16 December 2021
EMA/15620/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ngenla

International non-proprietary name: somatrogon

Procedure No. EMEA/H/C/005633/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Ngenla
Applicant:	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles BELGIUM
Active substance:	somatrogon
International Non-proprietary Name/Common Name:	somatrogon
Pharmaco-therapeutic group (ATC Code):	Subject to final ATC code
Therapeutic indication(s):	Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.
Pharmaceutical form(s):	solution for injection
Strength(s):	24 mg/ 1.2 ml and 60 mg/ 1.2 ml
Route(s) of administration:	subcutaneous use
Packaging:	cartridge (glass) in a pre-filled pen
Package size(s):	1 pre-filled pen

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List of abbreviations

ADA	anti-drug antibodies
AE	adverse event
ANCOVA	analysis of covariance
BA	bone age
BM	bone maturation
BMI	body mass index
CA	chronological age
CDC	Centers for Disease Control and Prevention
CHO	Chinese hamster ovary
CI	confidence interval
cm/year or cm/yr	centimetres/year
CRF	case report form
CSR	clinical study report
CTP	carboxy-terminal peptide
FAS	full analysis set
FCS	fully conditional specification
FSFV	first subject first visit
GH	growth hormone
GHD	growth hormone disorder
hGH	human growth hormone
HT	height
HV	height velocity
IGF-1	insulin-like growth factor-1
IGFBP-3	insulin-like growth factor-binding protein-3
ISI	Integrated Summary of Immunogenicity
LHCF	last height carried forward
LS	least squares
LSLV	last subject last visit
LSM	least squares mean
M12	month 12
mg/kg/wk	milligrams/kilogram/week
min, max	minimum, maximum

MNAR	missing not at random
MOD-4023	somatrogon
N, n	total number, number
NI	non-inferiority
OLE	open-label extension (also referred to as LT-OLE; long-term OLE)
PAHT	predicted adult height
PD	pharmacodynamic
pGHD	paediatric growth hormone disorder
PK	pharmacokinetic
PP	per protocol
PPS	per protocol set
QoL	quality of life
QoLISSY	Quality of Life in Short Stature Youth
rhGH	recombinant human growth hormone
SAP	Statistical Analysis Plan
SAS	safety analysis set
SAWP	Scientific Advice Working Party
SC	subcutaneous(ly)
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	standard deviation
SDS	standard deviation score
STAT5b	signal transducer and activator of transcription factor 5b
UK	United Kingdom
US / USA	United States / United States of America
Y1/Y2/Y3/Y4	year 1 / year 2 / year 3 / year 4

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Pfizer Europe MA EEIG submitted on 3 February 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Ngenla, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 30 April 2020.

Ngenla was designated as an orphan medicinal product EU/3/12/1087 on 24 January 2013 in the following condition: treatment of growth hormone deficiency.

The applicant applied for the following indication: long-term treatment of paediatric patients with growth disturbance due to insufficient secretion of growth hormone.

The applicant later decided to update the indication and the final applied indication was as follows: treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Ngenla as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Ngenla.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0121/2017 on the granting of a product-specific waiver for all subsets of the paediatric population from birth to less than 18 years of age.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance somatrogon contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
22 Sep 2011	EMEA/H/SA/2160/1/2011/SME/III	Prof. Brigitte Blöchl-Daum and Dr Caroline Auriche
22 Sep 2011	EMEA/H/SA/2160/2/2011/PED/SME/III	Prof. Brigitte Blöchl-Daum and Dr Caroline Auriche
19 Nov 2015	EMEA/H/SA/2160/1/FU/1/2015/PA/PED/III	Dr Kolbeinn Gudmundsson, Dr Ferran Torres and Prof. Kerstin Westermark
23 June 2016	EMEA/H/SA/2160/1/FU/2/2016/PA/II	Dr Kolbeinn Gudmundsson, Dr Andreas Kirisits and Dr Daniel O'Connor

The applicant received Protocol assistance on four occasion as mentioned in the table above for the development of somatrogon for growth hormone deficiency. The Protocol assistance pertained to the following Quality, Pre-Clinical and Clinical aspects:

- Viral clearance validation studies
- Drug substance specifications
- Drug product specifications
- Potency testing
- Comparability testing for manufacturing changes throughout development
- Strategy for handling of manufacturing changes
- Analytical comparability exercise between different pharmaceutical presentations
- General non-clinical strategy
- Safety pharmacology
- Timing of IGF-1 measurement in children and adults for safety monitoring
- Design of the phase 3 programme in adults
- Paediatric development: definition of the paediatric population, PK/PD sampling strategy, dosing regimen and adjustment, design of phase 3 study in children, endpoints, statistical analysis plan, non-inferiority margin, sample size estimation, interim analysis and sample size re-estimation, safety database, trial duration, plans for single arm long-term extension study.
- Generation of data on improved adherence/preference, patient reported outcome investigations, proportion of adults and children to be included and conduct in Anglophone countries only
- Demonstration of Significant Benefit to maintain Orphan Designation

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Martina Weise

The application was received by the EMA on	3 February 2021
The procedure started on	25 February 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 May 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 May 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	31 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	24 June 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 Sep 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	19 Oct 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 Oct 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 November 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	18 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	01 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Ngenla on	16 December 2021
The CHMP adopted a report on similarity of Sogroya with Ngenla on (see Appendix on similarity)	16 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Somatrogon is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.

Human growth hormone (hGH) deficiency is the consequence of low or absent secretion of growth hormone from the pituitary gland. hGH is a 191-amino-acid pituitary protein that stimulates the hepatic production and release of insulin-like growth factor-1 (IGF-1) into the systemic circulation.

hGH and IGF-1 are instrumental in the promotion of linear growth in children, and in the control of metabolism and body-mass composition in adults.

The somatotroph cells of the anterior pituitary gland produce hGH. Secretion of hGH is under strict hormonal homeostatic control. Growth hormone-releasing hormone (GHRH) and ghrelin are the most significant stimulators of its production while somatostatin produces the strong inhibitory action.

In children, growth hormone disorder (GHD) results in inadequate circulating IGF-1 levels and is manifested as abnormal linear growth. Paediatric subjects develop at a slower rate than would be expected based on the growth charts.

2.1.2. Epidemiology

The incidence of short stature associated with GHD has been estimated to be approximately 1:4000 to 1:10,000.

2.1.3. Aetiology and pathogenesis

Childhood GHD can be congenital, acquired or idiopathic. Underlying causes of two of these three types of GHD in children have been identified.

Children with GHD will not all necessarily continue their deficiency into adulthood, or at least will not necessarily require continuation of GH treatment once their linear growth has reached its limit.

2.1.4. Clinical presentation, diagnosis

In neonates, clinical presentations of congenital pituitary GHD include profound hypoglycaemia, hypoglycaemic seizures, prolonged jaundice, and microphallus and cryptorchidism in boys. The patients diagnosed at younger ages generally have more severe GHD, are more likely to suffer from multiple pituitary hormone deficiencies and tend to have had more complications at birth.

The age of presentation varies with respect to the time of onset and the degree of GHD.

Children with complete absence of growth hormone secretion are usually diagnosed before reaching the age of 3 years, whereas those with lesser degrees of deficiency present at older ages. Although sharing the fundamental condition of deficiency, the paediatric population treated for their abnormal linear growth is clinically distinct from the adult GHD population.

The diagnosis of GHD in childhood is a multifaceted process requiring comprehensive clinical and auxological assessment, combined with biochemical tests of the GH-insulin-like growth factor (IGF) axis, radiological evaluation and pituitary MRI. The diagnosis of severe GHD is usually straightforward, as there are well defined clinical, auxological, biochemical, and radiological abnormalities. However, the diagnosis of moderate GHD can be associated with normal values within the IGF axis and a normal MRI.

In a child with slow growth, whose history and auxology suggest GHD, testing for GH/IGF-I deficiency requires IGF-I/IGFBP-3 levels and GH provocation tests after hypothyroidism has been excluded. In suspected isolated GHD, two GH provocation tests (sequential or on separate days) are required.

2.1.5. Management

The current standard of care for paediatric GHD is daily subcutaneous (SC) injection of recombinant human growth hormone (rhGH).

rhGH treatment improves growth outcomes as demonstrated by increased height velocity and normalization of adult height. rhGH treatment also has positive effects on the metabolic consequences of GHD including improved body composition (fat/lean mass) and reduction in lipids (total cholesterol, LDL-cholesterol, and triglycerides), and improvements in QoL/psychosocial aspects of paediatric GHD.

Treatment response is assessed by measurements of height and growth velocity and is generally continued until final height, epiphyseal closure, or both have been recorded. Early intervention produces the most optimal outcome as growth potential decreases overtime. In some individuals with persistent GHD, rhGH therapy is continued throughout adulthood.

Treatment algorithms are based on the body weight of the growing child which corrects for the higher physiological need for growth hormone during growth compared to adults. IGF-I plasma concentrations should be maintained in the normal age and sex-adjusted range for safety reasons. Periodic checks of IGF-I levels are required because they may increase over time, even if the growth hormone dosage does not change.

Injection frequency has been found to be positively correlated with growth response and final height among children with idiopathic GHD treated with daily rhGH. The burden of daily administration contributes to nonadherence and can thus limit the therapeutic benefits of rhGH treatment.

Non-adherence rates vary widely depending on study methodology and non-adherence/ compliance definitions but have been reported to be 36% to 49% across a variety of studies and as high as 66% when compliance is defined as taking 85% of the prescribed doses (missing >1 dose/week) and is based on used vials returned.

Several different technological approaches to prolong the duration of action have been evaluated including sustained-release preparations that utilize microsphere encapsulation (Nutropin Depot), pegylated formulations (Jintrolong), non-covalent albumin binding (Sogroya), prodrugs (TransCon31), and Fc GH fusion formulations (GX-H9, albutropin Nutropin Depot was withdrawn by the applicant before a final position could be reached by the CHMP . Currently one long-acting GH formulation has been approved in the EU, Sogroya (INN somapacitan).

Therefore, having additional long-acting formulations would be beneficial for patients and care givers.

2.2. About the product

Somatrogon (also referred to as MOD-4023) is a long-acting rhGH with receptor binding properties and a mechanism of action analogous to hGH. Somatrogon is a glycoprotein produced in CHO cells by recombinant DNA technology. It comprises the amino acid chain sequence of hGH and one copy of the CTP from the beta chain of hCG at the N-terminus and 2 copies of CTP (in tandem) at the C-terminus. The glycosylation and CTP domains account for the half-life of somatrogon, which allows once-weekly dosing.

Somatrogon binds to the growth hormone (GH) receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signalling, somatrogon binding leads to activation of the STAT5b signalling pathway and increases the serum concentration of

IGF-1 was found to increase in a dose-dependent manner during treatment with somatrogon partially mediating the clinical effect. As a result, GH and IGF-1 stimulate metabolic changes, linear growth and enhance growth velocity in paediatric patients with GHD.

Two strengths are proposed: 24 mg and 60 mg solutions for injection in prefilled pens, each of 1.2 ml volume. The recommended dose is 0.66 mg/kg body weight administered once weekly by subcutaneous (SC) injection.

2.3. Type of application and aspects on development

This procedure is subject to a centralised procedure. No request for an accelerated assessment, conditional marketing authorisation or approval under exceptional circumstances was made. Quality, non-clinical developmental and clinical development matters were discussed with EU Competent Authorities at a national level and with the EMA through scientific advice/protocol assistance requests. The advice was followed by the applicant for the most part.

In the quality development of somatrogon, the applicant has applied relevant ICH and EMA/CHMP quality guidelines related to the development, quality control, manufacturing and stability of biological/biotechnological drug substances and drug products.

Two paediatric studies were conducted for the intended indication. A Phase 3 registration study (CP-4-006) and a supportive Phase 2 dose finding study (CP-4-004), contributed both safety and efficacy data to the evaluation of somatrogon for the proposed indication (treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone).

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as a solution for injection containing 24 mg in 1.2ml or 60 mg in 1.2 ml of somatrogon as active substance.

Other ingredients are: trisodium citrate dihydrate, citric acid monohydrate, L-histidine, sodium chloride, m-Cresol, poloxamer 188 and water for injection.

The product is available in a 3 ml Type 1 clear glass cartridge presented in a disposable prefilled pen for subcutaneous injection.

2.4.2. Active Substance

2.4.2.1. General information

The INN is somatrogon. Somatrogon is a recombinant chimeric fusion protein of human growth hormone (hGH) with one copy of the C-terminal peptide (CTP) from the β-chain of human chorionic gonadotropin at the N-terminus and two copies of CTP at the C-terminus. It is produced in CHO cells. The CTP domains with multiple O-linked glycosylation sites account for an extended half-life of somatrogon allowing for weekly dosing. The predominant somatrogon glycoforms include the molecule with 15 or 16 monosialylated, core-1 O-glycans. Additionally, each CTP region contains hydroxyproline residues, which range from 0-5 hydroxy additions per intact somatrogon molecule. Somatrogon binds to the growth hormone receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism.

2.4.2.1. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Sufficient documentation has been provided to support that all aspects of active substance (AS) manufacture and testing are conducted in a satisfactory GMP environment.

Somatrogon AS manufacturing process consists of typical upstream and downstream bioprocessing steps commonly seen in recombinant protein production, with five upstream bioprocessing steps and ten downstream steps. Production starts with thawing of a vial of the working cell bank (WCB). Cells are expanded in flasks and culture bags before being transferred to the single use production bioreactor. The production bioreactor culture is then harvested and clarified.

After clarification of the harvest, further purification is performed via several chromatography and filtration steps. After purification the active substance is formulated. At the end, the active substance is filtered (0.2 µm) and filled into containers and frozen until transported frozen to the finished product manufacturing site.

In general, the manufacturing process is sufficiently well described and has adequate controls in place. The scale of the manufacturing process is defined by the size of the production bioreactor

The overall control strategy i.e. process parameters and in process test ranges are acceptable and based on the process characterisation data and have been shown to lead to an active substance of the intended and consistent quality.

Control of materials

The applicant has provided a list of all raw materials used in AS manufacture including where in the process they are used. All raw materials used in upstream and downstream steps are either Ph. Eur. grade or testing performed on the materials is in general extensive and ensures control. No raw materials of human origin are used in manufacture of the master cell bank (MCB), WCB or AS.

Somatrogon is expressed in CHO cells. A 2-tiered master cell bank/working cell bank (MCB/WCB) system is in place. MCB and WCB testing is extensive and includes confirmation of sterility, absence of mycoplasma, in vitro and in vivo adventitious agents testing. Test methods were suitably qualified (full reports were provided). Testing is in accordance with ICH Q5A. Testing also confirms cell identity and genetic stability / confirmation of desired genetic manipulation. The protocol for introduction of future WCBs has been provided and is considered acceptable.

Process Validation

The somatrogon commercial manufacturing process has been validated by demonstrating that the process met pre-defined acceptance criteria for performance when run within defined process parameters. The acceptable ranges for the process control parameters were defined based upon risk assessments and process characterisation studies as discussed in S.2.6. The validation of the manufacturing process is therefore adequate as the parameters tested are sufficiently supported by process characterisation studies and therefore relevant for ensuring control and quality of the AS. All process controls (i.e., process control parameters and in-process tests) were met by all PPQ batches. Batch release (S.4.4) for the PPQ lots met acceptance criteria and demonstrates batch to batch consistency.

The applicant claims the batches demonstrate that process related impurities are removed to acceptable safety levels.

The hold times are adequately supported by microbial data and extensive biochemical data from representative small-scale studies held beyond the routine in-process hold range.

Performance of resins and membranes over the registered lifetimes is adequately supported by small scale studies and at scale the applicant will continue to evaluate resin lifetime at scale. More cycles are planned for each UF/DF membrane, these are ongoing at scale. Sufficient details of the parameters and respective acceptance criteria included in the ongoing validation studies are presented in the dossier.

Manufacturing process development

Development history is presented with clear chronological description and discussion of significant changes made to the manufacturing process.

Comparative process descriptions and tables/summaries of process changes have been provided. Two comparability studies are presented. These studies employ an extensive panel of testing methods and acceptably demonstrate comparability between processes. In response to a D120 query, additional data from comparability studies from earlier processes was provided as some of these batches were used in early clinical studies. Overall, the applicant has provided adequate details of all comparability studies conducted to support that the material used in clinical studies is comparable.

The applicant provided extensive details of the extractables studies conducted with the contact material during active substance manufacturing that were identified as high risk components following a risk assessment No extractable compounds were observed, the data provided is considered acceptable.

The applicant has provided a detailed overview of how their process and its control strategy have been developed. Extensive process characterisation data is presented. The overall approach for process characterisation is stepwise and included evaluation of historical data, risk assessments to define characterisation study design, establishment of quality target ranges (QTRs) for relevant critical quality attributes (CQAs), assessment of suitability of scale-down models and execution of process characterisation studies. This approach is endorsed and the classification of critical process parameters (CPPs) is clearly based upon an understanding of the CQAs of the molecule as well as an understanding of the manufacturing process, its process parameters and material attributes. The acceptable ranges and criticality classifications are in general acceptable and the ranges registered in S.2.2 have been adequately justified by the process characterisation studies.

Characterisation

A broad and adequate panel of analytical methods was used to evaluate primary structure, post-translational modifications, charge and size heterogeneity, higher order structure, and biological activity of somatrogon AS, and no further characterisation tests are requested. The process-related

impurities are identified. No testing of these impurities is proposed during routine in-process testing, as noted above this is considered to be acceptable as the toxicological risk is considered negligible. The product-related impurities are adequately controlled through AS release and stability specifications. The characterisation is robust and has adequately covered the main attributes of the active substance. Tests used in the characterisation were as follows.

2.4.2.1. Specification

The proposed panel of release tests for somatrogon AS at release and during long-term stability studies covers identity, quantity, purity, potency, and microbial assurance. In general, the panel of tests are in line with ICH Q6B and are considered appropriate for routine control of somatrogon AS.

Analytical procedures and reference standards

The analytical method descriptions include details of reagents, sample preparation, operating conditions, and system suitability tests (SSTs) and are considered acceptable. From the method descriptions presented, it is clear how the data is interpreted, the results calculated and how system suitability is ensured for each method with suitable acceptance criteria for all test samples and control samples.

In development a rat weight gain assay was used and transitioned to the cell based assay (CBA) for potency

The proposed specifications are clearly linked to the manufacturing process data obtained throughout development including data obtained from batches used in the pivotal clinical studies using the commercial manufacturing process and earlier batches used in preclinical and early clinical studies, demonstrating manufacturing consistency. Stability batches were also considered when setting the specifications. The applicant has shown no discernible trends over time when stored at the proposed condition on attributes, thereby supporting the criteria being the same at release and on stability. The approach used to set the specifications is clearly presented, including details of how the tolerance intervals (TI) are calculated. A list of batches used for the establishment of specifications is presented, highlighting what batches were including in the statistical analyses using TI and the batches that were included as supportive data for clinical exposure reference and manufacturing history, not used in tolerance interval analysis. The specifications are considered acceptable.

The history of all reference standard material throughout development of somatrogon is present in the dossier and considered acceptable. The information provided is considered acceptable, traceability between primary and working reference standard as well as between current and future working standards (through the primary standard) is ensured.

Batch analysis

The applicant has provided a summary table of all AS batches manufactured during development and indicates their use (toxicology/nonclinical studies, exact number of clinical studies, stability and process validation). The dates of release of these batches range from 2008 to 2019. Different release tests were employed throughout development and sufficient analytical method bridging studies is presented and discussed in S.2.6. Results, specifications and test methods applicable at the time of release are clearly presented. All batches met the acceptance criteria in place at the time of testing. Batch-to-batch consistency is demonstrated, including the patterns of heterogeneity (charge variants and glycan content). The results for the tests for purity, impurities and product-related substances are largely consistent throughout development.

Container closure

Somatrogon AS is filled into 1 L sterile, transparent polyethylene terephthalate co-polymer G (PETG) bottles with screw closures. The choice of the container/closure is justified and supported by pharmacopoeial compliance of the materials and stability data for the AS which is stored in PETG bottles. The bottles are supplied sterile.

2.4.2.1. Stability

In terms of time points, temperature conditions and the type of testing performed, stability studies are performed in accordance with ICH guidance. The proposed shelf-life for somatrogon AS is 36 months at the recommended storage condition is endorsed.

Data from a total of ten batches is presented to support the long-term storage conditions. The studies will continue through the 60-month time point. In addition to the tabulated summary results for each batch, the applicant has presented figures for all long-term batch data allowing for ease of assessment of data over time. All batches remained within specification over the course of the long-term stability studies with no discernible trends observed. The data support that the AS is very stable and the data do not give rise to any concern that the AS would go out of specification by 36 months. As sufficient real time data is available for the commercial site the proposed shelf life of 36 months is considered acceptable.

Results from the accelerated conditions showed that excursions above the recommended storage condition up to 5 ± 3 °C are acceptable for up to 6 months and excursions above the recommended storage condition up to 25±2 °C/60±5% RH are acceptable for up to 2 weeks.

Freeze-thaw data was provided for one batch that underwent three cycles of freeze-thaw cycles and no change in product quality was noted through 36 months. It is agreed that somatrogon AS may undergo up to 3 freeze-thaw cycling temperature excursions during the 36-month shelf life.

The applicant also demonstrated on one primary batch that AS is photo-labile at the ICH photostability conditions.

The post-approval stability protocol has been provided and is aligned with ICH Q1A and thus considered acceptable. Post-approval, one batch will be placed on annual stability and tested. The stability-indicating tests are included and considered suitable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Ngenla is presented as a solution for injection containing 24 mg in 1.2 ml (20 mg/ml) or 60 mg in 1.2 ml (50 mg/ml) of somatrogon as active substance for subcutaneous injection.

Other ingredients are: trisodium citrate dihydrate, citric acid monohydrate, L-histidine, sodium chloride, m-Cresol, poloxamer 188 and water for injection. Excipients are all commonly used in parenteral biological medicinal products and comply with their respective European Pharmacopoeia monographs.

The product is available in a 3 ml Type 1 clear glass cartridge enclosed in a single-patient, multiple-use disposable prefilled pen (PFP). Together they form a single integral product intended exclusively for use in the given combination. The target fill volume for both the 24 mg/1.2 ml and 60 mg/1.2 ml cartridges is 1.519 mL which includes an overfill of 0.319 ml to ensure a nominal volume of 1.2 ml is available.

