unclear whether the caregivers had a good understanding of the format/content of this instrument.

- *Many of the items in the QoLISSY-Parent version do not assess "observable" concepts. For example, the following items assess the child's feelings:*
    - *Item 2.2.: My child feels small around others his/her age*
    - *Item 3.6: (S)he is sad because of his/her height*
    - *Item3.5: (S)he is insecure because of his/her height*

There is insufficient information to fully assess the other measurement properties of the QoLISSY. For example, there is no data on responsiveness (i.e., ability to detect change).

Given the QoLISSY endpoint was exploratory, a full analyses report (with confidence intervals, p-values etc.) was not included in the submission rather, the Applicant provided a high-level summary of the results (mean, median, range) of the QoLISSY core domain scores. Hence, it is not known which items were driving the total core domain score of QoLISSY.

Review Conclusions

1. While the results from Study CP-4-006 demonstrated numerical increases in QoLISSY core total scores for both treatment groups (somatrogon and Genotropin) at month 12, the findings are uninterpretable for the following reasons:
    a. The open-label study design. Patients' knowledge of treatment assignment may lead to systematic overestimation or underestimation of the treatment effect, the magnitude of which is currently unknown. Further, in the absence of evidence regarding the measurement properties, it is also unclear whether the tool is sufficiently sensitive and reliable enough to directly compare the two active treatments.

    b. The COA research objectives and endpoint definitions are unclear.

    c. There is insufficient information to determine whether the instrument is fit-for-purpose for the context of this development program.

    d. The threshold(s) for meaningful withing-patient score change is unknown as the applicant did not utilize anchor-based methods, which are the primary methods used to interpret meaningful within-patient score changes in COA endpoints.

Appendices:
Appendix A: QoLISSY-Child version
Appendix B: QoLISSY-Parent version

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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11/16/2021 07:21:00 AM

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11/18/2021 11:27:07 AM