Feature	24 mg Prefilled Pen	60 mg Prefilled Pen
Somatrogon solution concentration	20 mg/mL	50 mg/mL
Nominal volume	1.2 mL	1.2 mL
Color scheme	Lilac pen cap, dose button, and label	Blue pen cap, dose button, and label
Dose increments	0.2 mg / 10 µL	0.5 mg / 10 µL
Maximum dose	12 mg (600 µL)	30 mg (600 µL)

Each pen presentation contains multiple doses of somatrogon finished product solution. The dose is variable, set within the range of 10 to 600 µl using a manual dial dose setting mechanism. The healthcare provider will prescribe the most appropriate strength of product from the two available presentations, based on the dose which is defined by a patient's body-weight.

The prefilled pen is provided without needles, which must be procured separately, but are referenced in the SmPC. Compatibility studies have been performed with 31G x 8 mm (BD Micro-Fine), 31G x 5mm (BD Micro-Fine), 31G x 6 mm (NovoFine) and 32G x 4mm (NovoFine). The 31G x 8 mm and 32G x 4 mm needles were selected as worst-case for the study with respect to potential to influence flow resistance and finished product quality attributes. To simulate conditions of normal use, PFPs were cycled weekly, five times, between 30ºC (for four hours) and 2-8ºC (for rest of the week). After 28 days the finished product solution (FPS) was expelled through either a 31G x 8 mm or 32G x 4 mm pen needle for analysis of pre-defined quality attributes. Control samples were expelled from the pen without a needle attached. All assay results met predetermined expected results and there was no significant change in tested parameters at the final timepoint. The assay results are highly comparable for both needles, therefore only the 31G x 8 mm needle was chosen for the remaining studies.

The impact of weekly simulated doses over the 28-day in-use period was also evaluated. The 24 mg (lot 3ET1900074) and 60 mg (lot 3ET1900075) PFPs were cycled weekly, five times, between 30ºC and 2-8ºC. After each 4-hour hold at 30ºC, a dose was simulated by attaching a new 31G x 8 mm needle and expelling a dose of 240 µl from the PFP. All assays were tested at the initial and last timepoint and a selection of stability indicating assays were tested at interim timepoints. All results met predetermined expected results and there were no significant changes in tested parameters at the final timepoint. The concentration of m-Cresol was maintained throughout the 28-day in-use period and resealability of the cartridge met the requirements of ISO 11608-2: 2012. Studies on post-expiry PFPs were also performed and all results remained within acceptance criteria. It is therefore endorsed that the formulation and container closure system support the safe use of FPS throughout the shelf life and in-use period of the finished product. Updated results from ongoing leachables studies in the commercial container closure over shelf life have been requested.

There is no overage of active substance.

The formulation has been developed based on extensive formulation studies, and the proposed commercial formulation has been used in pivotal clinical studies. For early clinical trials the product was presented as a frozen liquid in a vial, but for the phase 3 paediatric clinical studies the preserved liquid formulation was developed. A concentration of 10 mg/ml somatrogon FPS was included in the clinical studies but has not been selected for onward commercial development, however it has been used in supportive stability and development studies.

Antimicrobial Effectiveness Testing for m-Cresol does not comply with the Ph. Eur. 5.1.3 criteria A for parenteral products at the lower limit proposed at the end of shelf life. The applicant proposes that criteria B is a more appropriate standard for this multi-use product and has justified this on the basis that the product is intended for weekly administration, so the initial timepoint of 6 hours from Criteria A is less relevant. In addition it is not possible to increase further the concentration of m-Cresol in the finished product formulation. This justification is accepted.

The use of poloxamer 188 as a stabiliser is supported by freeze/thaw studies. In addition, the applicant has studied the impact of differing levels of silicone on glass cartridges. After 3 months storage at 2-8ºC there was no significant impact on quality parameters, stability profile or functional performance observed.

Photostability studies on the bulk finished product solution have been performed in accordance with ICH and there are no changes to quality parameters observed following exposure to light levels that are representative of product exposure during routine manufacture. Therefore, no specific precautions are required during filling to protect the product from light.

Changes to the product and manufacturing process throughout the clinical development programme are clearly outlined in the dossier. The change from frozen vial to single-patient use pen is supported by a comprehensive analytical comparability assessment. In addition, a relative bioavailability study (CP-4-011) was conducted and demonstrated bioequivalence for the two formulations with the exception of Cmax (not considered to be clinically significant because IGF-1 exposure was bioequivalent).

The applicant has provided a comprehensive overview of the pharmaceutical development of this medicinal product combined with an integral medical device. The cartridge and pen are pre-assembled and intended for single-patient, multiple use.

The applicant included a Notified Body Opinion on the device constituent (PFP), in accordance with Article 117 of the Medical Device Regulation, confirming full compliance with the relevant GSPRs.

The QTPP for the prefilled pen is considered appropriate. Pen assembly is an automated process and the commercial process remains unchanged from earlier clinical and stability processes. Before use, the patient or healthcare professional is required to prime the pen in order to expel air and ensure accurate dosing. The product information includes detailed instructions for the patient on how this dose priming is to be achieved. The pen assembly is checked (factory priming) to ensure that the plunger stopper is correctly positioned to enable user-priming to be performed. The applicant confirms that dose accuracy testing is performed on each dosing mechanism batch received from the supplier (supported by results of a study which demonstrate that the assembly process does not impact on dose accuracy testing of the PFP).

A process characterisation study examined the effects of mechanical stress (shock, vibration, rotation) and time out of refrigeration (TOR) on the finished product (also referred to as DP) due to the assembly process. Additional mechanical stresses at the maximum permitted TOR hours were evaluated. All results met acceptance criteria demonstrating that the assembly process does not impact on the quality of the FPS. Container closure integrity results confirm that the assembly process does not compromise the integrity of the cartridge.

The somatrogon PFP has been developed based on existing platform technology. The pen is supplied pre-assembled with needles to be sourced separately. The needles named in the Instructions for Use include Becton Dickinson BD MicroFine (or UltraFine) (31 gauge), NovoNordisk NovoFine (31 gauge) and NovoFine plus (32 gauge), all with a length of 8 mm.

Design verification studies were performed on the commercial pen presentation using a surrogate solution to demonstrate that the design outputs meet the input requirements. Data has been presented which confirms that the surrogate solution can be considered as representative of the somatrogon finished product solution.

Design verification studies have been performed and this includes dose accuracy testing and needle compatibility testing for the needle types specified in the Instructions For Use. The fill volume of the cartridge was finalised post-design verification, and so confirmatory studies were also performed to

ensure that a cartridge could deliver the nominal volume of 1.2 ml. Functional characteristics testing demonstrated that at room temperature functionality of the pen meets acceptance criteria (force to remove and replace pen cap injection button (axial) force). Extrusion of the FPS through the recommended needles was evaluated and results confirm that there is no impact on FPS quality attributes following injection through one of the four named needle types.

A user capability study confirmed that the axial force was possible for a range of subjects aged 10 and older. Syringeability (maximum force and extrusion force) have also been confirmed. The human factors validation test has taken into account changes in pen design following clinical study CP-4-006 and no changes were considered to impact pen performance data.

A comprehensive hazard analysis by FMEA has identified and considered potential risk to the design of the process. Overall, the applicant has considered all relevant aspects of design of the device and its appropriateness for use with the finished product.

2.4.3.1. Manufacture of the product and process controls

Manufacturing sites are adequately supported by valid MIA or GMP certificates as verified on EudraGMPD.

The manufacturing process for finished product manufacture is an aseptic filling process with sterile filtration immediately prior to filling.

There are two batch sizes registered for the FPS, which are adequately supported by validation data. Acceptable ranges for input process controls (CPPs, non-CCPs, CMAs) and control limits/ acceptance criteria for output process controls (IPTs) are registered in the dossier for each unit operation. Reworking is not permitted but reprocessing is proposed during pre-hold filtration or storage in the event of the bioburden reducing filter failing to meet the post-use integrity test. The filter integrity test is reported as a 'pass' or 'fail', Refiltration is supported by qualification studies where a double refiltration of 50 mg/ml FPS demonstrated no impact to product quality. In addition, the applicant has provided additional information on the steps taken in the event of filter integrity failure of one of the filters in sequence.

The control strategy for somatrogon FPS includes ongoing monitoring and controls to ensure a continuous state of control, and combines input material controls, in-process testing, batch records, release testing and process monitoring. Methods for in-process tests are adequately. Following a query raised at D180, the applicant assigned an acceptance/rejection limit of Not More Than 10 CFU/100 mL for the bioburden test prior to the sterilising step (sterile filtration of bulk drug product solution for both 20 mg/ml and 50 mg/ml).

Process validation was performed on consecutive PPQ batches manufactured at commercial scale; three batches for each strength of product (20 and 50 mg/ml). All PPQ batches met the pre-defined acceptance criteria as per the validation protocol. The applicant has used a traditional approach for PV, testing unit operations at the upper and lower limits of the range for relevant process parameters. Process verification will continue throughout the lifecycle of the product.

Process development studies support the CPPs. Hold time studies have been performed to establish hold times for active substance, bulk finished product and finished product solution. Studies were performed initially at laboratory scale and verified at commercial manufacturing scale on two lots of FPS during process qualification. A summary of the results of the full scale maximum hold time challenge study have also been provided for review. Hold times registered as CPPs have additionally been validated on three PPQ batches and demonstrate that at the upper limit of hold time there is no

impact on product quality. A summary of the results of the hold time studies for full scale PPQ batches at maximum challenged hold times has been provided.

The filter for sterile filtration is supported by shear stress testing studies which demonstrate that even under worst-case operating conditions the FPS is not impacted by filtration shear-induced aggregation. Filter validation studies on PPQ batches have demonstrated that the PVDF filter is appropriate for bioburden reduction and sterile filtration of the bulk FPS.

Media fill runs met the protocol acceptance criteria and support the maximum filling times for the larger batch size. Requalification is performed twice annually.

NORs and PARs for the CPPs are adequately supported by PQ studies. Shipping and handling conditions have been extensively and comprehensively studied and the applicant has demonstrated that the FPS is stable to agitation during transportation. The impact of x-ray exposure during transportation has been evaluated and there is no impact on product stability.

The immediate cartridge container closure system (type 1 glass, elastomeric plunger stopper) complies with relevant Ph. Eur. monographs. Extractable studies have been performed and potential leachables identified are being monitored as part of ongoing process validation under real time storage conditions using qualified methods. Data has been presented to the 12 month timepoint and is acceptable.

Each batch of prefilled pens is manufactured from a single batch of cartridges (which may be pooled from more than one batch of finished product solution). Reprocessing has been described at two unit operations – pen assembly and packaging and is supported by validation. In-process tests are registered and are considered sufficient to control the assembly and packaging process. Three process validation lots are presented at the upper, lower and middle of the batch size range. Each PV lot included one reprocessing step and all batches passed acceptance criteria, demonstrating that the manufacturing process is consistently able to manufacture prefilled pens of appropriate quality.

Shipping validation supports the transport of prefilled pens by road freight or by air. Simulated transportation studies under controlled temperature and pressure conditions representing worst case support that the quality attributes of the finished product solution or the functionality aspects of the prefilled pen are not adversely impacted by distribution conditions. Container closure integrity testing passed acceptance criteria demonstrating integrity of the container closure system during transport. Passive temperature thermal conveyance studies were performed on representative finished product.

Overall, the applicant has adequately described the manufacturing and control of this appropriately validated manufacturing process for both the cartridge and the prefilled pen.

For the finished product specification, the applicant has presented a panel of release tests which are in accordance with ICHQ6B, Ph. Eur. 01/2012:2031 Monoclonal antibodies for Human use and Ph. Eur. 04/2015:0520 Parenteral Preparations. Each method has a reference to the monograph where relevant, and includes a unique code linking to the laboratory method. Tests are included for identity, appearance, pH, osmolality, protein concentration, potency, particulates, impurities and microbiological characteristics: endotoxin and sterility.

Analytical procedures are described in the dossier. Pharmacopoeial methods are described with reference to their Ph. Eur. monograph. For the most part descriptions of non-pharmacopoeial methods are brief but do include sufficient detail on key operating conditions. System suitability parameters and assay acceptance criteria are also registered. It is therefore accepted that sufficient detail has been registered for non-pharmacopoeial methods. The method capability during the validation of methods is described by total analytical error limits.

Non-compendial methods have been validated in accordance with ICHQ2(R1). Compendial methods which were verified and confirmed as suitable for use. Verification of the sterility method was

performed in accordance with Ph. Eur. 2.6.1 and demonstrated that the FPS does not have bacteriostatic or fungistatic activity which interferes with the method. Method verification of the endotoxin test, in accordance with Ph. Eur. 2.6.14, confirmed that the FPS does not interfere with the method either by inhibition or enhancement.

Batch data has been provided for a number of batches manufactured from the different DP manufacturing processes. All batches met specifications in place at time of release and meet commercial acceptance criteria.

No additional impurities were described other than those identified in the active substance. An elemental impurities risk assessment has been performed in accordance with ICH Q3D. Quantitative elemental impurity screening by ICP-MS was performed on PPQ batches and all 24 elements from ICHQ3D were below the control threshold. This is considered sufficient assurance that there are no elemental impurities of concern in the finished product.

A comprehensive risk assessment has been performed to identify potential risk factors for nitrosamine formation in the active substance, finished product solution and primary packaging processes. No risk of nitrosamine formation was identified.

The applicant justifies the proposed release and stability specifications on the basis of the control strategy and the QTPP, pharmacopoeial requirements and manufacturing experience from other products. Specifications have been set based on a number of different finished product solution lots including clinical lots, early phase frozen liquid vials, and PV batches from the intended commercial process. Early clinical batches in vials have been used as supportive data for clinical exposure references but not used in tolerance interval analysis. If significant degradation trends are observed on storage, then different limits will apply to release and stability criteria. Otherwise both release and stability data are used for specification setting to reflect manufacturing process and assay variability. The same limit will be applied for release and stability acceptance criteria. This approach is considered justified as the stability data provides more opportunities to quantify assay variability whereas release data provides more information on process variability due to the larger number of datasets for batches at release.

While the specifications have been justified in general, a number of specifications were further tightened throughout the procedure.

The applicant is recommended to re-evaluate the end of shelf life and in-use acceptance criteria after the full in-use dataset is available, and submit this to the Agency by Q3 2023 when the analysis is complete (see Recommendation).

The proposed potency limits for release and end of shelf life were tightened reflecting a change in specification setting approach and is in line with the observed minimum and maximum values to date during long-term stability.

2.4.3.1. Stability of the product

The applicant claims a shelf life of 36 months at 2-8ºC based on stability studies performed in accordance with ICH guidelines, using container closure systems identical to those registered for routine storage. The analytical methods used in the stability monitoring programme are the same as those used for release testing. The stability indicating nature of the tests has been verified and testing intervals registered in the dossier are in accordance with ICH Q5A and are acceptable.

The approach to base stability of commercial material using data from an earlier process is accepted considering that comparability of the active substance has been demonstrated. All results are within

acceptance criteria for all batches at all timepoints. Overall, it is agreed that the stability of the DP over long-term storage conditions has been demonstrated and support the claimed shelf life of 36 months.

In addition to real-time studies the applicant has performed studies under accelerated, thermal stress and thermal cycling conditions.

For accelerated studies at 25°C and 30°C, all quality attributes for the four primary and two secondary lots remained within specification limits at the 1-month interval These results confirm the stability indicating nature of the test methods and also support temporary temperature excursions up to 30°C/75% RH for up to 1 month. As out of specification results were noted after one week of storage at 40°C/75% RH, it is agreed that excursions above 30ºC cannot be supported.

Thermal cycling studies moving between freezer / room temperature and refrigerated conditions replicate temperature excursions which may occur during use.

The proposed in-use conditions for the patient are 28 days at 2-8°C. The pen should be returned to the refrigerator after each weekly SC injection, and there is no provision for long term in-use storage outside of refrigerated conditions. However, in-use stability studies support that the finished product can be stored for up to 4 hours at 25ºC before returning to 2-8°C, for up to six cycles, this wording is reflected in the SPC.

As an x-ray scanner is used for routine detection of headspace volume during the filling process, the applicant has additionally studied the impact of exposure to x-ray on quality attributes over the shelf life of the product. To date up to 12 months data is available for the 24 mg and 60 mg FPS post-x-ray exposure under real-time storage conditions and all results remain within specification. Excursions above the recommended storage condition up to 25±2 °C/60±5% RH are allowable for up to 2 weeks after exposure to x-ray. As this is sufficiently supported by data, it is considered acceptable.

Photostability has been evaluated in an ICH compliant study and it is confirmed that the finished product solution is not photolabile. There is no requirement for a warning to protect from light in the product information. Overall, the applicant has demonstrated a logical and comprehensive approach to evaluation of stability of the finished product under real time and in-use storage conditions. Additional data has been provided and it is concluded that the requested shelf life of 36 months at 2-8ºC can be accepted.

Stability data has been presented for two lots each of 24 mg and 60 mg somatrogon prefilled pen on primary stability, and 1 lot each of 24 mg and 60 mg are on additional stability. Primary stability refers to the formal stability studies from which stability data are submitted for the purpose of establishing a shelf life and is generated using the clinical presentation of the pen. The additional stability studies support the proposed shelf life and are from the commercial presentation of the pen. The primary studies are complete, and the additional studies remain ongoing. Results for all batches of primary stability lots were within acceptance criteria and support a 36-month shelf life at 2-8°C. There are no significant changes in appearance or function of the pen, confirming that the pen remains within the acceptance limits when stored at the recommended storage condition of 2-8°C throughout the proposed shelf life. Three months data from the additional stability lots also show no change compared to primary lots tested, supporting the position that the clinical presentation pen is fully representative of the commercial presentation pen. Results for accelerated studies at 25°C and 30°C show that all parameters comply with acceptance conditions, confirming that pen functionality is maintained at elevated temperatures. Results through 36 months for the pen primary lots for in-use testing showed no significant changes in appearance or functional attributes through the study, supporting an in-use shelf life of 28 days. Results from thermal stress studies show no significant change when exposed to 40ºC for 2 weeks, or to -5°C for 3 months, confirming that pen functionality is maintained at excursions in temperature above or below the recommended storage condition. Thermal cycling study

results are also presented in the dossier and confirm that pen functionality is maintained at short-term temperature excursions both above and below the recommended storage conditions.

Stability testing on functional properties of the assembled pen were performed. The studies show that the applied procedures are suitable and confirm the performance of the pen.The available data support functional performance of the pen through to 36 months when stored at the recommended storage condition of 2-8°C with an in-use period of 28 days during the shelf-life during shelf life.

2.4.3.1. Adventitious agents

There are no materials of animal and/or human origin introduced during routine manufacture of somatrogon. As required, a risk assessment of the transmission of BSE from materials of animal origin used in the culture and banking of the host cell line has been performed and concludes that the risk posed for potential BSE infectious agent introduction is low. The risk assessment identifies the control elements in place (including the manufacturer quality system, source of starting materials/tissue collection process, scientific knowledge, passage number, viral testing and process clearance capacity) to reduce the risk of transmission of TSE agent or virus. It is agreed that the risk of transmission of BSE is minimal.

Non-viral agents (mycoplasma, bioburden) are controlled through AS in process testing using Ph. Eur. methods that have been verified as fit for purpose.

The programme of testing for the MCB, WCB and End of production (EOP) limit of *in vitro* cell age (LIVCA) for virus contamination was conducted as per ICH Q5A and is discussed in S.2.3, the cell banks are free from viral contamination apart from Type A retrovirus which are commonly observed in CHO cells.

Viral clearance studies have been performed using small scale models. The small-scale model are sufficiently described and are deemed suitably qualified. The conditions used during the studies reflect the conditions of the commercial-scale process described in section S.2.2 and characterised as described in section S.2.6. Each step has been evaluated at the worst case; i.e. where less viral removal / clearance would rationally be expected. Four steps of the purification process were evaluated, with three model viruses. The applicant has justified the choice of model viruses based on their physical properties and infectious abilities. It is agreed that the chosen viruses represent relevant models, which possibly may contaminate AS due to rodent origin of cell lines, and as per the relevant EMA and ICH guidelines include viruses that show the robustness of the process and the ability to remove and/or inactivate other viruses exhibiting a range of biochemical and biophysical properties

The data provided ensure the viral and adventitious agent risk associated with somatrogon is negligible.

2.4.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The active substance somatrogon is a C-terminal peptide (CTP)-modified recombinant human growth hormone that binds to the growth hormone receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Somatrogon is manufactured in a CHO cell line. The description of the manufacturing process and process controls is considered adequate. The active substance manufacturing process is sufficiently controlled to ensure routine production of material that meets the intended quality and that is representative of material used in the clinical development programme. The active substance is adequately characterised using a suite of appropriate analytical tests. The proposed active substance release tests are acceptable. Analytical procedures are well

described and shown to be fit for purpose. Batch release data has been provided and adequately show that the commercial process in capable of producing an active substance within specifications. A two tiered reference standard system is in place. The container closure system is acceptable. The proposed active substance shelf life of 36 months is adequately supported by real time data and thus endorsed.

The material has been shown to be acceptably safe from an adventitious agents and viral safety perspective.

The finished product is presented as a solution for SC injection in a pre-filled pen at concentrations of 24 mg/1.2 ml or 60 mg/1.2 ml. The product is formulated using widely used excipients and includes m-Cresol as preservative. A comprehensive overview has been provided detailing the pharmaceutical and development of the product from early clinical trial formulations of 10 mg/ml frozen liquid in a vial to the current 20 mg/ml or 50 mg/ml solution for injection in a multi-dose pre-filled pen for SC administration. The product is manufactured under GMP and the process consists of receipt and mixing of formulated AS and sterile filtration and filling. The process is well characterised. Process validation data supports the proposed process. Release and stability specifications ensure adequate control of the product. It is considered that the process control strategy sufficiently guarantees consistent and satisfactory quality/performance of the product. The analytical methods are suitably validated. The primary packaging is adequately described, and the cartridges are supplied sterile. The product appears to be stable and safe for use for the proposed shelf life of 36 months at 5°C and for 28 days at 2-8ºC with removal at weekly intervals for sub-cutaneous injection. The device is appropriately supported by a Notified Body Opinion confirming full compliance with the relevant GSPR from annex 1 of Regulation (EU) 2017/745.

Overall, the somatrogon quality dossier is of high quality and the documentation provided for the manufacture, control and stability of the active substance and finished product are sufficiently detailed.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- the applicant is recommended to re-evaluate the end of shelf life and in-use acceptance criteria after the full in-use dataset is available and submit this to the Agency by Q3 2023 when the analysis is complete.

2.5. Non-clinical aspects

2.5.1. Introduction

The non-clinical package includes comparative *in vitro* pharmacology studies, comparing somatrogon to another recombinant human growth hormone, somatropin (Bio-Tropin), with respect to binding affinity, induction of cell proliferation and STAT5b phosphorylation. *In vivo*, the ability of somatrogon to induce weight gain and IGF-1 in both normal and hypophysectomized rats was also compared to

somatropin. Secondary pharmacodynamics were assessed in a panel of *in vitro* off-target receptor binding assays. Stand-alone safety pharmacology studies were not conducted but standard safety pharmacology endpoints were included in the repeat-dose toxicology studies. Single and repeat-dose pharmacokinetic studies were conducted in Sprague-Dawley rats and rhesus monkeys following sub-cutaneous administration of somatrogon. The toxicokinetics and immunogenicity of somatrogon were also assessed in the pivotal repeat-dose toxicology studies in rats and monkeys and in the pivotal embryo-foetal development study in rats. Non-pivotal single dose toxicology studies were conducted in rats and monkeys and GLP-compliant repeat-dose toxicity studies were also conducted in rats and monkeys, with dosing up to 4 weeks in rats and both 4-week and 26-weeks dosing periods in monkeys. The sponsor provided a justification for the absence of a chronic repeat-dose toxicity study in a second species. Genotoxicity and carcinogenicity studies have not been conducted to support this biologic medicinal product, in line with relevant guidance. However, due to concerns regarding potential carcinogenic effects of growth factors, a carcinogenicity assessment was conducted. Developmental and reproductive toxicology studies were conducted in rats covering all stages of the reproductive cycle. The sponsor provided a justification for the absence of a segment II study in a second species. Stand-alone local tolerance studies have not been conducted, but local tolerance has been evaluated at the injection sites in repeat-dose toxicology studies. The sponsor has provided a justification for the absence of ERA studies.

The data submitted were assessed on the legal basis of the application, applicable guidelines and other scientific criteria and was found to be acceptable by the CHMP.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

Primary pharmacodynamic data indicate that the rat and rhesus monkey are pharmacologically relevant species. The binding affinity of somatrogon to GHR is approximately 2-fold lower in rhesus monkey in comparison to human receptors, but the difference in somatrogon binding affinity between human and rat GHR was not statistically significant. Literature data (*Vottero et al. 2003*) showed that human GHR and rhesus monkey GHR exhibit 94.1% similarity in protein sequence. For rat and human GHR, there is 68.9% comparability in the amino acid sequence (*Baumbach et al. 1989*). The essential residues of the hGHR that interact with the hGH (R43, W104, E127, K167, W169, and N218 receptor residues as reported by *De Vos et al. 1992*) are conserved in rhesus monkeys, while four amino acids out of six are conserved in rats. Results from a sequence alignment analysis support this statement regarding the reported similarities between rat and human Growth Hormone-Binding Protein as well as between rhesus monkey and human Growth Hormone-Binding Protein.

In order to enable comparability between somatropin and somatrogon, the concentration of the latter was calculated based on its hGH content. In some studies, the hGH content of 72.6% was used for the total dose, that is related to the glycosylated product. In other studies, 72.6% hGH was related solely to the protein backbone, i.e. excluding glycans, which is equal to 57.8% hGH in the glycosylated product, corresponding to the equimolar, both methods reflect similar hGH content relative to somatrogon (72.6% of 30,469 Da or 57.8% of 38,254 Da).

Of note, the binding affinity of somatrogon is 8-13-fold lower than the binding affinity of somatropin for hGHR. Similarly, somatropin induced cell proliferation approximately 33-43-fold more potently than

somatrogon in vitro and somatrogon-induced STAT5b phosphorylation required higher concentrations than somatropin, indicating reduced in vitro activity of somatrogon compared to somatropin.

In vivo

In vivo data indicate similar weight gain in hypophysectomied rats following a single SC administration of 0.55 and 1.1 mg protein/ kg somatrogon (reportedly equivalent to 0.4 and 0.8 mg/kg hGH) as compared to daily 0.1 mg/kg somatropin. Also, repeated SC dosing of 0.48 mg protein/kg/dose somatrogon (reportedly equivalent to 0.35 mg/kg hGH), administered every 4 days for 12 days, produced a similar increase in weight gain as daily somatropin (0.1mg/kg/dose). Therefore, despite *in vitro* data indicating reduced somatrogon activity compared to Bio-Tropin with respect to binding affinity, cell proliferation and STAT5b phosphorylation, *in vivo* data from hypophysectomised rats suggest equivalent activity in terms of body weight gain but with fewer injections and a slightly lower total hGH dose. Furthermore, the IGF-1 response following a single SC injection of somatrogon to hypophysectomied rats was higher (Cmax 3x to 4x higher) than following daily injection of somatropin of similar molarity, i.e. somatrogon 0.6 mg protein/kg (reportedly equivalent to 0.35 mg/kg hGH) vs somatropin 0.35 mg/kg, and somatrogon 1.8 mg protein/kg (reportedly equivalent to 1.05 mg/kg hGH) vs somatropin 1.05 mg/kg. The Tmax of IGF-1 following treatment with somatrogon was 36-48 hours as compared to 20-24 hours for somatropin, supporting the extended action of somatrogon. This difference between *in vitro* potency and *in vivo* activity of somatrogon vs somatropin is attributed to both exposure and differing binding parameters for the GHR. While somatrogon has a slower association constant in comparison to somatropin, the dissociation constants are more similar, therefore longer stimulation at the receptor reduced the impact of the slower association rate in in vitro studies. Hence, the apparent difference in *in vitro* potency between somatropinand somatrogon is reduced as the treatment time in cell-based assays is increased. *In vivo*, somatrogon induces a relatively high Cmax with a prolonged half-life, leading to sustained activation of the receptors and translating into higher levels of IGF-I production and subsequent weight gain in non-clinical studies.

Results from these studies indicate that somatrogon was pharmacologically active at all dose levels tested in the 4-week study (1.8, 18 and 90 mg/kg). In support of sustained somatrogon activity, pre-dose IGF-1 levels were higher on day 19 compared to pre-dose levels on day 1. However, the IGF-1 response was not dose proportional (higher circulating IGF-1 at the mid dose than the high dose in both males and females). In contrast, in the 26-week study, somatrogon (1.5, 15, or 30 mg/kg) produced a dose-related increase in IGF-1. Furthermore, the IGF-1 responses to somatropin (3.6 mg/kg/day) and the intermediate (15 mg/kg) and high (30 mg/kg) doses of somatrogon were similar, while low dose somatrogon (1.5mg/kg) induced IGF-1 concentrations greater than control but less than somatropin. It is concluded that the evaluation of dose-response relationships in animals with normal functioning pituitaries is complex due to the presence of endogenous GH and the induction of normal levels of IGF-1, but the considerable increase in IGF-1 response from Day 1 to 91 is evidence that somatrogon has biological activity similar to growth hormone.

2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamics were assessed with an *in vitro* assay, assessing the off-target receptor binding of somatrogon and comparing them to somatropin. From a panel of 70 receptors somatrogon showed no significant affinity to any of the screened receptors with the exception of the glutamate (NMDA PCP site) receptor. Similar inhibition was demonstrated by both somatrogon and somatropin for this site (69.95% and 83.98%, respectively). Therefore, it is concluded that the binding is GH- and not CTP-mediated, in addition there were no indications of effects on the central nervous system, based on review

of clinical signs from the rat and monkey toxicology studies, hence it was not considered to represent a safety concern. The fusion of CTP to rhGH does not affect the off-target binding profile of somatrogon.

2.5.2.3. Safety pharmacology programme

Stand-alone safety pharmacology studies with somatrogon have not been conducted, somatrogon was tested for potential effects on the respiratory, central nervous, and/or cardiovascular systems in the pivotal repeat-dose toxicity study in rats and the pivotal repeat-dose toxicity studies in rhesus monkeys. This is acceptable, in line with ICH S6(R1).

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies have not been conducted to support somatrogon. This is acceptable, due to the nature of this biologic product and the specificity of its pharmacological activity.

2.5.3. Pharmacokinetics

Single-dose pharmacokinetic (PK) and toxicokinetic (TK) studies were conducted following SC administration of somatrogon in Sprague-Dawley rats and rhesus monkeys. The TK and immunogenicity of somatrogon were evaluated as part of pivotal repeat-dose toxicity studies in rats (up to 4-weeks) and rhesus monkeys (up to 26-weeks) following repeat SC administration. An embryo-foetal development (EFD) study conducted in gravid rats confirmed somatrogon dose proportional exposure to the foetus. No protein binding, distribution, metabolism or excretion studies have been carried out.

A number of bioanalytical methods such as quantitative determination of somatrogon in rat serum (including foetal and pregnant rat serum) and rhesus monkey serum, quantitative determination of somatropin in monkey serum, qualitative determination of antibodies to somatrogon, CTP and somatropin in rat and monkey serum and qualitative determination of neutralising antibodies to somatrogon and somatropin in rat and rhesus monkey serum were developed and in general successfully validated.

Enzyme-linked immunosorbent assays (ELISAs) were used for the quantification of total IGF-1 in rat and monkey serum to support the GLP repeat-dose studies in Sprague-Dawley rats and rhesus monkeys.

For the quantitative determination of IGF-1 in toxicology studies in rhesus monkeys, a commercially available human IGF-1 immunoassay was used. This is acceptable, given the identical amino acid sequences of rhesus monkey and human IGF-1 and the exploratory purpose of the non-clinical study.

The pharmacokinetics of somatrogon in relation to pharmacodynamic response was evaluated in comparison to the marketed somatropin after single injection in hypophysectomised rats. C_{max} was significantly higher for somatrogon than for the comparator. The terminal half-life of somatrogon was dose-independent and 4.5 times longer than for somatropin. As a result, the AUC of somatrogon was 10 times higher compared to somatropin. Finally, T_{max} was observed at 8 h for somatrogon in contrast to 0.5 h for the comparator. Consistent with these results, somatrogon led to higher IGF-1 levels at later time points, which supports its long-lasting action. Commercially available kits for determination of hGH and IGF-1 were used, and the respective assay description included validation parameters. Given the rather exploratory nature of the study, this is considered sufficient.

Both IGF-1 and IGFBP-3 are biomarkers for GH treatment, and it was confirmed that IGFBP-3 was not measured in the nonclinical studies. IGFBP-3 was however measured in Phase I Clinical studies and it is considered that IGFBP-3 was unlikely to confound the interpretation of the nonclinical IGF-1 data.

Single-dose PK and TK studies were conducted following SC administration of somatrogon in rats and rhesus monkeys (toxicology species). The TK and immunogenicity of somatrogon were evaluated as part of pivotal repeat-dose toxicity studies in rats (4-week toxicity study) and rhesus monkeys (4-week and 26-week toxicity study) following repeat SC administration. Exposure (as assessed by Cmax and AUC) increased in an approximately dose proportional manner. In general, there were no apparent sex-related differences in systemic exposure.

Three copies of the CTP (1 copy being fused at the N-terminus and 2 copies at the C-terminus) of the beta chain of the human chorionic gonadotropin (hCG) are fused to the therapeutic protein hGH to form somatrogon. It is expected that glycosylation of the negatively charged, heavily sialylated CTP portion of somatrogon could increase the plasma half-life as a result of decreased renal clearance and/or reduced clearance via the asialoglycoprotein receptors. This was demonstrated in both a single dose study, and the repeat dose study. In the single-dose study, in rats somatrogon had a half-life of ~ 7h compared to 1.5 h for somatropin. In the repeat dose study, in monkeys somatrogon had an average half-life of ~ 18h compared to an average half-life of 4.5 h for somatropin. As expected, exposure of somatrogon was higher than somatropin in rats and monkeys because of the significantly longer t½.

The incidence of anti-somatrogon antibodies was higher in rats than rhesus monkeys and antibodies were detected for both the hGH and carboxy-terminal peptide (CTP) domain of somatrogon in both species. ADAs were also detected in the control group in the rat study. Following an investigation exposure of this group to somatrogon could not be ruled out. The presence of ADA in the control group did not impact the conclusions drawn for the TK analysis in this study. Neutralizing antibodies were detected, however, exposure to somatrogon and the insulin-like growth factor (IGF)-1 responses were not affected in these animals. The incidence of anti-drug antibody (ADA) induction to somatropin was similar to that observed with somatrogon.

No protein binding studies have been conducted with somatrogon. This is accepted. Based on the literature it is expected that binding of growth hormone, and by extension somatrogon to its binding protein in plasma and the circulating extracellular domain of growth hormone will be approximately 50% (*Baumann, 1988, Baumann, 1990a, and Baumann, 1990b*).

An EFD study conducted in gravid rats confirmed somatrogon exposure to the foetus. Foetal concentrations were much lower than maternal concentrations but increased with increasing maternal dose. Exposure of the foetus to somatrogon resulted in the expected pharmacologic effect, namely that somatrogon elicited an increase in F1 mean body weights (both sexes).

The expected consequence of the metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids. Therefore, the metabolic and excretory pathways are generally understood. Highly glycosylated, negatively charged, heavily sialylated CTP residues prolong serum half-life as compared to somatropin. Literature evidence suggests that this may be a result of decreased renal clearance and/or reduced clearance via the asialoglycoprotein receptor. Due to its high molecular weight, somatrogon is not excreted in urine. Instead, it is supposed to be primarily metabolised by proteolytic catabolism. For these reasons, no specific metabolism or excretion studies were conducted. The lack of metabolism and excretion studies is acceptable.

Somatrogon and somatropin demonstrated comparable induction profiles of CYP1A2, CYP2B6, and CYP3A4 under the conditions of the *in vitro* hepatocyte study. Primary human hepatocytes from three different donors were used. This study evaluated the potential for somatrogon (with Genotropin as a

comparator) to induce CYP1A2, CYP2B6, and CYP3A4 mRNA expression and/or enzyme activity was conducted in 3 donors of human cryopreserved hepatocytes with somatrogon at concentrations of 100, 500, or 1000 ng/mL. The drug concentrations of somatrogon evaluated (100, 500, and 1000 ng/mL) were consistent with predicted steady-state drug concentrations based on the population pharmacokinetic analysis for study CP-P-004 in paediatric patients to whom a dose of 0.66 mg/kg/week somatrogon was administered. In this study, the Cmax for post-hoc estimate was 690 ± 261 ng/mL (range: 140 – 1410 ng/mL). Somatrogon and somatropin are not considered to be inducers of CYP1A2 and CYP2B6 but may be considered weak inducers of CYP3A4 enzyme.

Considering the extensive clinical experience with rhGH in patients, somatrogon is expected to act by the same pharmacological mechanism as hGH via binding to the growth hormone receptor, no new DDI are expected beyond those already known for rhGH products.

Considering all the data available, concomitant use is unlikely to require changes in doses of a CYP3A metabolized drug when administered with somatrogon.

The pharmacokinetics of somatrogon was compared with three lots of the drug. Similar concentration vs. time profiles for somatrogon and IGF-1 were observed. Samples were stored at -20 °C and no data on stability of the test item in rat serum at this temperature has been provided. However, since the purpose of the study was to compare the pharmacokinetics for three lots of somatrogon and the three lots were handled in the same way, it is considered that stability issues at -20 °C had a low impact on the study conclusions.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Two non-pivotal single dose toxicity studies were performed with somatrogon, one in rats and one in monkeys. Neither study was GLP compliant. This is acceptable due to the availability of GLP-compliant repeat-dose toxicity studies in both species.

In the rat study, cage-side observations and clinical signs were reported for a 7-day observation period, following SC administration of 3.6, 36 or 180 mg/kg somatrogon and on day 7 animals were euthanized but no necropsy was performed. Blood samples were collected for toxicokinetic evaluation pre-dose and a 1, 2, 4, 8, 24- and 72-hours post-dose on day 1 only. All animals survived to end of study and there were no test article-related effects on clinical signs or body weights. In general, mean AUClast and Cmax increased with increasing dose and no sex-related differences are reported.

In the monkey study, cage-side observations and clinical signs were reported for a 14-day observation period, following SC administration of 1.8 or 90 mg/kg somatrogon and at study termination animals were returned to stock colony. Haematology/coagulation, clinical chemistry, and urinalysis parameters were evaluated (prior to initiation of dosing, on Day 7, and prior to study termination). Blood samples were collected for toxicokinetic evaluation pre-dose and at 1, 2, 4, 8, 24, 48, and 72 hours post-dose on day 1 only. All animals survived to end of study and there were no test article-related effects on clinical signs, body weight or clinical pathology. In general, mean AUClast and Cmax increased with increasing dose and there were no sex-related differences.

In summary, somatrogon was well-tolerated following single SC injection up to 180mg/kg in rats and up to 90mg/kg in monkeys based on cage-side observations, body weight and clinical pathology in monkeys.

2.5.4.2. Repeat dose toxicity

Repeat-dose toxicity studies were conducted in rats (4-weeks) and rhesus monkeys (4-weeks and 26-weeks), both are considered pharmacologically relevant species based on available pharmacology data and all 3 studies were GLP-compliant, with somatrogon administered via the SC route (the intended clinical route of administration).

Rat

In the 4-week rat study, somatrogon was administered SC twice weekly at doses of 0, 3.6, 36, or 180 mg/kg. All animals survived to terminal euthanasia. There were no adverse test article-related effects on clinical signs, coagulation, urinalysis, or macroscopic parameters. Test-article related findings of increased body weight gain and increased food consumption in male and female rats were reported at ≥36 mg/kg somatrogon and attributed to anticipated pharmacological activity, which is plausible. A clinical pathology finding of slight anaemia, reported at 180mg/kg in both sexes, was reversible and considered non-adverse. Dose-dependent increased triglycerides were also reported in both sexes at ≥36 mg/kg, which were mostly reversible and considered consistent with findings reported previously for growth hormone and non-adverse. Data from the literature indicate that the reported mammary gland changes (feminization [males] and lobular hyperplasia [females]) have previously been reported in rats administered rhGH and are therefore not unique to somatrogon. Most animals from the control group and 180 mg/kg group developed antidrug antibodies that were specific for the hGH and CTP domain of somatrogon and were neutralising. However, since these antibodies did not affect the exposure nor the biological responsiveness (weight gain and IGF-1) the issue was not further pursued. Aside from clinical and/or microscopic effects related to local irritation at the site of injection, all the effects noted following the repeated SC administration of somatrogon were considered to be directly or indirectly associated with its anticipated pharmacological activity and were partly or fully reversible following a 2-week recovery phase. Therefore, doses up to 180 mg/kg were tolerated and the NOAEL was 180 mg/kg and was associated with mean Day 26 Cmax and AUC last values of 95.7 µg/mL and 3280 µg•h/mL, respectively.

Monkey

In the 4-week monkey study somatrogon was administered SC every 6 days (5 total doses) at doses of 0, 1.8, 18 and 90mg/kg. Mortality in one high dose female was not associated with any clinical findings prior to death and no test article-related macroscopic or microscopic findings were evident at necropsy, this death was not considered treatment-related. All remaining animals survived to scheduled termination. No adverse test article-related findings were observed in clinical observations, body weights, ophthalmic, electrocardiographic, clinical pathology, macroscopic, or organ weight parameters. Reversible minimal to mild acute inflammation, perivascular mononuclear cell infiltration and fibroplasia at injection sites at ≥18mg/kg were considered non-adverse. A low positive antibody titer to only the hGH component of somatrogon was noted in a single male animal at 90 mg/kg; the antibodies were not neutralising against somatrogon or hGH. No antibodies to the carboxy-terminal peptide (CTP) region were formed. The NOAEL was the high dose of 90 mg/kg, associated with Day 19 mean Cmax and AUClast values of 119 µg/mL and 4100 µg•h/mL, respectively.

Chronic repeat-dose toxicity was assessed in only one species, rhesus monkey. This approach was agreed by the CHMP in a previous scientific advice. Rhesus monkey was chosen following concerns of a possible immune response developing in rats. These concerns are considered plausible on the basis of the high incidence of neutralizing anti-somatrogon antibodies which occurred in the 4-week repeat dose toxicity study in rats at the high dose of 180mg/kg. The absence of a chronic toxicity study in a second species is acceptable.

In the 26-week monkey study, somatrogon was administered SC every 5 days at doses of 0, 1.5, 15 or 30mg/kg for 26 weeks. An additional comparator group was also included in this study, to which Bio-Tropin was administered SC once daily at a dose of 3.6mg/kg/day. The use of a daily use somatropin as comparator is endorsed and Bio-Tropin is an identical somatotropin to Genotropin, an authorised medicinal product in the EU used as a comparator in clinical studies.

There were no test article-related macroscopic findings or organ weight changes. Microscopic evaluation revealed changes at the injection site only. The primary finding was minimal infiltration of mixed cells in both the somatropin and somatrogon groups, these effects were largely resolved after the recovery phase. The NOAEL was considered to be 30 mg/kg and was associated with Day 1 mean C_{max} and AUC last values of 50.9 µg/mL and 1430 µg•h/mL, respectively. It is notable that no effect on body weight is reported following SC administration of somatrogon to monkeys in both the 4-week and 26-week repeat-dose studies. Indeed, there were no toxicologically relevant effects related to the known action of growth hormone in the chronic study. It was questioned if the exposure levels in this study were adequate. However, the doses of 180 and 30 mg/kg in the 4-week rat and 26-week monkey study provided exposure multiples of 234x and 71x, respectively based on Cav. While the exposure margins based on AUC are generally lower than that for Cav, they are still considered acceptable as the mid-and high dosed animals from the 4-week rat and 4-week monkey study and the 26-week monkey study exhibited exposures >10-fold higher than relevant clinical exposure, as recommended by ICH S6(R1).

2.5.4.3. Genotoxicity

A genotoxicity assessment has not been conducted for somatrogon. This is acceptable, in line with ICH S6(R1) for biotechnology-derived pharmaceuticals.

2.5.4.4. Carcinogenicity

Standard carcinogenicity bioassays are also generally not indicated or required for biotechnology-derived pharmaceuticals in accordance with ICH S6(R1). In addition, ICH S1A guideline states that carcinogenicity studies are not generally needed for endogenous substances given essentially as replacement therapy (ie, physiological levels). However, somatrogon is a long acting growth factor and to allay any concern regarding carcinogenicity, the applicant performed a carcinogenicity assessment.

There were no findings in the repeat dose toxicity studies with somatrogon that were indicative of carcinogenic potential. There were no adverse effects observed in rats and rhesus monkeys given somatrogon. The findings noted in the 4- and 26-week studies were consistent with the pharmacological activity of the drug or related to local effects at the injection site. Although it may be feasible to complete a study of longer duration, formation of ADA and injection site findings may prevent completion of a traditional, 2-year carcinogenicity study. The clinical studies evaluating the safety and efficacy of somatrogon that support this marketing application included intensive monitoring of IGF-1 concentrations, including pre-defined criteria for dose reduction in the case of excessive IGF-1 concentrations or adverse events. However, non-physiological tissue distribution which may be an attribute of somatrogon, is unknown as distribution studies were not carried out. The lack of carcinogenicity studies is acceptable.

2.5.4.5. Reproductive and developmental toxicity

Developmental and reproductive toxicity (DART) studies were conducted in only one species, an approach that was agreed by CHMP in the scientific advice received in 2011 and is considered acceptable. The pivotal reproductive and developmental studies included fertility and early embryonic development (FEED), embryo foetal development (EFD) and pre- and post-natal development (PPND) studies conducted in Sprague Dawley rats. All DART study reports include statements of compliance with OECD principles of GLP, with the exception of the toxicokinetics for the rat EFD study which was non-GLP. Pfizer conducted additional toxicokinetic analyses on the EFD study that were not conducted with OCED GLP but are FDA GLP-compliant, which is acceptable. Toxicokinetic data is not reported for some studies, but the TK available from the repeat-dose toxicology studies together with the data from the EFD study are considered sufficient. A NOAEL is reported at the high dose in all pivotal DART studies of 30 mg/kg.

A safety margin of 14x the maximum recommended human dose (MRHD) based on AUC is reported in section 5.3 of the SmPC regarding these EFD data, which is acceptable.

In the FEED study, somatrogon was administered via SC injection every 2 days to male and female Sprague Dawley rats at doses of 0 (control), 3, 10, or 30 mg/kg. All animals survived to terminal euthanasia except for 3 males whose death was not considered test article-related. Test-article related findings of increased mean body weight and food consumption were reported at doses ≥ 10 mg/kg in males and ≥3 mg/kg in females, these findings are associated with anticipated pharmacological activity of somatrogon and considered non-adverse. Oestrous cycle length and copulatory interval were significantly longer at 10 mg/kg and the number of oestrous cycles was significantly lower at ≥3 mg/kg. However, there were no effects on mating, fertility, and fecundity indices. Significantly higher number of *corpora lutea* at ≥10 mg/kg and implantation sites at 30 mg/kg were observed and a slightly higher pre-implantation loss at ≥10 mg/kg were observed, but all other uterine parameters were similar to controls. These findings are reflected in section 5.3 of the SmPC. There were no test article-related effects on the sperm parameters (motility, concentration, and morphology). At necropsy, there were no test article-related macroscopic findings. A few test article-related higher organ weights were observed at ≥10 mg/kg in females and at 30 mg/kg in males and were related to higher body weight. Based on the results, the NOAEL for male and female systemic toxicity and for reproduction and fertility was 30 mg/kg.

In the pivotal EFD study, somatrogon was administered via SC injection every 2 days from GD 6 to 18 to time-mated female Sprague Dawley rats (25/group) at doses of 0 (control), 3, 10, or 30 mg/kg. Blood samples for determination of the serum test article concentrations and toxicokinetic parameters were collected from an additional 9 animals/dose, pre-dose and at 1, 2, 4, 8, 24, and 48 hours post-dose on GDs 6 and 18; blood samples were collected from 3 control animals on GDs 6 and 18 at 8 hours post-dose. In addition, blood was collected from the toxicokinetic foetuses at 24 hours post-dose on GD 18. One 10 mg/kg female was found dead on GD 15, with red discoloration of the adrenal glands, red fluid in the oral cavity near the pharynx, and red discoloration of the lung and mainstem bronchi reported at necropsy, in the absence of similar macroscopic findings in any of the other treated animals this was not considered test article-related. No test article-related clinical signs were noted. Test article-related, statistically significant and dose-dependent higher mean body weight and body weight gain were observed at ≥3 mg/kg and in food consumption at ≥10 mg/kg, compared with controls. These findings were associated with the pharmacological activity of the test article considered not adverse and are reflected in section 5.3 of the SmPC. There were no test article-related effects on macroscopic findings, uterine parameters, foetal body weight, sex ratio, or external, skeletal, and visceral variations or malformations. Maternal exposure as assessed by C_{max} and AUC generally increased with increasing dose except for C_{max} on GD 18 at 30 mg/kg, which was lower than

anticipated. Pooled foetal serum samples collected at 24 hours post dose on GD 18 were 2.51, 5.09, and 14.9 ng/mL at maternal doses of 3, 10, and 30 mg/kg/dose respectively, confirming somatrogon exposure to the foetus. Foetal concentrations were much lower than maternal concentrations and were dose-proportional, increasing with increasing maternal dose. The NOAEL for maternal toxicity and the NOEL for developmental toxicity was 30 mg/kg.

In the PPND study, somatrogon was administered via SC injection in the scapular region every 2 days from GD 6 to LD 20 to time-mated female pregnant/lactating Sprague Dawley rats (25/group) at doses of 0 (control), 3, 10, or 30 mg/kg. Increased mean body weight, body weight change, and/or food consumption were observed in F0 females at ≥ 10 mg/kg during gestation and/or lactation, compared with controls. Isolated, statistically significant higher body weight change was also observed at 3 mg/kg. All F0 females survived to terminal euthanasia, with the exception of one 30 mg/kg female, euthanized in moribund condition on LD 5, with clinical signs of decreased activity, rapid breathing, right hind limb impaired, pale and cold to touch, and macroscopic observations including enlarged adrenal glands, liver, and spleen, and entire body icteric. Enlarged adrenal glands were also observed in other somatrogon-treated animals (n=1, 2, and 8 females at 3, 10, and 30 mg/kg, respectively), but none of these animals exhibited adverse clinical signs and therefore the mortality of the 30 mg/kg female was not considered test article-related, which is acceptable. No test article-related clinical signs were observed in F0 females and the findings of enlarged adrenal glands was considered related to the higher body weights observed, which is associated with the anticipated pharmacological activity of somatrogon and considered non-adverse. Dose-dependent higher mean F1 male and female pup body weights were observed beginning on LD 7 and through post-natal day 28 at ≥10 mg/kg, compared with controls. This is consistent with the anticipated pharmacological activity of somatrogon and appropriate wording has been included in section 5.3 of the SmPC. A slight increase in stillborns was observed in the 10 and 30 mg/kg dose groups. Since the number of stillborn/litter did not exceed the historical control range, it was concluded that the higher stillborn index in the 10 and 30 mg/kg/dose groups is not somatrogon-related. At 30 mg/kg, the mean copulatory interval for F1 females was slightly higher at 4.5 days compared with controls; this is consistent with findings from the EFD study and other growth hormone products. As there was no effect on mating indices, this longer copulatory interval was not considered adverse, but wording has been included in section 5.3 of the SmPC regarding this effect. However, exposure of the F1 females occurred indirectly via transplacental and/or milk transfer. Furthermore, the investigation of potential effects on fertility and reproduction of somatrogon on the F1 generation were carried out in F1 pups which were at least 80 days of age and possible exposure via milk transfer might have occurred until PND 21 at the latest. This suggest a different mechanism of this effect in the F1 animals, possibly resulting from the higher body weight observed in these animals due to the pharmacological action of somatrogon. The clinical relevance of these effects is likely to be low given that somatrogon is intended as a growth hormone replacement treatment in growth hormone deficient patients, to bring them to normal physiological GH levels.

The NOAEL for F0 maternal toxicity and for reproductive performance and evaluation of the F1 offspring was reported as 30 mg/kg, the highest dose tested.

No juvenile toxicity studies were performed, this was considered acceptable in the absence of novel target organs of toxicity associated with the CTP modifications and considering the extent of human use experience with GH therapies.

2.5.4.6. Toxicokinetic data

Single-dose PK and TK studies were conducted following SC administration of somatrogon in rats and rhesus monkeys (toxicology species). The TK and immunogenicity of somatrogon were evaluated as part of pivotal repeat-dose toxicity studies in rats (4-week toxicity study) and rhesus monkeys (4-week and 26-week toxicity study) following repeat SC administration. In rats, blood samples for determination of serum test article concentrations and toxicokinetic parameters were collected from 3 animals/sex/dose/time point pre-dose and at 1, 2, 4, 8, 24, 48, and 72 hours post-dose on Days 1 and 26 (after the last dose). In monkeys, blood samples for determination of serum test article concentrations and toxicokinetic parameters were collected pre-dose and at 2, 4, 8, 24, 48, 72, and 96 hours post-dose on Days 1 and 19. Exposure (as assessed by Cmax and AUC) increased in an approximately dose-proportional manner. In general, there were no apparent sex-related differences in systemic exposure.

Three copies of the CTP (1 copy being fused at the N-terminus and 2 copies at the C-terminus) of the beta chain of the human chorionic gonadotropin (hCG) are fused to the therapeutic protein hGH to form somatrogon. It is expected that glycosylation of the negatively charged, heavily sialylated CTP portion of somatrogon could increase the plasma half-life as a result of decreased renal clearance and/or reduced clearance via the asialoglycoprotein receptors. In rats, somatrogon had a half-life of ~ 7h compared to 1.5 h for somatropin. In monkeys, somatrogon had an average half-life of ~ 18h compared to an average half-life of 4.5 h for somatropin. As expected, exposure of somatrogon was higher than somatropin in rats and monkeys because of the significantly longer t½.

The incidence of anti-somatrogon antibodies was higher in rats than rhesus monkeys and antibodies were detected for both the hGH and carboxy-terminal peptide (CTP) domain of somatrogon in both species. ADAs were also detected in the control group in the rat study. Following an investigation exposure of this group to somatrogon could not be ruled out. The presence of ADA in the control group did not impact the conclusions drawn for the TK analysis in this study. Neutralizing antibodies were detected, however, exposure to somatrogon and the insulin-like growth factor (IGF)-1 responses were not affected in these animals. The incidence of anti-drug antibody (ADA) induction to somatropin was similar to that observed with somatrogon.

The safety margin from the NOAEL in the rat repeat-dose toxicology study is acceptable at 116.7-fold the reported clinical exposures at 0.66 mg/kg/week, based on exposure (AUC∞). Although the binding affinity of somatrogon to GHR is approximately 2-fold lower in rhesus monkey in comparison to human receptors, the exposure margins from the NOAEL reported in the repeat-dose monkey studies are also considered sufficient at 149.8-fold and 121-fold the clinical exposures at 0.66 mg/kg/week for the 4-week and 26-week studies respectively, based on exposure (AUC∞).

2.5.4.7. Local Tolerance

Stand-alone local tolerance studies with somatrogon have not been conducted, which is acceptable since local tolerance at the site of injection was evaluated during the repeat-dose toxicology studies during routine clinical observations, and macroscopic and microscopic examinations. Some evidence of injection site reactions was reported, but these changes were reversible upon cessation of dosing and advice regarding rotation of injections sites was included in the SmPC. In the carcinogenicity assessment, the sponsor cites data from the literature indicating repeated SC administration of rhGH and an hGH analogue to rats over a timeframe of 2 years can result in marked fibrosis at the site of injection (*Farris et al, 2007; Bartholomew et al, 2014*). However, these were daily injections to rats (~700 administrations) and therefore may not be of relevance to the intended weekly administration of

somatrogon in the clinical setting.

2.5.4.8. Other toxicity studies

Studies to address the presence of anti-somatrogon antibodies were performed in both rats and rhesus monkeys. The incidence of ADA was higher in rats than rhesus monkeys, and antibodies were detected for both the rhGH and CTP domain of somatrogon in both species. Neutralizing antibodies were detected; however, exposure to somatrogon and IGF-1 responses were not affected in these animals.

No phototoxicity studies have been conducted with somatrogon as protein biotherapeutics and their catabolites (peptides and amino acids) are not considered to have phototoxic potential. Similarly, no studies on immunotoxicity, dependence, the catabolism of somatrogon or impurities were conducted. The CHMP found this to be acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, somatrogon is not expected to pose a risk to the environment and as per the EMA Q&A document on ERA (EMA/CHMP/SWP/44609/2010 Rev.1), it is agreed that the ERA can consist of a justification for not submitting ERA studies.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The pharmacological effects of somatrogon were examined in both *in vitro* and *in vivo* in the pharmacologically relevant species, rats and monkeys. A high degree of similarity in the aminoacid sequence between GHRs from rat and human and from monkey and human was reported. The essential residues of the hGHR that interact with the hGH appear to be conserved in rhesus monkeys and four aminoacids out of six conserved in rats. The binding affinity of somatrogon to GHR is approximately 2-fold lower in rhesus monkey in comparison to human receptors. Of note, the binding affinity of somatrogon is 8-13 fold lower than the binding affinity of somatropin for hGHR. The potential clinical relevance of this difference in *in vitro* activity between somatrogon and somatropin was not discussed, although seen in binding affinity, induction of cell-proliferation and STAT5b phosphorylation data. However, *in vivo* data indicate similar weight gain in hypophysectomied rats following a single SC administration of 0.55 and 1.1 mg protein/ kg somatrogon (equivalent to 0.4 and 0.8 mg/kg hGH) as compared to daily 0.1 mg/kg somatropin. The difference between *in vitro* potency and *in vivo* activity of somatrogon vs somatropin is attributed to both exposure and differing binding parameters for the GHR. While somatrogon has a slower association constant in comparison to somatropin, the dissociation constants are more similar, therefore longer stimulation at the receptor reduced the impact of the slower association rate in *in vitro* studies. Hence, the apparent difference in *in vitro* potency between somatropin and somatrogon is reduced as the treatment time in cell-based assays is increased. *In vivo*, somatrogon induces a relatively high C_{max} with a prolonged half-life, leading to sustained activation of the receptors and translating into higher levels of IGF-I production and subsequent weight gain in non-clinical studies.

For better comparability between somatropin (Bio-Tropin) and somatrogon, the concentration of the latter was calculated based on its hGH content. In some studies, the hGH content of 72.6% was used for the total dose, that is related to the glycosylated product. In other studies, 72.6% hGH was related to the protein backbone excluding glycans, which is equal to 57.8% hGH in the glycosylated product (more appropriate as it corresponds to equimolar doses), but both methods reflect similar hGH content relative to somatrogon (72.6% of 30,469 Da or 57.8% of 38,254 Da).

Secondary pharmacodynamics were assessed with an *in vitro* assay, assessing the off-target receptor binding of somatrogon and comparing them to somatropin. From a panel of 70 receptors somatrogon showed no significant affinity to any of the screened receptors except for the glutamate. Because of the similar off target binding profile seen with somatropin, the applicant concludes that the fusion of CTP to rhGH does not affect the off-target binding of somatrogon.

Safety pharmacology endpoints were incorporated into the repeat dose toxicity studies in line with ICH S6. Pharmacodynamic drug interaction studies have also not been conducted. This is acceptable due to the nature of this biologic product and the specificity of its pharmacological activity.

Pharmacokinetics

Single-dose pharmacokinetic (PK) and toxicokinetic (TK) studies were conducted following SC administration of somatrogon in Sprague-Dawley rats and rhesus monkeys. Validated assays were used to support the quantification of somatrogon and detection of antibodies to somatrogon in the GLP repeat-dose toxicity studies in rats and rhesus monkeys.

A number of bioanalytical methods such as quantitative determination of somatrogon in rat serum (incl. foetal and pregnant rat serum) and rhesus monkey serum, quantitative determination of somatropin in monkey serum, qualitative determination of antibodies to somatrogon, CTP and somatropin in rat and monkey serum and qualitative determination of neutralising antibodies to somatrogon and somatropin in rat and rhesus monkey serum were developed and in general successfully validated.

It is noted that at the time these studies were carried out, the Bioanalytical guideline was still under development and the applicant relied on the acceptance criteria for bioanalytical method validation as described in the scientific literature of that time. Deviations from the currently accepted standards are acknowledged and accepted for this reason.

Commercially available enzyme-linked immunosorbent assays (ELISAs) were used for the quantification of IGF-1 in rat and monkey serum to support the GLP repeat-dose studies in Sprague-Dawley rats and rhesus monkeys. All IGF-1 measured was total IGF-1.

Both IGF-1 and IGFBP-3 are biomarkers for GH treatment. IGFBP-3 was not measured in nonclinical studies but was measured however in Phase I Clinical studies. IGFBP-3 was produced in response to somatrogon. Although it was not measured in the nonclinical studies is considered unlikely that IGFBP-3 would confound the interpretation of the nonclinical IGF-1 data.

In the TK analysis of the repeat dose toxicity studies exposure to somatrogon (as assessed by Cmax and AUC) increased in an approximately dose proportional manner and there were no apparent sex-related differences in systemic exposure. As expected, due to the three copies of CTP fused to hGH to form somatrogon, exposure of somatrogon was higher than somatropin in rats and monkeys because of the significantly longer t½.

The incidence of anti-somatrogon antibodies was higher in rats than rhesus monkeys and antibodies were detected for both the hGH and carboxy-terminal peptide (CTP) domain of somatrogon in both species. Neutralizing antibodies were detected, however, exposure to somatrogon and the insulin-like growth factor (IGF)-1 responses were not affected in these animals.

No distribution or protein binding studies were conducted. Based on the literature, it is expected that binding of growth hormone, and by extension somatrogon to its binding protein in plasma and the circulating extracellular domain of growth hormone will be approximately 50%.

The results of an *in vitro* hepatocyte study suggest that somatrogon and somatropin are not inducers of CYP1A2 and CYP2B6 but may be considered weak inducers of CYP3A4 enzyme. Considering the extensive clinical experience with rhGH in patients, somatrogon is expected to act by the same pharmacological mechanism as hGH via binding to the growth hormone receptor, no new DDI are expected beyond those already known for rhGH products.

Toxicology

Somatrogon was well-tolerated following single and repeat dose SC injection up to 180mg/kg in rats and up to 90mg/kg in monkeys. Chronic repeat dose toxicity was assessed in one species only, monkey, in agreement with CHMP.

Single-dose PK and TK studies were conducted following SC administration of somatrogon in rats and rhesus monkeys (toxicology species). Exposure (as assessed by Cmax and AUC) increased in an approximately dose-proportional manner. In general, there were no apparent sex-related differences in systemic exposure.

Developmental and reproductive toxicity (DART) studies were conducted in only one species, an approach that was agreed by CHMP. The applicant carried out FEED, EFD and PPND studies. In these studies, there were no unanticipated toxicities that differ from what is known about GH. A NOAEL is reported at the high dose in all pivotal DART studies of 30 mg/kg. These reproduction and developmental studies with somatrogon have some limitations, TK analysis was only performed in the pivotal EFD study, but not in the FEED and PPND studies. TK data from the EFD study was used in the calculation of a safety margin to human and in section 5.3 of the SmPC the sponsor reports an exposure margin of 14x the maximum recommended human dose from the AUC reported at the 30mg/kg dose in the EFD study in rats, which is acceptable.

Environmental risk assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, somatrogon is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

The non-clinical dossier supports the approval of this application.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the

Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 4 Tabular overview of clinical studies

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects Treated	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status
CP-4-001	A Phase 1, randomized, double-blinded, placebo-controlled, single-dose, dose-escalation study to evaluate the safety and pharmacokinetics of a long acting hGH product (MOD-4023), in healthy volunteers	somatrogon 4 mg somatrogon 7 mg somatrogon 21 mg placebo	6 6 6 6	Sex: 24 M/ 0 F Mean/Median Age (min/max): 27.7/26.0 (18, 45) years	single dose	04 Oct 2009/ Completed
CP-4-007	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 (MOD-4023) in healthy Caucasian and Japanese volunteers	somatrogon 2.5 mg somatrogon 7.5 mg somatrogon 15 mg	12 12 12	Japanese subjects: 21 Sex: 21 M/ 0 F Mean/Median Age (min/max): 34.6/35.0 (21, 45) years Caucasian subjects: 21 Sex: 21 M/ 0 F Mean/Median Age (min/max): 29.7/29.0 (22, 40) years	single dose	09 Jan 2015/ Completed
CP-4-011	A Phase 1, single-center, randomized, cross-over, clinical study investigating the comparability of somatrogon in two different drug product presentations	somatrogon 12 mg pen and vial	49	Sex: 49 M/ 0 F Mean/Median Age (min/max): 37.5/38.0 (20, 51) years Race: W/B/O/A: 46/3/0/0	single dose of each presentation	18 Jan 2019/ Completed
CP-4-004 and OLE	A Phase 2, open label, randomized, multi-center, dose finding, and safety study of different somatrogon dose levels in pre-pubertal children with growth failure due to GHD with an open-label extension (OLE)	*Periods I and II:* somatrogon 0.25 mg/kg/week somatrogon 0.48 mg/kg/week somatrogon 0.66 mg/kg/week	13 15 14	Sex: 10 M/ 3 F Mean/Age range (min/max): 6.7 (4.1, 11.2) years Race: W/B/O/A: 12/0/1/0 Sex: 9 M/ 6 F Mean/ Age range (min/max): 6.2 (3.1, 10.3) years Race: W/B/O/A: 14/1/0/0 Sex: 9 M/ 5 F Mean/ Age range(min/max): 6.6 (3.0, 10.8) years Race: W/B/O/A: 14/0/0/0	Periods I and II: 12 months in total	Main Study: 18 Jun 2012/ Completed OLE: 26 Feb 2014/ Ongoing

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects Treated	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status
		Genotropin® 0.034 mg/kg daily	11	Sex: 8 M/ 3 F Mean/ Age range(min/max): 6.2 (4.3, 9.5) years Race: W/B/O/A: 10/0/1/0		
		Period III (OLE) somatrogon 0.25 mg/kg/week somatrogon 0.48 mg/kg/week somatrogon 0.66 mg/kg/week	16 17 15	Sex: 32 M/ 16 F Mean/Median Age (min/max): 7.67/6.87 (4.2, 12.2) years Race: W/B/O/A: 45/1/2/0	Period 3: 12 months	
		Period IV (long term OLE) 0.66 mg/kg/week	44	Sex: 30 M/ 14 F Mean/Median Age (min/max): 8.66/7.87 (5.2, 13.2) years Race: W/B/O/A: 43/1/0/0	Period 4: 24-36 months (through switch to pen)	
		Period V (long term OLE on pen)	40	Sex: 28M/ 12F Mean/Median Age (min/max): 11.33/10.77 (7.2, 15.9) Race: W/B/O/A: 40/0/0/0	Switch to pen through product registration	
CP-4-006 and OLE	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 Eligible subjects who completed the 12-month main study could continue treatment with somatrogon in a single-arm, LT-OLE study to collect additional long-term safety and efficacy information.	somatrogon 0.66 mg/kg/week	109	Sex: 82 M/ 27 F Mean/Median Age (min/max): 7.83/7.92 (3.01, 11.96) years Race: W/B/O/A: 81/0/3/24	12 months	19 Apr 2017/ Completed
		Genotropin® 0.034 mg/kg daily	115	Sex: 79 M/ 36 F Mean/Median Age (min/max): 7.61/7.84 (3.05, 11.85) years Race: W/B/O/A: 86/2/5/21		
		OLE: Originally randomized to somatrogon	104	Sex: 78 M/ 26 F Mean/Median Age (min/max): 8.89/8.86 (4.33, 13.40) years Race: W/B/O/A: 79/0/4/21	Until registration	Ongoing
		Originally randomized to Genotropin	108	Sex: 72 M/ 36 F Mean/Median Age (min/max): 8.69/8.90 (3.89, 13.05) years Race: W/B/O/A: 83/2/6/17		

Protocol No.	Study Design and Objective	Treatment Groups	No. of Subjects Treated	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status
C0311002	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	Sequence 1 Period 1: Genotropin (dose subject was on at time of enrollment) Period 2: somatrogon (0.66 mg/kg /wk) Sequence 2 Period 1: somatrogon (0.66 mg/kg /wk) Period 2: Genotropin (dose subject was on at time of enrollment)	43 44	Sex: 34 M/ 9 F Mean/Median Age (min/max): 10.8/12.0 (4, 16) years Race: W/B/O/A: 39/3/1/0 Sex: 38 M/ 6 F Mean/Median Age (min/max): 10.7/11.0 (3, 17) years Race: W/B/O/A: 42/1/0/1	Period 1: 12 weeks Period 2: 12 weeks	7 Feb 2019/ Completed

A = Asian; B = Black; F = Female; GHD = Growth Hormone deficiency; M = Male; max = maximum; min = minimum; MOD-4023 = somatrogon;
NA = Not applicable; No = Number; O = Other; OLE = Open-label extension; W = White.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Clinical pharmacology data to support the registration for somatrogon were collected in 7 clinical studies. These included studies in adults and children with GHD and one on-going open-label extension (OLE) study in children with GHD. In addition to the individual studies, 6 population PK and PK/PD analyses were conducted.

Absorption

The absorption PK parameters of somatrogon at the proposed SC dose of 0.66 mg/kg/week estimated from the population PK analysis of 42 pre-pubertal GHD children are summarized below.

Table 5 Pharmacokinetic Parameters Derived from Population Pharmacokinetic Analysis

PK Parameter	Somatrogon 0.66 mg/kg/week		
	Mean ± SD	Median	Min - Max
C_{max} (ng/mL)	690 ± 261	650	140 - 1410
T_{max} (hr)	-	8	6 - 18
AUC (ng.hr/mL)	21800 ± 6460	20300	6110 - 35000
Accumulation factor	1.02 ± 0.004	1.02	1.01 – 1.03

Source: Module 5.3.3.5 PMAR-EQDD-C031c-DP3-853, Table 16

The absolute bioavailability of subcutaneously administered somatrogon with reference to the intravenous route has not been determined. In the population PK analysis, the relative bioavailability in GHD adults was ~44% of the relative bioavailability in GHD children.

A phase 1 randomised, double-blind placebo controlled, single dose, dose-escalation study in healthy adult male volunteers has been conducted. The study enrolled 24 subjects into 3 dose cohorts (4 mg, 7 mg and 21 mg).

Exposure expressed as C_{max} and AUC (AUC0-t and AUC0-∞) increased with increasing dose, but somewhat more than dose proportionally. The duration of exposure to somatrogon was dose related, and one or more values in the arm dropped to BLQ at points beyond 48, 72, and 96 hr in the 4, 7, and 21 mg dose arms, respectively.

As somatrogon was only administered by SC injection in this study, bioavailability (F) was not determined. The mean time to reach peak concentrations ranged between 11-14 hours following SC injection. There was a dose-related, but more than dose proportional, increase in the serum concentrations of somatrogon after single SC doses of 4 mg, 7mg and 21 mg, which lasted for 48 to 96 hrs. The mean half-life of somatrogon was dose independent ranging from 20.8 to 23.6 hours.

Serum samples from all subjects prior to dosing and at 14 days and 30 days following administration of somatrogon were negative for anti-somatrogon antibodies.

Another phase 1, single-centre, open-label randomised, 2×2 crossover (Ref Test | Test Ref) study was conducted in healthy male volunteers with a washout of two weeks. The aim was to establish bioequivalence between single SC (12 mg) doses of somatrogon, delivered via either the pen formulation proposed for marketing, or in a vial delivered by a needle and syringe. The GeoMean AUCt values were similar between the 2 treatment groups and Cmax was slightly lower in the pen relative to vial treatment groups. The median t1/2 value following administration in pen and vial groups was 23.20 hours and 20.05 hours, respectively.

A phase 2 open-label, randomised, multicenter, parallel group, dose-finding study enrolled fifty-three (36 males and 17 females) paediatric subjects with GHD. Age ranged 3.0 to 11.2 years for male subjects and ranged 4.3 to 9.2 years for female subjects.

Subjects were randomised to receive one of three doses of somatrogon once weekly (0.25, 0.48 or 0.66 mg/kg) or somatropin (Genotropin 0.034 mg/kg daily). After administration of the second dose at the assigned dose level, 4 samples were collected per patient.

In this phase 2 study, the PK of somatrogon was evaluated in 42 paediatric subjects with GHD naïve to treatment with rhGH. Somatrogon exposure increased in a dose-dependent manner. The mean T1/2 for somatrogon for each dosing group, ranged between 18.3 to 36.1 hours, supportive of once weekly dosing.

Distribution

The distribution PK parameters of somatrogon at the proposed dose of 0.66 mg/kg/week estimated from the population PK analysis of 42 pre-pubertal GHD children are summarized below.

Table 6 Distribution Pharmacokinetic Parameters Derived from Population Pharmacokinetic Analysis (N=42)

PK Parameter	Somatrogon 0.66 mg/kg/week		
	Mean ± SD	Median	Min - Max
Vc/F (L/kg)	0.812 ± 0.528	0.716	0.317 – 3.77
Vp/F (L/kg)	0.169 ± 0.0389	0.157	0.109 – 0.243

Source: Module 5.3.3.5 PMAR-EQDD-C031c-DP3-853, Table 15.

Protein binding of somatrogon was not investigated, this was accepted by the CHMP.

Elimination

The mean ± SD apparent clearance and effective t½ calculated from the individual *post hoc* estimates of the population PK analysis of data from paediatric subjects were 0.0336 ± 0.0142 L/hr/kg and 28.3 ± 1.52 hour, respectively.

No information on the route of excretion of somatrogon was provided and specific metabolism studies were not conducted. This is acceptable. Somatrogon is expected to be primarily degraded by proteolytic catabolism (*Lobo et al., 2004; Mascelli et al., 2007*).

Dose proportionality and time dependencies

In two studies conducted in healthy male subjects, following SC injection of different somatrogon strengths, Cmax and AUCinf increased with increasing dose, but was not strictly dose proportionally.

In another study, conducted in adults with GHD, there was a dose-related increase in the mean serum concentrations and mean values of Cmax and AUCtau from Cohort 2 to Cohort 3 to Cohort 1A representing 37%, 55.5%, and 123.4% of the cumulative weekly dose required for daily rhGH. Log-log plots (power model) of the individual patient values for Cmax and AUCtau were reasonably linear with slopes, i.e. the exponents of the power model, close to 1.0 (1.159 ± 0.143 and 1.167 ± 0.122, respectively), indicating linear PK over a ~40-fold dose range. The mean values for CL/F, Vz/F, and t½ were comparable for all three cohorts with no apparent trends, further supporting the linearity of the PK of somatrogon.

The mean half-lives observed for somatrogon in the clinical studies of children with GHD ranged between 18.3 to 36.1 hours, which correspond to accumulation ratios of 1.001 to 1.04. Based on the population PK analysis of somatrogon in GHD children, the mean ± SD *post hoc* estimated accumulation ratio was 1.02 ± 0.004 and t½ was 28.3 ± 1.52 hours. Thus, there is minimal accumulation of somatrogon with weekly dosing.

Immunogenicity

No subjects testing positive for hGH ADAs at screening entered the main study CP-4-004. During study period, the overall ADA incidence was 23.8% (10/42) for somatrogon. None of the subjects tested positive for NAb. The total ADA incidence was reduced from the initial 10 patients to five patients between six and 12 months, indicating presence of transient anti-somatrogon Abs. The presence of ADAs did not affect the IGF-1 profiles.

In the open label extension period, among 48 subjects who entered the OLE to receive somatrogon, 18 subjects (37.5%) tested ADA+ for somatrogon. This included 10 subjects who had previously tested ADA+ in the main study. No subjects tested positive for Nabs. Throughout OLE Years 1-3 approximately 25% of subjects tested ADA+ and in Year 4, 2 subjects (5.3%) tested ADA+.

ADA status did not appear to have a significant effect on IGF-1 response in this study. IGF-1 SDS by treatment, year in the OLE (including LT-OLE and LT-OLE PEN). In addition, ADA status did not appear to effect efficacy in terms of annualised height velocity or change in height SDS.

In the other main study CP-4-006, no subjects testing positive for hGH ADAs at screening were enrolled. Of the 109 subjects in the somatrogon group, 84 subjects (77%) tested positive for ADA at any time during the 12-month treatment period. Median time to the first ADA+ result was 6 months,

and 83/84 subjects had persistent ADA+ results. Two subjects in the somatrogon group tested positive for NAb. Both subjects continued to grow and tolerate treatment well.

Among 115 somatropin-treated subjects, 12 subjects (10.4%) tested ADA+ for hGH at 6 months (Week 26) and 7 subjects (6.1%) tested positive for hGH at 12 months (Week 52), suggesting that transient anti-hGH antibodies had developed.

In the OLE period, among 38 subjects who received somatrogon in the main study period, 26 subjects (68.4%) tested ADA+ at Month 6 in the LT-OLE, all of whom had previously tested ADA+ in the main study. Among 41 subjects who received somatropin in the main study period, 8 subjects (19.5%) tested ADA+ at Month 6. No subjects tested positive for NAb. ADA status did not appear to have a significant effect on IGF-1 SDS or height SDS response in this study.

Special populations

Subjects with renal impairment were excluded from enrolling in either of the paediatric clinical studies. In the population PK analysis, which included data from adults with GHD (CLcr 65 – 291.1 mL/min) and from children with GHD and normal renal function, baseline CLcr was not found to be a significant covariate on the PK of somatrogon.

No data were provided on impaired renal function and this was found acceptable to the CHMP, since somatrogon is expected to have a low renal clearance.

Gender was not identified as a significant covariate in any of the population PK analyses conducted. Simulations based on the popPK model of data from the pivotal phase 3 study (CP-4-006) in pre-pubertal children with GHD indicated that girls had slightly higher (~15%) somatrogon exposure (Cavg,ss) than boys.

The influence of race was studied during a phase 1 randomised, double-blind placebo controlled, parallel group, single dose trial in 42 healthy adult male Caucasian and Japanese volunteers. There was no apparent difference between Japanese and Caucasian subjects with respect to PK parameters for the 2.5 mg and 7.5 mg dose cohorts. For the 15 mg dose cohort, the geometric mean Cmax was lower and the median Tmax longer in Japanese compared to Caucasian subjects but the geometric mean values for AUCinf were comparable, possibly suggesting a slower rate of absorption. The geometric mean T1/2 was independent of ethnic group. Moreover, race was not found to be a significant covariate in any of the population PK analyses performed. Simulations based on the popPK model of data from the pivotal phase 3 study (CP-4-006) in pre-pubertal children with GHD indicated that White and Asian children had similar somatrogon exposure.

Body weight was included as a covariate on clearance and volume parameters in all paediatric population PK models. Based on a population PK analysis where simulations were conducted assuming all paediatric GHD patients received 5 repeated weekly doses of somatrogon at a 0.66 mg/kg dose, it has been found that this dose should provide reasonably consistent exposures over the anticipated weight range in potential paediatric patients.

In the population PK analyses of somatrogon concentration data collected in paediatric GHD subjects, after accounting for body weight effects, age was not identified as a clinically relevant covariate. Simulations based on the popPK model of data from the pivotal phase 3 study (CP-4-006) in pre-pubertal children with GHD showed that somatrogon exposure in children aged 6-12 years was ~35% lower than children aged <6 years, due to differences in body weight between the two groups.

As doses of somatrogon are administered on the basis of weight, further dose adjustment based on age among paediatric patients is not required.

Pharmacokinetic interaction studies

In vitro

The effects of somatrogon and somatropin (Genotropin at similar hGH content) on induction of specific human cytochrome P450 (CYP) enzymes (CYP1A2, CYP2B6, and CYP3A4) following exposure of human hepatocytes to test articles were compared with those of prototypical inducers (omeprazole, phenobarbital and rifampicin). The ability of somatrogon (up to 1000 ng/mL) and somatropin (up to 726 ng/mL) to induce CYP1A2, CYP2B6, and CYP3A4/5 was determined in primary cultures of human hepatocytes and compared to the effects of prototypical inducers. Somatrogon and somatropin demonstrated comparable induction profiles of CYP1A2, CYP2B6, and CYP3A4 under the conditions of the study. Somatrogon and somatropin were not considered to be inducers of CYP1A2 and CYP2B6 but may be considered weak inducers of CYP3A4.

A different study assessed somatrogon cross reactivity and interference during hCG quantification in blood and urine pregnancy tests. Serum samples containing either hCG or somatrogon were evaluated for hCG concentrations in order to assess potential interference using a quantitative pregnancy blood test. The results supported the conclusion that somatrogon did not cross react with the hCG antibodies used in commonly used pregnancy tests to product false positive responses and did not interfere with the detection of hCG in blood or urine to produce a false negative result.

In vivo

Clinical DDI studies between somatrogon and co-administered drugs have not been performed and this was found acceptable by the CHMP.

2.6.2.2. Pharmacodynamics

Growth is regulated through complex mechanisms involving GH, IGF-1, IGFBP-3 and their complexes. GHD is the consequence of low or absent secretion of GH from the pituitary gland. In children, GHD results in inadequate circulating IGF-1 levels and abnormal linear growth.

IGF-1 was the primary PD biomarker used in all clinical development studies. IGFBP-3 levels were also assessed. In addition to statistical analyses of these endpoints, population PK/PD analyses were performed to establish the exposure-response relationship.

IGF-1 and IGFBP-3 were converted to SDS (standard deviation score) values using the tables by *Bidlingmaier et al, 2014*. The SDS reflects the number of standard deviations below or above a reference population mean and allows for comparison of IGF-I and IGFBP-3 data across gender and age.

Mechanism of action

Somatrogon acts by the same pharmacological mechanism as hGH via binding to the GHR, i.e. it stimulates production and release of IGF-1 into the systemic circulation and local milieu. hGH and IGF-1 are instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in children and adults. These factors are regulated through complex feedback mechanisms involving hGH, IGFBP-3 and their complexes.

Primary and Secondary pharmacology

Primary pharmacology

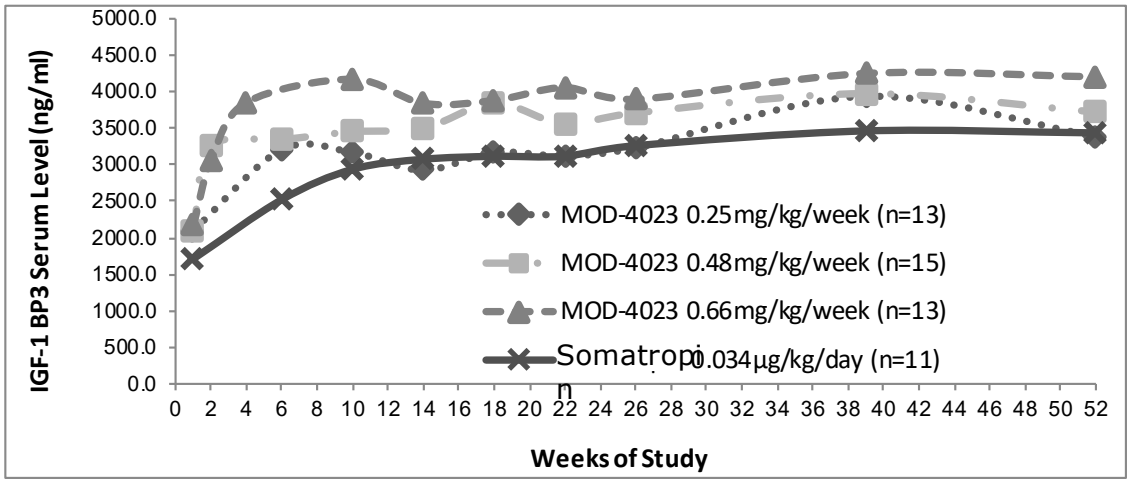
Study CP-4-004

In this phase 2 study, 53 paediatric GHD patients, naïve to treatment with rhGH, were randomised to receive one of three doses of somatrogon once weekly (0.25, 0.48 or 0.66 mg/kg) or somatropin (Genotropin) 0.034 mg/kg daily.

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 monitoring the weekly profile on Day 3 or 4 post-dosing or when monitoring it on monthly basis through 12 months. IGF-1 SDS levels increased gradually in a dose-dependent manner until an IGF-1 SDS ≈ 0 was achieved, and then stabilized for the duration of the 12 months of the study without reaching excessive IGF-1 values (>+2 SDS) for all, but one subject in 0.66 mg/kg/week dosing group, whose dose was reduced.

IGFBP-3 increased in a dose-dependent manner following administration of somatrogon, reaching steady-state values around week 15. Mean concentration-time profiles of the IGFBP-3 weekly trend over 12 months are presented below.

Figure 4 Average IGFBP-3 – Weekly Trend for Patients Completing 12 Months of Treatment (Periods I and II)

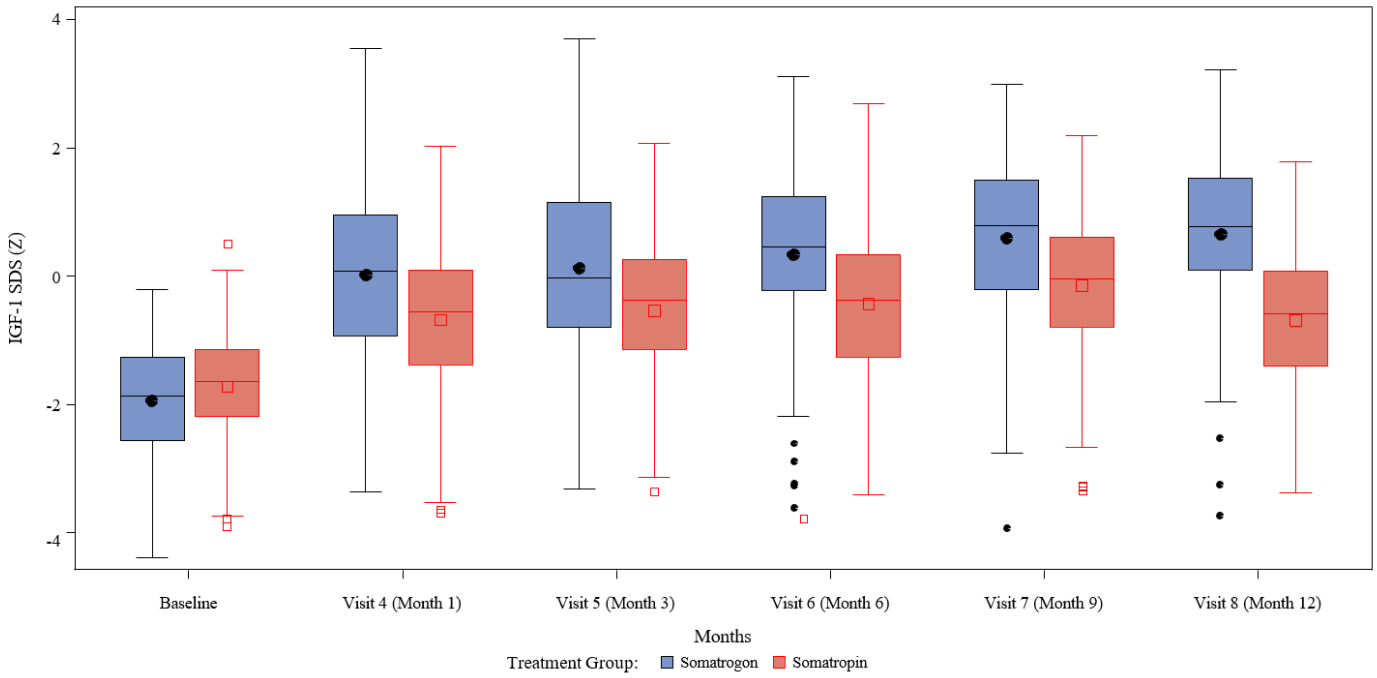


Source Report CD-04-0388 v1, see Appendix 16.1.9.3 and Listing 16.2.8.3

In this Phase 3 study, the PD parameters of somatrogon and somatropin (Genotropin) were evaluated in 109 and 115 paediatric subjects with GHD, respectively. Subjects were randomised to receive somatrogon 0.66 mg/kg once weekly or somatropin 0.034 mg/kg daily for 12 months.

Mean absolute serum IGF-1 levels, relative to baseline, increased across post-baseline study visits for both treatment groups. Mean IGF-1 SDS values in the somatrogon group approached 0 as early as 1-month post-baseline and remained above 0 up to 12 months (0.65 SDS at 12 months). Mean IGF-1 SDS values in the somatropin group remained near 0 SDS at all subsequent post-baseline visits, ranging from -0.69 SDS to -0.16 SDS.

Figure 5 Box Plot of IGF-1 SDS Over Time – Full analysis set



	Baseline	Visit4 (Month 1)	Visit5 (Month 3)	Visit6 (Month 6)	Visit7 (Month 9)	Visit8 (Month 12)
Treatment	N	N	N	N	N	N
Somatrogon	109	107	109	107	108	107
Somatropin	115	115	113	113	113	110

Baseline is defined as the last non-missing measurement prior to the start of study drug.
Source Data: Table 14.2.4.1

Mean serum IGFBP-3 levels post-dose generally increased across study visits for both treatment groups. Mean IGFBP-3 SDS post-dose values for the somatrogon group approached 0 at 1-month post-baseline and remained close to 0 (ranging from -0.27 to -0.02 SDS) through 12 months. Mean IGFBP-3 SDS post-dose values for the somatropin group reached values ranging from -0.84 to -0.53 SDS throughout the post-baseline visits.

Secondary pharmacology

In vitro, somatrogon exhibited a similar binding pattern as rhGH suggesting that fusion of CTP to rhGH leading to the long-acting nature of somatrogon did not affect the off-target binding profile of the test article as compared with rhGH.

Daily GH inhibits 11βHSD-1, a microsomal enzyme that catalyses the conversion of cortisone to cortisol, and also activates prednisone and prednisolone, resulting in lower cortisol concentrations and potentially unmasking central hypoadrenalism or causing exogenous glucocorticoid therapy to be less effective. No studies have been performed to assess the potential impact of somatrogon co-administration on blood sugar control in subjects with diabetes, either type 1 or type 2, controlled with either insulin or oral glucose lowering drugs. However, GH is generally antagonistic to insulin.

Further safety concerns known to be associated with daily rhGH include thyroid function impairment.

PK/PD analyses

- **Phase 2 study CP-4-004**

Two population PK/PD analyses were performed using data from paediatric GHD subjects enrolled in study CP-4-004. One was based on the data collected during the main study, whereas the other included data collected in the main study as well as data collected up to 4 years after the beginning of the study in the OLE portion.

The PD analysis was based on an indirect-response model developed by Sun *et al.* (1999), in which IGF-1 production is a function of the concentration of GH (or an analog); somatrogon increased production/release of IGF-1, described by a sigmoid Emax model.

The PD model indicated that increasing somatrogon doses increases the IGF-1 response. Based on simulations, mean IGF-1 values for Cohort 3 (0.66 mg/kg/wk) were typically > 0 SDS, ~centered at zero for Cohort 2 (0.48 mg/kg/wk), and consistently much lower than < 0 for Cohort 1 (0.25 mg/kg/wk).

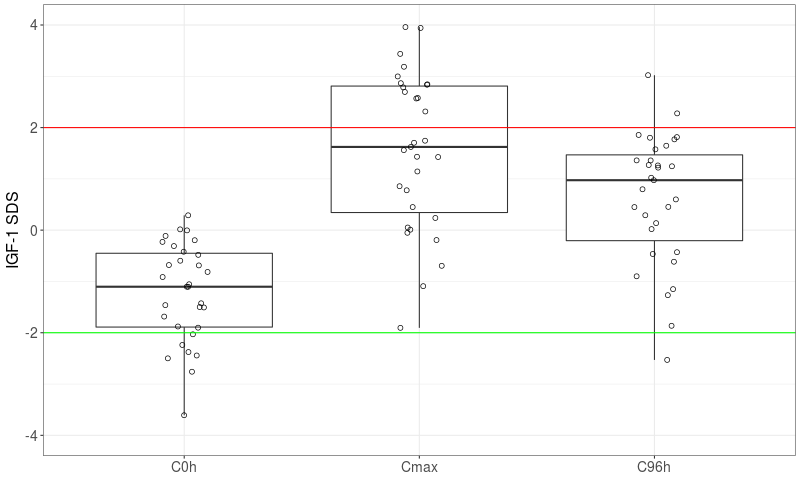
In a supplemental analysis, somatrogon and IGF-1 concentrations were simulated at intervals of 0.04 days during a dosing interval at steady state. These showed that predicted IGF-1 SDS on Day 2 (48 hours post-dose) approximated peak values in many subjects. IGF-1 SDS on Day 4 (96 hours post-dose) approximated mean values in many subjects.

IGF-1 analysis

Based on prior knowledge, an indirect response model was used to describe the IGF-1 concentration time profile and it was assumed that somatrogon stimulates the IGF-1 production in a concentration dependent manner described by a sigmoidal Emax model. The PK parameters were fixed to the individual Bayesian estimate values from a popPK analysis.

Using the final model, individual IGF-1 SDS versus time profiles after 4 years of treatment were simulated for each patient. The frequency for IGF-1 SDS values ≥ -2 and IGF-1 SDS values ≤ +2 at trough IGF-1 SDS, peak IGF-1 SDS and 4 days post dose after 4 years of somatrogon administration were 77.4%, 58.1% and 90.3%, respectively.

Figure 6 Boxplot for simulated IGF-1 SDS C0h, Cmax, C96h repository

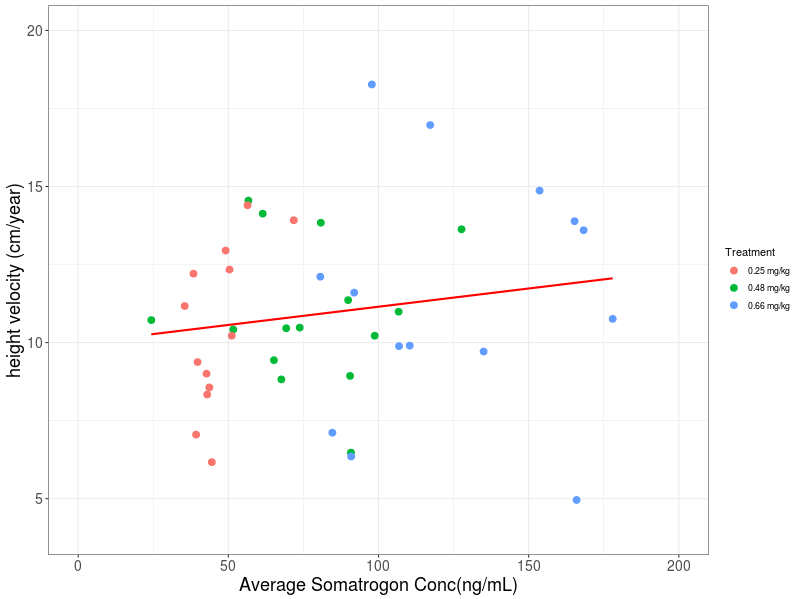


Repository artifact ID FI-8959073.
Red line is IGF-1 SDS=2; Green line is IGF-1 SDS=-2; IGF-1 SDS=IGF-1 standard deviation score

Height velocity analysis

The relationship between average somatrogon concentration and height velocity (HV) at the end of 1-year treatment of pre-pubertal GHD children is presented below. No significant effect of average somatrogon concentration on HV was observed, but a positive trend of HV did occur with an increase in average somatrogon concentration.

Figure 7 Relationship between exposure and HV at the End of 1 Year in pre-pubertal GHD children



Repository artifact ID FI-4881442.
Red circles represent treatment group for somatrogon 0.25 mg/kg; Green circles represent treatment group for somatrogon 0.48 mg/kg; Blue circles represent treatment group for somatrogon 0.66 mg/kg; Average
Somatrogon Conc=average somatrogon concentration of up to 1 year; cm=centimeter; ng=nanogram; mL=milliliter; mg=milligram; kg=kilogram

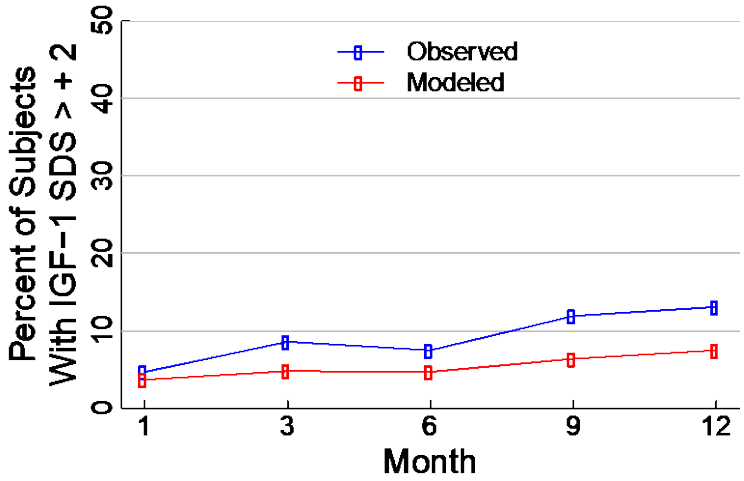
- **Phase 3 study CP-4-006**

The dataset included the IGF-1 observations and *post hoc* (individual) PK parameters for somatrogon obtained from the optimal popPK model. The indirect-response Emax model developed by *Sun et al,1999* fit the data well. Two models, each with two covariates, yielded nearly identical fits and objective functions.

Optimal Model #1: Baseline IGF-1 increased with age and with BMI.

In a supplemental analysis, *post hoc* (individual) IGF-1 estimates at intervals of 6 hours throughout each dosing interval in which a sample was obtained were simulated. As shown in Figure 2, the percentage of subjects with IGF-1 SDS values > +2 increased over time and the incidence of IGF-1 values > +2 was larger with observed values compared to modelled values.

Figure 8 Percent of subjects with IGF-1 SDS values > +2 at each post-dose visit



This analysis confirmed that IGF-1 samples obtained early (<72 hours) in the dosing interval do not represent mean IGF-1 SDS during the dosing interval; these early samples showed a positive bias and were more likely than samples obtained later in the dosing interval to yield an IGF-1 SDS > +2. Therefore, when the goal of monitoring clinical therapy is to estimate mean IGF-1 SDS value during the dosing interval, clinical samples should be obtained close to 96 hours post-dose. If a sample is obtained earlier than 72-hours post-dose, that value should not be considered as representative of the mean IGF-1 SDS during the dosing interval.

2.6.3. Discussion on clinical pharmacology

The pharmacokinetics are mainly derived from HV and the 2 paediatric studies and corresponding modelling. The main PK-relevant phase 2-study in children CP-4-004 utilised a specific limited sampling scheme. Sparse PK data obtained in the paediatric phase 3-study CP-4-006 were only used for popPK modelling. In view of the proposed indication applied for (in children) and the weight-based dosing in the target population, the pharmacokinetic and pharmacodynamic assessment focussed on the paediatric study data.

Pharmacokinetics

Bioanalytical methods

PK assays

The methods for determination of somatrogon serum levels are adequately described and for the most part have been validated according to EU guidance (Guideline on bioanalytical method validation EMEA/CHMP/EWP/192217/2009) addressing precision, accuracy, dilutional linearity, selectivity, sample stability, specificity (tolerance to endogenous hGH) and calibration curve performance. As per EU guidance (EMEA/CHMP/EWP/192217/2009 Rev. 1), the applicant demonstrated that the reference material was well characterised and confirmed a link between the batches and batches dosed clinically.

ADA and Nab assays

The methods for anti-somatrogon/anti-hGH ADA analysis follow the recommendations of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and have been appropriately validated addressing precision, sensitivity, drug tolerance, selectivity, sample stability and robustness. For the anti-hGH ADA assay, the applicant has justified that the reagents used would detect either endogenous hGH or somatropin (depending on the treatment arm during the study).

In addition, differing approaches were used to derive cut-points across the ADA assays. It is noted also that all paediatric studies used the floating cut-point approach which is acceptable. Otherwise, an appropriate false positive rate (1%) was applied and the number of individuals used to derive cut-points has been appropriately justified.

For all ADA assays the applicant has confirmed that the tolerance of the assay for somatrogon (or hGH) exceeds the actual levels of the therapeutic in the samples used for ADA testing.

At low PC concentrations, the drug tolerance of the Nab assay is as low as 0.05 µg/mL. According to PK data, C_{max} of somatrogon is between ~690 ng/mL to ~ 1µg/mL; at this level, interference with the analysis of neutralising potential of ADAs would be expected. It has been clarified that for most clinical samples, somatrogon (and hGH) drug levels were below the assay drug tolerance. The response in relation to hGH NAb drug tolerance is acceptable. In relation to somatrogon, it appears that the methods used would only be capable of detecting in the order of 50 µg/ml NAb given the established drug tolerance and the clinical relevance of this detection threshold was queried. It has been clarified that all ADA+ samples were also tested for NAb activity with the hGH NAb assay which has sufficient sensitivity to detect clinically meaningful levels of NAb in the presence of somatrogon (detects 3.9 µg/ml of positive control (PC) in the presence of 246 ng/ml somatrogon). It is confirmed that only 5.5% (29 out of 524) of NAb negative samples exceeded the drug tolerance of the hGH NAb assay. Thus, the hGH NAb assay has sufficient drug tolerance to detect clinically meaningful levels of NAb in the presence of circulating somatrogon drug levels for the majority of samples across the clinical development program.

Bioanalytical methods for PD

Samples to measure insulin-like growth factor 1 (IGF-1) and insulin-like growth factor binding protein 3 (IGFBP-3) were analysed using standard commercial kits.

Population PK analyses based on the Phase 2 study CP-4-004

Two popPK analyses were performed using somatrogon data from paediatric GHD subjects enrolled in the Phase 2 study CP-4-004. The first analysis was based on concentration data collected in the main study, with the main purpose to develop a population PK model to be used subsequently in the PK/PD modelling of IGF-1 data. A two-compartment model appeared to describe the paediatric data adequately, although the VPCs were difficult to interpret. For children, the model in which the systemic parameters were weight-normalized was preferred over non-normalized and allometric-scaled models. Simulations demonstrated the longer duration of systemic exposure with somatrogon compared to r-

hGH, which supports less frequent dosing. Further, a simulation of repeated weekly dosing in paediatric subjects showed that somatrogon was not cumulative.

The second analysis used drug concentration and ADA data collected in the main study and in the OLE portion as well.

This analysis is considered important as PK parameter estimates from this model are reported in Section 5.2 of the SmPC. The methods used for model development and evaluation are acceptable. Data exclusions were adequately detailed and considered acceptable. The pooling of data from adult and GHD paediatric patients is appropriate given the sparse PK sampling of paediatric subjects.

The PK of somatrogon was characterised by a two-compartment model with a delayed first order absorption. All parameters, except Vp/F, were estimated with good precision. The degree of shrinkage for IIV was acceptable. GOF plots and VPCs showed that the model described the data reasonably well. The simulated steady-state estimates of t1/2 (~28 hours) and minimal accumulation (accumulation ratio 1.02) support the proposed weekly dosing interval for somatrogon treatment.

ETA on CL/F and Vc/F were highly correlated. As such, the condition number of the final model was greater than 1000. Although collinearity might compromise accuracy and precision of the parameter estimates, in this analysis, the parameter estimates of eta on CL/F and eta on Vc/F were reasonable and parameter estimates were relatively precise. Therefore, the high condition number did not seem to have a meaningful impact on the final model.

The estimates for the allometric exponents in the model (1.26 and 1.74 for CL/F and V/F, respectively) were unusually high. However, the deviation of the exponent for allometric scaling did not invalidate the adequacy of the population PK model as shown in the various diagnostic plots and visual predictive checks.

Population PK analyses based on the Phase 3 study CP-4-006

Two population PK analyses were performed using somatrogon data from paediatric GHD subjects enrolled in the pivotal phase 3 study CP-4-006. The first analysis was performed prior to the availability of ADA results and its main purpose of was to develop a population PK model to be used subsequently in the PK/PD modelling of IGF-1 data. A two-compartment linear model with an absorption lag time fit the data well. Consistent with one of the popPK models based on study CP-4-004, the model with clearance and volume parameters scaled by weight was preferred over models with allometric scaling. This supports the proposed weight-based dosing regimen for somatrogon.

PK Parameter estimates for the present study (CP-4-006) differed from those for CP-4-004, the phase 2 study for somatrogon. The differences were considered likely due to the markedly different sampling regimens in these studies. This is accepted.

The second analysis was performed after ADA results were available.

The purpose of this analysis was to characterise the popPK of somatrogon in pre-pubertal GHD children participating in the pivotal Phase 3 study CP-4-006, to confirm covariates identified in the previous popPK analysis, and to assess the impact of a change to the day of dosing.

The goodness of fit plots suggested that the final model described the data well with no obvious bias. VPCs showed that the final model described the central tendency and spread of the data adequately. Consistent with previous popPK studies, the estimate of the t1/2 (~33 hours) and minimal accumulation (accumulation ratio 1.03) supports the weekly dosing interval for somatrogon treatment.

The adequacy of the model was demonstrated in the various diagnostic plots and visual predictive check.

Simulations showed that the increase in somatrogon AUC168 caused by a one-time change in the day of dosing, either advancing or delaying dosing by up to 72 hours, will return to bioequivalence range (80 – 125%) within the 2nd or 3rd dose after the change. As such, it is agreed that a one-off change in the day of weekly administration can be made as long as the advance or delay is less than or equal to 3 days. Similarly, if a dose is missed, as a one-off, it can be administered provided no more than 3 days have elapsed since the missed dose. Accordingly, section 4.2 of the SmPC provides adequate directions.

Absorption

The absolute bioavailability of subcutaneously administered somatrogon with reference to the intravenous route has not been determined. This was acceptable to the CHMP.

No immunogenic response was observed in any somatrogon cohort.

Bioequivalence in terms of AUCt and AUC∞ between the two formulations (pen and vial) was demonstrated in a phase 1 study. The lower bound of the 90% confidence interval for the ratio of Cmax was below 80% and therefore bioequivalence for this parameter was not demonstrated, however bioequivalence analyses were performed on baseline normalised PD markers IGF-1 and IGFBP-3, which demonstrated bioequivalence. Use of baseline corrected values for these endogenous PD markers is in line with the relevant guidance. In general, safety was comparable between formulations, although the limitations in the comparisons of safety profiles in a crossover study design are acknowledged.

As part of standard of care, injection sites are rotated for medications administered by SC injection to avoid potential injection site reactions, including lipoatrophy. Whilst there are no comparative bioavailability data for describing somatrogon PK parameters after injection at different sites, there are data from studies of administration of rhGH, which show no differences in IGF-1 levels following injection at different sites. Thus, any differences in bioavailability between the sites do not appear to have clinical relevance. The instructions for rotating the injection site in Section 4.2 of the SmPC are considered acceptable.

Elimination

The applicant has presented no discussion on the metabolism or excretion of somatrogon, which is likely via proteolytic catabolism. This was accepted by the CHMP.

Dose proportionality and time dependency

In healthy volunteers, somatrogon exposure increased more than proportionally to the increase in dose. However, in the phase 2 study in adult subjects with GHD linear PK over a ~40-fold dose range was shown. Further, sparse sampling in the phase 2 study in paediatric subjects with GHD suggested approximately dose proportional increases in exposure in terms of Cmax and AUCinf.

Following multiple weekly administrations of somatrogon, no relevant accumulation of somatrogon is expected in children with GHD.

Intra- and inter-individual variability

Intra-individual variability was not formally evaluated, and this was found acceptable by the CHMP. Inter-individual variability in somatrogon PK in paediatric GHD patients is moderate to high.

Pharmacokinetics in target population

Somatrogon was not administered to healthy paediatric subjects and therefore no direct comparison with paediatric GHD subjects included in studies CP-4-004 and CP-4-006 is possible.

In the phase 2 study CP-4-004, the PK of somatrogon was evaluated in 42 paediatric subjects with GHD naïve to treatment with rhGH. Somatrogon exposure appeared to increase in a dose-dependent manner. The mean T1/2 for somatrogon for each dosing group, ranged between 18.3 to 36.1 hours, supportive of once weekly dosing.

Immunogenicity

Immunogenicity data were collected throughout the clinical development programme and the applicant has submitted an integrated summary of immunogenicity discussing results from pivotal paediatric studies supporting the proposed indication.

The incidence of ADAs appeared to be dose related in phase II study CP-4-004 in paediatric subjects with GHD with no ADAs reported in the lowest dose (0.25 mg/kg sc QW) cohort and a comparable incidence in the 0.48 mg/kg and 0.66 mg/kg groups (33 and 35 % respectively). They also appeared transient in this study with lower incidence at 12 months relative to 6 months treatment (5/42 and 10/42 respectively). A comparison of ADA positive and negative groups in terms of PD response (IGF-1 SDS) and efficacy in terms of annualised HV or change in height SDS did not indicate a relevant effect of ADAs.

Higher incidence of ADAs was reported in paediatric relative to adult studies, with the majority of subjects (84 of 109; ≈77 %) testing positive for ADAs over the course of the pivotal phase III study CP-4-006 with incidence in adult studies ≈8-11 %. It is noted that this represents a higher incidence than observed in the CP-4-004 PII DRF study, the cause of the apparent heterogeneity in the incidence of immunogenicity is not clear. In general, these ADAs were specific for hGH rather than CTP, and very few were reported as neutralising (3 positive NAb test results, among the 397 somatrogon samples assessed for neutralizing antibody activity which the applicant notes fell within the false positive range for the neutralizing assay. NAb in these subjects did not result in a significant effect of IGF-1 SDS nor mean height velocity. Again, a comparison ADA positive and negative groups in terms of PD response (IGF-1 SDS) and efficacy in terms of annualised HV or change in height SDS did not indicate a relevant effect of ADAs. ADAs were higher in the somatrogon treated group relative to somatropin (Genotropin) treated subjects (≈10% incidence).

ADA positive subjects appear to exhibit a higher incidence of injection site reactions. See Clinical Safety for further discussion.

The population PK analysis of Phase 3 paediatric data showed a proportional decrease of 25.8% in CL/F when subjects tested positive for ADA. The reduction in clearance can be explained because somatrogon is a protein with a small molecular weight (~30 kDa). As such, the ADA immune complexes are usually sustaining in nature due to neonatal Fc receptor (FcRn) mediated recycling, resulting in a reduction in clearance (*Wang et al. 2016*). The reduction in CL/F corresponded with an estimated 45% increase in the average somatrogon concentration at steady state, based on *post hoc* estimates.

The increased somatrogon concentrations due to development of ADA are not likely to be clinically significant as there were no dose related adverse reactions among the paediatric subjects enrolled in CP-4-004 and there was no apparent relationship between the average somatrogon concentration and height velocity after the first year of treatment in the same subjects.

Special populations

- ***Renal impairment***

Given that somatrogon is expected to be primarily degraded by proteolytic catabolism, the lack of specific studies in patients with renal impairment is considered acceptable. It is accepted that somatrogon is expected to have low renal clearance and it is acknowledged that there are no data on the use of somatrogon in paediatric patients with renal impairment. Therefore, it is not possible to determine whether or not a dose adjustment is necessary.

- ***Hepatic impairment***

Given that somatrogon is expected to be primarily degraded by proteolytic catabolism, the lack of specific studies in patients with hepatic impairment is considered acceptable. The applicant discussed that liver cirrhosis/hepatic impairment is not a relevant concomitant or secondary medical condition in the paediatric target population. As well, the degradation of somatrogon is expected to be similar to proteins via ubiquitous proteolytic catabolism. Therefore, no dedicated study to investigate PK in subjects with hepatic impairment was performed. This argumentation can be followed based on the intended indication in paediatrics only.

- ***Gender***

It is agreed that a dose adjustment based on gender is not warranted in pre-pubertal children with GHD.

- ***Race***

Based on the existing data, it is agreed that a dose adjustment based on race is not warranted in pre-pubertal children with GHD.

- ***Weight***

Body weight has a significant impact on somatrogon PK and the use of weight-based (mg/kg) dosing is endorsed for paediatric GHD patients.

In the population PK analysis PMAR-EQDD-C031c-DP3-853, simulations for a weekly dose of 0.66 mg/kg showed that children with lower BW had a higher exposure than children with higher body weight. Compared to a 15 kg child, the exposure ratio was 1.1 for a 10 kg patient and 0.7 for a 54 kg patient. This level of variability is considered acceptable.

- ***Age***

Somatrogon is indicated for the treatment of children with GHD. At the proposed dose of 0.66 mg/kg/week, the Cavg,ss for children in 6 to 12 years age group is predicted to be approximately 35% lower than children from <6 years, due to difference in body weight between the two groups. This variability in exposure is considered acceptable.

It is agreed that additional dosing adjustment for age is not required over the range of 3 to 10 years.

Interactions

The applicant has conducted an *in vitro* study, which aimed to assess the potential for somatrogon to act as an inducer of hepatic CYP1A2, CYP2B6, CYP3A4 mRNA. As well as standard positive controls, the induction potential of somatropin was also assessed. For CYP1A2, CYP2B6, the presented results suggest the risk of clinically relevant induction is low and no further *in vivo* characterisation is warranted. The results that are reported in the submitted study suggest that somatrogon is a weak inducer of CYP3A4 (> 2-fold ≈ 5-10 fold vehicle control expression). Although, as per the EMAs 'Guideline on the investigation of drug interactions' (CPMP/EWP/560/95/Rev. 1 Corr. 2**), this positive *in vitro* finding should be confirmed by an *invivo* study, it is considered that given this is a known class related effect, this was adequately addressed through inclusion of appropriate wording in section 4.5 of the SmPC.

The applicant has conducted an *in vitro* assessment of the potential for the CTP component of somatrogon to interact with commercial pregnancy tests leading to a potential false positive result or to interfere with hCG detection resulting in a possible false negative result. Somatrogon was spiked at a range of concentrations in serum and urine samples which were then used to assess the risk of positive test results in a blood pregnancy test and a number of commercially available urine pregnancy kits respectively. The potential for interference with hCG was also assessed. No false positive or false negative

results were recorded in the study. Although it is considered unlikely that unchanged somatrogon will be present in urine, no discussion has been provided on somatrogon metabolism or elimination and/or the potential effects of somatrogon subunits/metabolites which may be present in urine on urine pregnancy test efficacy. There is no expectation that smaller polypeptide portions of somatrogon would interfere with pregnancy tests and this is considered to be a theoretical risk only, which was accepted by the CHMP.

Pharmacodynamics

Primary pharmacology

Study CP-4-004

In this phase 2 study, the PD parameters of somatrogon and somatropin were evaluated in 42 and 11 paediatric subjects with GHD naïve to treatment with rhGH, respectively. IGF-1 and IGFBP-3 increased dose dependently following weekly somatrogon administration. Mean peak IGF-1 concentrations were observed at 48 hours following SC administration of somatrogon, which is consistent with other studies.

The IGF-1 profiles of subjects who received weekly somatrogon (0.48 and 0.66 mg/kg/week) were reasonably comparable to that of subjects who received daily somatropin (Genotropin 0.034 mg/kg/day). Considering that patients did not receive a weight-based dose adjustment between weeks 26 - 52, the median IGF-1 levels did not point to obvious differences between PD responses of the 0.48 and the 0.66 mg/kg/week doses (neither did the IGF-1 SDS levels) over one year of treatment. It was noted that the decision of recommending 0.66 mg/kg/wk for the phase III study was not solely based on the results gained from the phase II PK and PD results but also on the observed efficacy and safety.

The somatrogon dose of 0.25 mg/kg/week failed to maintain normal IGF-1 serum levels throughout the week, indicating that IGF-1 levels will be at the lower part of the normal range or even below it with the use of this dose on a weekly basis.

During the OLE portion, IGF-1 levels continuously increased, with significant increases in year 4 in some patients. It is noted that in year 4 all patients were switched to the pen formulation. A broad range of individual IGF-1 levels was seen which could probably be due to high titers of developed ADAs in certain patients. As normal IGF-1 levels in adolescents are usually substantially higher than in younger children, it is supportive that the relevant measure of IGF-1 SDS level was overall shown to be maintainable below the upper limit of +2 SDS over time with the proposed dose. Considering this, it is probably not the pen formulation that resulted in increased levels.

Study CP-4-006

In this phase 3 study, the PD parameters of somatrogon and somatropin (Genotropin 0.034 mg/kg/day) were evaluated in 109 and 115 paediatric subjects with GHD, respectively. Consistent with study CP-4-004, mean IGF-1 SDS values were higher in the somatrogon group than those in the somatropin group. Mean IGF-SDS levels in the somatrogon group also increased gradually over time. At the proposed somatrogon dose of 0.66 mg/kg/week, subjects transitioned from negative IGF-1 SDS values to positive IGF-1 SDS during the 12-month treatment period. IGF-1 SDS values in the somatropin group) approached 0 across the post-baseline visits. IGFBP-3 SDS values remained near 0 SDS for both treatment groups.

Secondary pharmacology

No clinical secondary pharmacology studies were conducted. This is acceptable since the secondary PD effects of rhGH are well known.

Pharmacodynamic interactions

It is acceptable that no PD interaction studies were conducted. PD interactions with regard to corticoids and insulin were expected as known from marketed daily GH products.

Genetic differences in PD response

It is not to be expected that genetic differences modulate the pharmacodynamic response in children with growth hormone deficiency.

Population PK/PD analyses based on the Phase 2 study CP-4-004

Two population PK/PD analyses were performed using data from paediatric GHD subjects enrolled in the Phase 2 study CP-4-004.

In the first analysis, the indirect-response PD model previously developed by *Sun et al.* was used to link somatrogon concentrations to IGF-1 production.

The final paediatric model appeared to fit the paediatric data, although the VPCs were difficult to interpret. The PK/PD parameters support the positive effect of somatrogon on IGF-1 levels. Baseline IGF-1 was observed to increase with age, which is a known physiologic change.

In a supplemental analysis, peak IGF-1 SDS over the dosing interval was well predicted by values obtained on Day 2 post dose, while the mean IGF-1 SDS over the dosing interval was well predicted by values obtained on Day 4 post dose. This is consistent with other analyses.

In the second study, the IGF-1 concentration data following administration of somatrogon was adequately characterized by an indirect response model, in which the production rate of IGF-1 was stimulated by somatrogon. The diagnostic plots and VPCs for the final model indicate that the model describes the data reasonably well. The results demonstrate the positive effect of somatrogon on IGF-1 levels. Baseline IGF-1 was observed to vary with time since study start, which is consistent with other analyses. Baseline IGF-1 also varied with height. It was considered that the positive correlation between height and IGF-1 at baseline may be due to the fact that patients having higher IGF-1 concentrations before treatment started had grown more up to that point in time.

Based on simulations, the majority of paediatric GHD patients are predicted to remain within the clinical target range of -2 to +2 at trough IGF-1 SDS, peak IGF-1 SDS and 4 days post dose after 4 years of somatrogon administration. Given that IGF-1 SDS on Day 4 post dose approximates average values over the dosing interval, the findings provide support for the proposed somatrogon dose of 0.66 mg/kg/wk for the treatment of GHD in children.

Efforts to link somatrogon concentrations with height velocity were unsuccessful. This is consistent with the primary efficacy endpoint analysis result for the main study of Study CP-4-004.

Population PK/PD analysis based on the Phase 3 study CP-4-006

Consistent with previous analyses, an indirect-response Emax model fitted the IGF-1 data well and the PK/PD parameters supported the positive effect of somatrogon on IGF-1 levels.

Also consistent with previous analyses, the EC50 was 56.6 ng/mL, which is considerably lower than the popPK-modelled Cmax of 690 ng/mL in GHD children administered 0.66 mg/kg/wk (and provides support for the efficacy of the proposed dose in GHD children.

Mean and median of modelled mean IGF-1 values increased over time during the treatment period, which emphasises the need for IGF-1 monitoring and dose adjustment of somatrogon if needed.

The supplemental PD analyses confirmed that the most representative time to assess the mean IGF-1 SDS value over the weekly dosing interval was 96 hours after dosing. IGF-1 samples obtained early

(<72 hours) in the dosing interval may overestimate the mean IGF-1 SDS. This is consistent with the previous analysis of IGF-1 values from study CP-4-004. As such, when the goal of monitoring clinical therapy is to estimate mean IGF-1 SDS value during the dosing interval, clinical samples should be obtained close to 96 hours post-dose.

In view of a lower frequency of expected safety concerns compared to daily rGH, no specific safety exposure-response analyses were performed. For the patients that suffered from most severe injection site pain no consistent pattern for ADAs or the somatrogon AUC could be established. This is acceptable.

2.6.4. Conclusions on clinical pharmacology

The CHMP concluded that the pharmacology of somatrogon has been investigated to a satisfactory extent.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Study CP-4-004

This was a safety and dose finding study of different somatrogon (MOD-4023) dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children.

Aspects of this study have already been described in the clinical pharmacology section of this report.

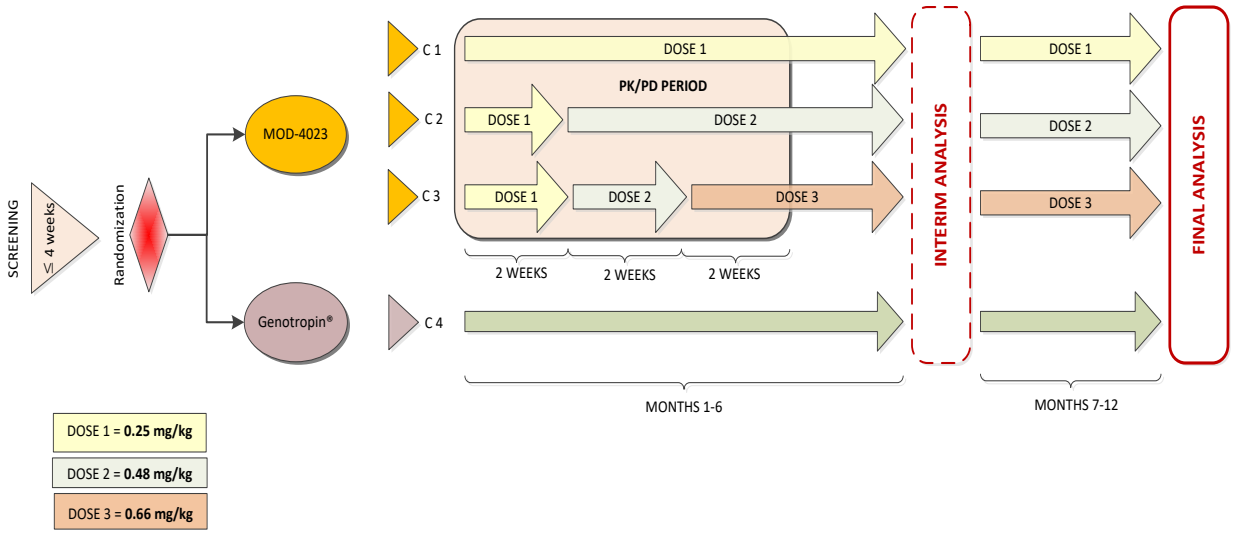
Study design

Eligible patients were to undergo the following treatment schedule consisting of a Screening Period lasting up to six weeks and two Treatment Periods (Treatment Periods I and II), which comprise the Main Study.

a. Period I: open-label six months repeated dosing including PK/PD sampling.

b. Period II: an additional open-label six months continuous repeated dosing.

Figure 8 Main study design (periods I and II)



In treatment Period I, eligible patients were to be randomised in a 1:1:1:1 ratio to one of three somatrogon cohorts, or to a somatropin cohort.

During the Period II of a six months, open-label, continuous dosing period, additional efficacy and safety data were to be collected. Patients were to be kept on the originally allocated dose levels/dose.

Period III and Period IV

Patients who completed Periods I and II in the Main Study were eligible to continue into an ongoing, open-label extension (OLE) period (Period III) for 12 months after completion of the Main Study and could also continue into a long-term OLE period (Period IV) after completing 12 months in Period III. The design of the Period IV OLE trial is described later in this report.

Study participants

Patients were to meet all inclusion criteria and not meet any exclusion criteria to participate in this study. Inclusion and exclusion criteria were similar to other studies in the development programme.

Treatments

Patients were to administer a weekly dose of one of the three different dose strengths of somatrogon based on equal molar conversion of the weekly cumulative somatropin dose.

Objectives

The primary objective of the study was:

1. To compare the safety, efficacy and tolerability of three somatrogon doses to that of a commercially available standard daily somatropin formulation (Genotropin), in pre-pubertal children with growth failure due to insufficient secretion of endogenous GH.

The secondary objectives were:

1. To evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of three different doses of somatrogon in pre-pubertal GHD children.
2. To select the optimal dose of somatrogon for the subsequent Phase 3 study on the basis of safety and efficacy.

Efficacy Evaluations

Primary Efficacy endpoint

- Annualized HV at 12 months expressed in cm/year

Secondary efficacy endpoints

- HV at six months
- Change in HTSDS (ΔHTSDS) at six months (from Screening)
- ΔHTSDS at 12 months (from Screening)

Sample Size

A sample size of up to 14 patients per cohort was chosen for this pilot investigation, to obtain up to 10 patients per cohort having ppGH stimulation test levels ≤ 7 ng/ml and up to four patients per cohort with ppGH levels > 7 and ≤ 10 ng/ml. The justifications for this sample size are based on feasibility, precision about the mean and variance, and regulatory considerations as previously described in the literature.

Randomisation and blinding

This was an open-label study. Due to different dose frequencies and dosing techniques, it was not practical to employ any blinding methods. A double-blind double-dummy design in this indication was deemed to be unethical. The sponsor was not blinded to the data at any time.

Statistical methods

Descriptive statistics, namely sample size (n), mean, SD, lower quartile, median, upper quartile, and range for the continuous variables and counts and percentages for the categorical variables, were to be computed. Statistical summaries were to be reported by cohort.

Results

Disposition of Patients

A total of 56 patients from 14 centres in seven countries were randomised in the study. Three patients were randomised and withdrew consent prior to receiving any study medication. Fifty-three patients (17 female and 36 male) were enrolled and received study investigational medication or somatropin (Genotropin). No patients were removed or withdrew from participation prematurely post dosing. The treatment groups were similar in their baseline characteristics.

Summary of main efficacy results

Primary Endpoint

The primary efficacy endpoint for the main study was the annual HV at 12 months. A summary of HV data at 12 months is presented below.

At the 12 month visit, mean HV in the FAS population for the MOD-4023 cohorts were 10.4 (95% CI: 8.9, 12.0), 11.0 (95% CI: 9.7, 12.2), and 11.4 (95% CI: 9.2, 13.7) cm/year in Cohorts 1, 2, and 3, respectively. The mean HV for the Genotropin group was 12.5 cm/year (95% CI: 11.0-13.9 cm/year). HV does not appear to differ substantially across MOD-4023 dose levels. Growth did however appear to increase with the dose level. The 95% CI for each of the MOD-4023 cohorts overlap with the CI for

Genotropin, with the highest MOD-4023 dose group (Cohort 3, 0.66 mg/kg/week) having the closest mean value. Results for the PP population differ only for Cohort 3, the assigned cohort for patient 08003 who was determined to be ineligible following study completion. Mean HV is higher with the exclusion of this patient (11.9 cm/year; 95% CI 9.8-14.1).

Secondary Endpoints

Height Velocity (cm/year) at 6 months

The mean HV at six months for the Genotropin cohort was 15.0 (95% CI: 13.1, 16.9). Results in the MOD-4023 cohorts at six months were 11.8 (95% CI: 9.6, 13.9), 12.5 (95% CI: 11.1, 13.8), and 13.0 (95% CI: 9.9, 16.0) for Cohorts 1-3, respectively. The 95% CI for all MOD-4023 cohorts overlaps the Genotropin CI. Additionally, data from the MOD-4023 cohorts are further suggestive of a dose response trend.

Change in HTSDS at Six and 12 Months

Mean change in HTSDS improved from six months to 12 months in all cohorts. In the FAS Population, at 12 months, the mean change in HTSDS for the Genotropin cohort was 1.51 (range 0.82, 2.38). Mean HTSDS change at the 12 Month time point for the MOD-4023 cohorts was 1.09 (range 0.32, 2.15), 1.19 (range 0.28, 2.05), and 1.35 (range 0.06, 2.47) for Cohorts 1, 2 and 3, respectively.

Table 7 HTSDS – Change from screening to six months (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	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)

Source: Table 14.2.2.2.1

**Cohort 3 lower level of height range attributable to Patient 08003, who was wrongly included in the study. The patient diagnosed with psychosocial dwarfism (exclusionary condition) following study completion.*

Table 8 HTSDS – Change from screening to 12 months (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	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 Table 14.2.2.3.1 *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.				

Conclusion

The primary efficacy endpoint of this study was the annual HV at 12 months.

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

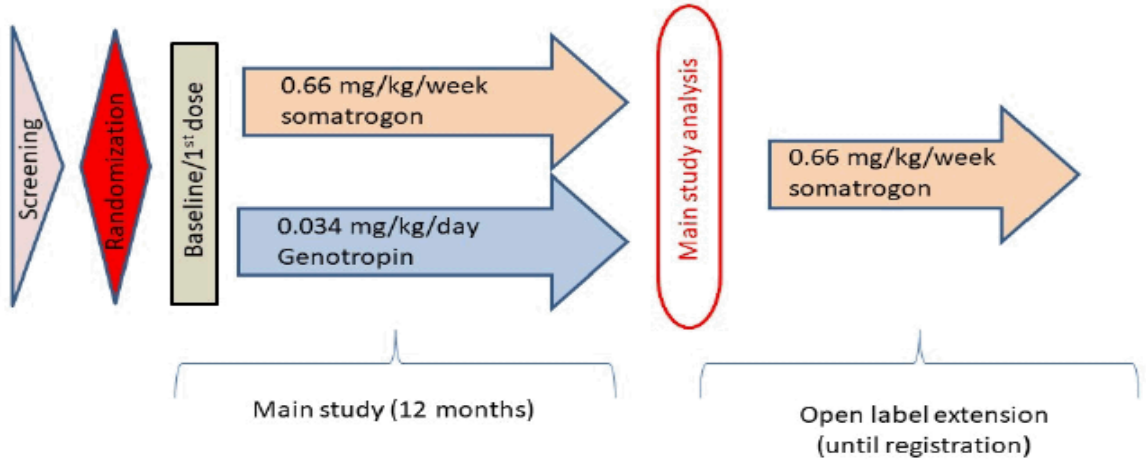
These results were confirmed in the sensitivity analyses and were also reflected in the results of the secondary efficacy outcomes, as described above.

Based on the results of this study, the decision was made to use the 0.66mg/kg/day dose.

2.6.5.2. Main study(ies)

Study CP-4-006

This was a phase 3, open-label, randomised, multicentre, 12 months, efficacy and safety study of weekly MOD-4023 compared to daily Genotropin therapy in pre-pubertal children with growth hormone deficiency.



Methods

- **Study Participants**

Patients enrolled were pre-pubertal children aged ≥3 years old and <11 years for girls or <12 years for boys with either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiencies. They were also treatment naïve.

The diagnosis of GHD was confirmed by two different growth hormone stimulation tests, defined as a peak GH level of ≤10 ng/mL, determined with a validated assay.

Additional criteria for enrolment were IGF-I SDS ≤–1.0, and delayed bone age (BA) was not older than chronological age (CA) and < 10 for females and < 11 for males. Annualized HV below the 25th percentile for CA (HV < -0.7 SDS) and gender was assessed according to the OPKO HV (Tanner, Prader and Hermanussen). Subjects born small for gestational age, with idiopathic short stature, or with other causes of short stature were excluded.

During the screening phase, patients had a head Magnetic resonance imaging (MRI) with contrast if possible after two GH stimulation tests, to ensure the inclusion/exclusion criteria were met and to determine the underlying GH cause.

- **Treatments**

Somatrogon and somatropin were both administered SC. Somatrogon was given in the morning hours once weekly, using the delivery device (pen), somatropin was given in the evening/bedtime hours once daily, using the delivery device (Genotropin pen). Both treatments were administered into the upper arms, buttocks, thighs, or abdomen (8 locations used, and these were rotated). The doses of somatrogon and somatropin were assessed every 3 months based on patient's body weight. Doses were determined by the IRT system and included an automatic rounding – either up or down. Doses could be decreased for safety reasons according to the pre-defined dose-adjustment criteria (based on the severity of AEs or repeated, elevated levels of IGF-1 SDS).

- **Objectives**

The primary objective was to demonstrate that weekly MOD-4023 administration is non-inferior to daily Genotropin administration at 52 weeks.

Secondary efficacy objectives were:

- To evaluate the safety and tolerability of weekly MOD-4023 administration.

To demonstrate successful operation (single injection) of the MOD-4023 single patient use, multi-dose, disposable pre-filled pen (PEN).

- Evaluation of participant and observer feedback on MOD-4023 device usability.
- To confirm the correct operation of devices returned for evaluation.

Objective of the open-label extension (LT-OLE):

To demonstrate long-term safety and efficacy of MOD-4023 in an OLE.

Other objectives:

To evaluate the effect of weekly MOD-4023 and daily somatropin (Genotropin) administration on QoL, as measured by the QoLISSY in a specific number of countries (determined by availability of validated translated tools) during the first 12 months of treatment.

- **Outcomes/endpoints**

Primary Efficacy Endpoint:

The primary efficacy endpoint during the main study is the Annual HV in cm/year after 12 months of treatment.

HV (cm/year) at Visit 8 (12 months) = (Ht at Visit 8 — Ht at Visit 2)/((Date of Visit 8 — Date of Visit 2)/365.25);

where Visit 2 is the Baseline visit.

(Note: HV at any other post-baseline *Visit xx* is also computed using formula above by replacing *Visit 8* with *Visit xx*).

The aim of the study was to demonstrate that in terms of the primary efficacy endpoint, Annual Height Velocity at 12 months, weekly somatrogon is non-inferior to daily somatropin by a non-inferiority margin of 1.8 cm/year.

Secondary Efficacy Endpoints (Auxology/Clinical):

- Annualized HV after 6 months of treatment;
- Change in Ht SDS at 6 and 12 months, compared to Baseline;
- Change in bone maturation (BM) at the end of 12 months, compared to Screening bone age (BM calculated as BA/CA).

Biochemical Endpoints:

- Absolute IGF-1 and IGF-1 SDS levels on day 4(-1) after MOD-4023 dosing across study visits;
- IGFBP-3 and IGFBP-3 SDS levels at on day 4(-1) after MOD-4023 dosing across study visits.

Safety endpoints: included adverse events, serious adverse events, incidence of anti-somatrogon antibodies. Biochemistry, lipids, thyroid function, fundoscopy, ECG.

During the LTE study the main endpoints were:

Auxology/Clinical Endpoints:

Annual HV in cm/year at each 12-month interval.

- Change in height SDS every 12 months (compared to the previous values).
- Change in bone maturation (BM) every 12 months, (compared to Week 52 BA)

  (calculated as BA/CA) at completion of LT-OLE year 1 and to previous values from LT-OLE year 2 onwards).

Biochemical Endpoints**:**

- IGF-1 and IGF-1 SDS levels on day 4 (-1) after MOD-4023 dosing across study visits.
- IGFBP-3 levels and IGFBP-3 SDS on day 4 (-1) after MOD-4023 dosing across study visits.

- **Sample size**

The non-inferiority (NI) margin for annual HV for was set at -1.8 cm/yr and detailed in the End of Phase 2 (Type B). This NI was based on the following considerations:

From historical data, HV response for the first year of daily GH ranged from 10.2 cm/yr, SD= 2.5 (*Wilton and Gunnarsson, 1988*) to 11.4 cm/yr, SD=2.5 (*MacGillivray et al., 1996*). Using the standard deviation (SD) of 2.5 from these references, a non-inferiority NI margin of -1.8 cm/yr 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/yr in the first year, a margin of -1.8 cm/yr would show that 84% of the growth rate from the reference daily GH treatment effect on the approved active control is retained.

The use of -1.8 cm/yr is the more conservative value based on the precedent set with these other studies.

The following assumptions were made in the sample size calculation:

- 2-sided alpha of 0.05. 80 % power.
- Between-patient SD of annual growth rate is 2.5 cm/year in all treatment groups.
- Non-inferiority margin is -1.8 cm/year.
- The true mean treatment difference (MOD-4023 – Genotropin) is -0.8 cm/year.

With these assumptions, 100 patients per group will provide 80 % power for the non-inferiority test. To allow for an approximate 10 % dropout rate, 110 patients were randomised to each treatment group (Total N=220 patients).

- **Randomisation and Blinding (masking)**

Randomisation:

Eligible patients were randomly assigned in a 1:1 ratio (centralized randomization for each region as defined in the stratification factors) to 1 of 2 treatment groups, MOD-4023 or somatropin (Genotropin) reference therapy) for 12 months.

Patients were stratified based on:

- Peak GH levels (≤3 ng/mL; >3 to ≤7 ng/mL; and >7 to ≤10a ng/mL)

- CA (≥3 years to ≤ 7 years, 0 days; and > 7 years, 0 days.)
- Regions: 1. Western Europe, Israel, Australia, New Zealand, Canada and USA; 2. Central and Eastern Europe, Greece, Turkey, Latin America and Asia except for India and Vietnam; 3. India and Vietnam

Blinding

Due to different administration frequencies for the treatment arms (somatrogon was administered once-weekly versus somatropin administered daily), the study was conducted in an open-label.

The applicant had a detailed blinding and unblinding plan in place.

- **Statistical methods**

Analysis of primary endpoint

The primary endpoint, annualized height velocity at week 52, was compared between somatrogon and daily somatropin by a non-inferiority comparison with a non-inferiority margin of 1.8 cm/year.

For the primary and secondary endpoint analyses performed by ANCOVA, multiple imputation assuming missing not at random using SAS PROC MI was used to impute missing results.

The imputation was by treatment group. The imputation model included the randomization stratification factors and baseline height standard deviation score (SDS). For the primary endpoint, annual HV, the imputed value in the somatrogon group was reduced by 1.8 cm/yr, the non-inferiority margin to avoid imputing to the common mean (*Koch 2008*).

Non-inferiority was concluded if the lower bound of the two-sided 95% CI for the mean treatment difference "somatrogon – somatropin", in the primary efficacy endpoint was ≥-1.8 cm/year.

The CI for the difference of means between the two treatments was derived from an ANCOVA. The ANCOVA model included classification terms for treatment, age group, gender, peak GH levels, and region. The model also included baseline height SDS as a covariate. The determination of non-inferiority was based on least squares means for the two treatments from the ANCOVA and the 95% CI of the differences between the treatments.

Descriptive statistics were reported for observed and change from baseline annual HV values at 12 months.

Once the primary endpoint of non-inferiority of somatrogon in comparison to Genotropin was met, an assessment of superiority of somatrogon over Genotropin at 12 months was performed. Superiority was achieved if the lower bound of the two-sided 95% CI for the mean HV difference of somatrogon – somatropin was ≥ 0 cm/year.

Secondary Efficacy Analyses:

A similar ANCOVA model as used for the primary endpoint was used to analyse:

- annualized HV at 6 months
- change in height SDS at 6 months
- change in height SDS at 12 months

Least square mean estimates for the two treatments and the 95% CI of the difference between the treatments were presented.

Descriptive statistics were reported for each of these endpoints.

Sensitivity analyses were conducted to test the robustness of the result using a tipping point approach with the Full Analysis Set. Specifically, a shift parameter was used to incrementally adjust the imputed values in the somatrogon arm.

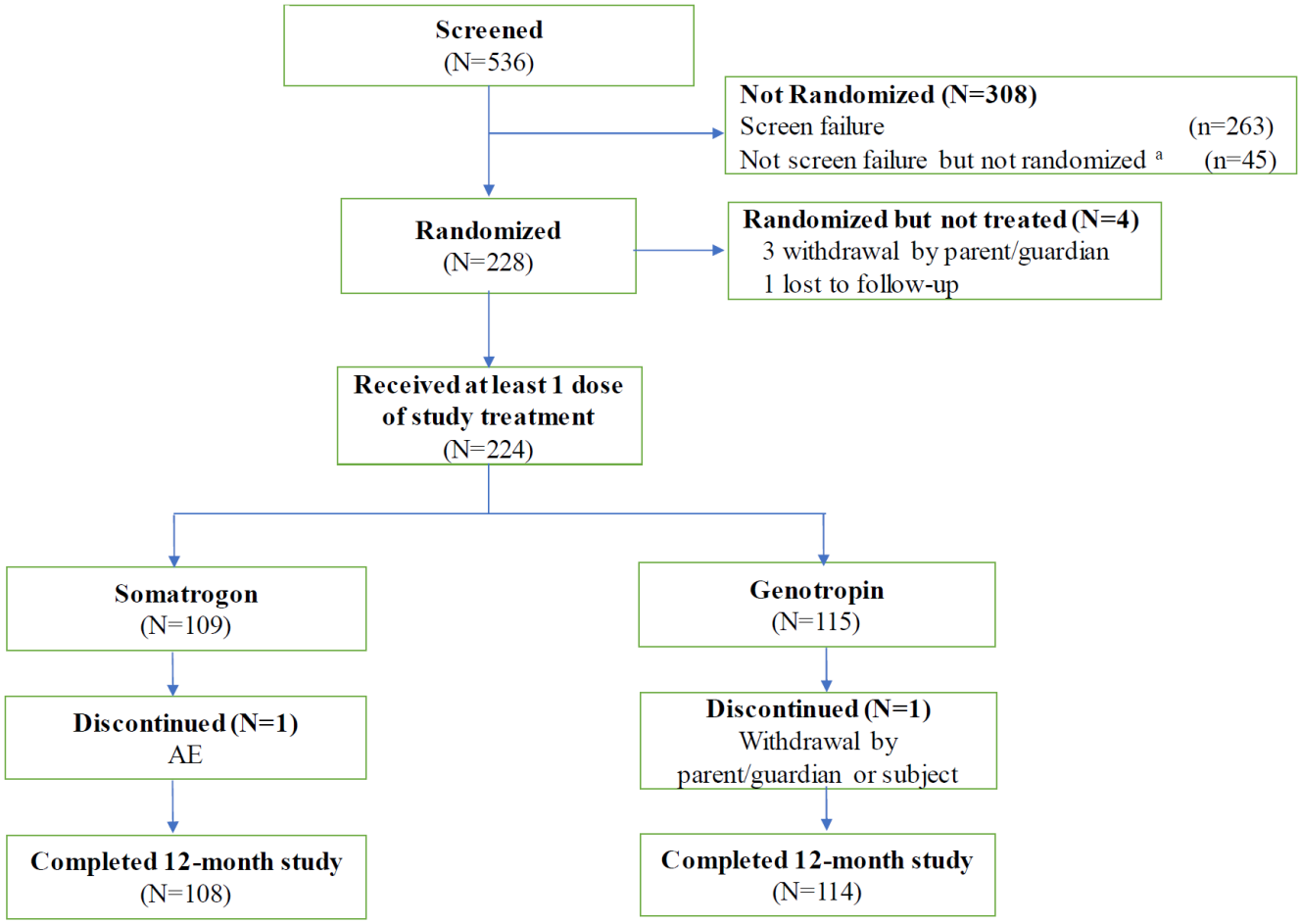
Values were to be shifted downwards in increments of 0.1 cm/year until the analysis no longer supported comparability.

Results

- **Participant flow**

536 patients were screened, 308 were not randomised (263 screen failures). 228 Patients were randomised, 4 were not treated (3 withdrawn, 1 lost to follow up). 224 patients received 1 dose. 109 received somatrogon, 115 somatropin; 1 patient from each withdrew, leaving 108 and 114 completing the study respectively.

Figure 9 Subject evaluation groups and disposition



These additional 45 subjects were in screening when the enrolment target was met and were not randomized to study treatment.
Reference: Tables 14.1.1.1, 14.1.1.2, and 16.2.1.3

- **Recruitment**

The study was initiated in April 2017. First Subject First Visit date was 19 April 2017. The study Completion Date, as per Last Subject Last Visit: 23 August 2019.

- **Conduct of the study**

There were a few protocol amendments that were submitted to regulatory authorities. Some country-specific amendments were developed in response to requests by a specific Health Authority.

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all ICH GCP Guidelines. In addition, all local regulatory requirements were followed.

All analyses were carried out as detailed in the final SAP (Version 4.0, 14 June 2019), with some exceptions, which were justified.

Minor protocol deviations were recorded for a few subjects for the LT-OLE laboratory data. The OLE laboratory data were excluded from the main study laboratory data and the main study laboratory data for the 12-month visit were used for analyses.

- **Baseline data**

Baseline demographic and other characteristics were balanced across both treatment groups.

The mean age was 7.72 years, 40.2 % were aged between 3 and 7 years, with 59.8% older than 7 years of age. 71.9% were males and 28.1 % females.

The majority of patients were Caucasian 71.9% followed by Asians which accounted for 20.1% with very small percentages from other races.

At baseline height cm was similar between both cohorts 109.8 cm for somatrogon, and 110.5 cm for somatropin.

Peak GH level per group (≤3 ng/mL; >3 to ≤7 ng/mL; and >7 to ≤10a ng/mL) were similar.

Bone age mean (SD) was 5.46 in somatrogon and 5.19 in somatropin, bone maturation mean (ratio of BA to CA) (SD) was 0.68 in somatrogon and 0.65 in somatropin. Height (SDS) mean (SD) was -2.94 in somatrogon and -2.78 in somatropin.

Table 9 Somatrogon protocol CP-4-006 (C0311009) demographic characteristics safety analysis set

	Somatrogon (N=109)	Somatropin (N=115)	Total (N=224)
Age (Years):			
N	109	115	224
Mean (SD)	7.83 (2.66)	7.61 (2.37)	7.72 (2.51)
Median	7.92	7.84	7.87
Range (min,max)	(3.01, 11.96)	(3.05, 11.85)	(3.01, 11.96)
>3 years to =<7	43 (39.4)	47 (40.9)	90 (40.2)
>7 years	66 (60.6)	68 (59.1)	134 (59.8)
Sex			
Male			161 (71.9)

Female	82 (75.2)	79 (68.7)	63 (28.1)
Race			
White	81 (74.3)	86 (74.8)	167 (74.6)
Black or African American	0	2 (1.7)	2 (0.9)
Asian	24 (22.0)	21 (18.3)	45 (20.1)
American Indian or Alaska Native	1 (0.9)	0	1 (0.4)
Native Hawaiian or Other Pacific Islander	0	1 (0.9)	1 (0.4)
Other	3 (2.8)	5 (4.3)	8 (3.6)
Unknown	0	0	0
MULTIRACIAL	0	0	0
Not reported	0	0	0
Ethnicity			
Hispanic or Latino	11 (10.1)	13 (11.3)	24 (10.7)
Not Hispanic or Latino	98 (89.9)	102 (88.7)	200 (89.3)
Height (cm)			
N	109	115	224
Mean (SD)	110.0 (15.33)	109.9 (13.90)	109.9 (14.58)
Median	109.8	110.5	110.3
Range (min,max)	(75.10, 139.6)	(77.10, 144.3)	(75.10, 144.3)
Weight (kg)			
N	109	115	224
Mean (SD)	19.70 (7.12)	19.16 (5.66)	19.42 (6.40)
Median	19.30	18.10	18.60
Range (min,max)	(8.00, 46.10)	(8.30, 42.80)	(8.00, 46.10)
BMI (kg/m**2)			
N	109	115	224
Mean (SD)	15.76 (2.22)	15.56 (1.69)	15.66 (1.97)
Median	15.18	15.22	15.20
Range (min,max)	(12.29, 26.44)	(12.47, 22.17)	(12.29, 26.44)

Percentages are based on the number of subjects in the treatment group. Data are n (%) unless otherwise indicated.
The denominator to calculate subjects aged 7 years and 0 days is stratified into the >=3 years
Source Data: Table 16.2.4.1.1

- **Numbers analysed**

A total of 228 subjects were randomised at 84 sites. Of the 228 subjects who were randomised, 4 subjects (3 in the somatrogon group; 1 in the somatropin group) did not receive study drug (3 withdrawn by parent/guardian, 1 lost to follow up during the screening phase). The number of subjects who completed the 12-month main study and entered the OLE study was balanced across both treatment groups.

Table 10 Somatrogon protocol CP-4-006 (C0311009) disposition events summary safety analysis set

Number (%) of Subjects	Somatrogon (N=109) n (%)	Somatropin (N=115) n (%)	Total (N=224 n (%)
Discontinued	1 (0.9)	1 (0.9)	2 (0.9)
Adverse Event	1 (0.9)	0	1 (0.4)
Death	0	0	0
Lost to Follow-Up	0	0	0
Withdrawal by Parent/Guardian or Subject	0	1 (0.9)	1 (0.4)
Other, specify	0	0	0
Completed, rolled over to Open Label Extension (OLE)	104 (95.4)	108 (93.9)	212 (94.6)
Completed, not rolled over to OLE	4 (3.7)	6 (5.2)	10 (4.5)

Source Data: Table 16.2.1.3

212 of the 222 subjects who completed the main study entered the OLE period. As of the data cut-off date (01 November 2019), 205 subjects were continuing somatrogon treatment. Of the 7 subjects who discontinued from the OLE period, 5 discontinued due to AEs and 2 due to withdrawal by the parent/guardian or subject.

Table 11 Somatrogon protocol CP-4-006 (C0311009) - OLE disposition events summary safety analysis set

Number (%) of Subjects	Originally Randomized to Somatrogon (N=104) n (%)	Originally Randomized to Somatropin (N=108) n (%)	Total (N=212) n (%)
Discontinued	2 (1.9)	3 (2.8)	5 (2.4)
Adverse Event	0	3 (2.8)	3 (1.4)
Death	0	0	0
Lost to Follow-Up	0	0	0
Withdrawal by Parent/Guardian or Subject	2 (1.9)	0	2 (0.9)
Other, specify	0	0	0

Source Data: Table 16.2.1.3.1 Output File

- **Outcomes and estimation**

Primary Endpoint: Annual HV at 12 Months

A somatrogon dose of 0.66 mg/kg administered once weekly was non-inferior to somatropin administered once daily with respect to annual HV at 12 months.

Table 12 Somatrogon protocol CP-4-006 (C0311009) – summary of efficacy outcome - Annual HV at 12 Months (ANCOVA model using multiple imputation with MNAR/FCS Method) full analysis set

End Point Analysis Method Statistics	Somatrogon (N=109)	Somatropin (N=115)	Treatment Mean Difference
Annual Height Velocity at 12 Months (cm/year)			
ANCOVA [a]			
LS Means Estimate [b]	10.10	9.78	0.33
95% CI [c]			-0.24 ,0.89
Observed			
N	108	113	
Mean (SD)	10.18 (2.42)	9.68 (2.46)	
Median	9.66	9.21	
Range (min, max)	4.57, 17.80	4.90, 17.60	

[a] Results based on an analysis of covariance (ANCOVA) model with classification terms for treatment, age group, gender, peak GH levels, and region. Baseline height SDS included as a covariate.
Missing data is imputed by multiple imputation using SAS PROC MI with MNAR/FCS Method.
The delta-adjusted pattern imputation is applied: the imputed value in the somatrogon group will be reduced by 1.8 cm/yr. [b] The treatment mean difference will be calculated as Somatrogon – Somatropin.
[c] Non-inferiority will be concluded if the lower bound of the two-sided 95% CI is >= -1.8.
Source Data: 16.2.6.3.1

The results of the additional sensitivity analyses of annual HV at 12 months (MNAR using FCS option in PPS, MNAR using Monotone option in FAS and PPS, observed data in FAS, and LHCF approach in FAS populations) were generally consistent with the primary analysis outcome.

Secondary Endpoints

Change in HT SDS from Baseline at 12 Months

The change in HT SDS from baseline improved at each visit and was comparable between the somatrogon and somatropin groups at Month 12.

Table 13 Somatrogon protocol CP-4-006 (C0311009) – summary of efficacy outcome - Change in Height SDS at 12 Months (ANCOVA model using multiple imputation with FCS Method) full analysis set

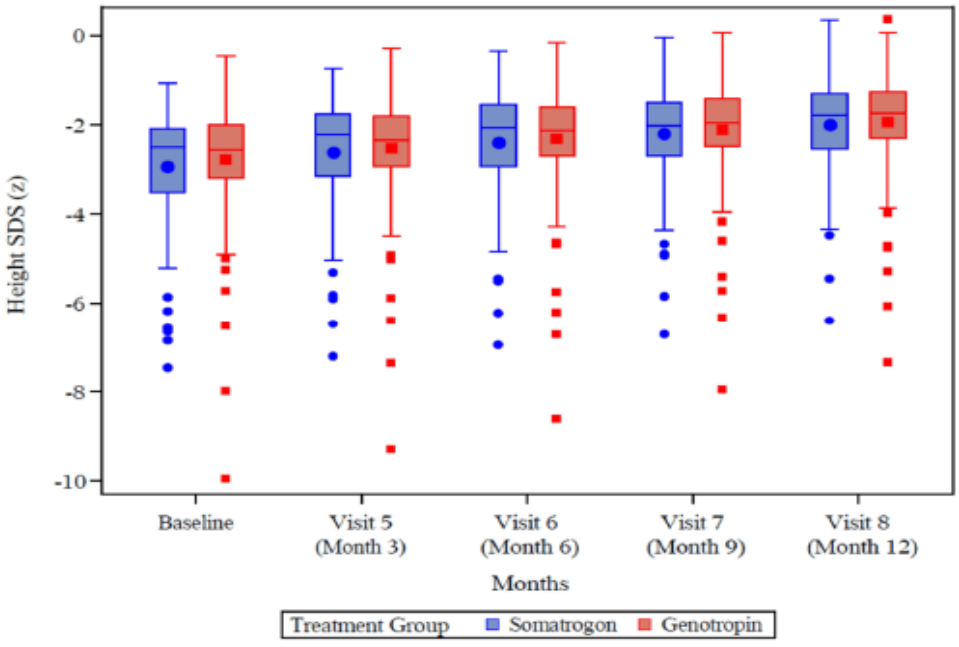
End Point Analysis Method Statistics	Somatrogon (N=109)	Somatropin (N=115)	Treatment Mean Difference
Change in Height SDS at 12 Months			
ANCOVA [a]			
LS Means Estimate [b]	0.92	0.87	0.05

95% CI		-0.06 ,0.16
Observed Change		
N	108	113
Mean (SD)	0.93 (0.55)	0.84 (0.51)
Median	0.81	0.73
Range (min, max)	0.15, 3.92	0.03, 2.60

[a] Results based on an analysis of covariance (ANCOVA) model with classification terms for treatment, age group, gender, peak GH levels,
and region. Baseline height SDS included as a covariate.
Missing data is imputed by multiple imputation using SAS PROC MI with FCS Method. [b]
The treatment mean difference will be calculated as Somatrogon - Somatropin.
Source Data: 16.2.6.3.1

CP-4-006 HT SDS Over 12 Months, FAS Population

Figure 10 CP-4-006, HT SDS through 12 Months, FAS population



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

Note: The closed circles inside boxes are means, lines inside boxes are medians. The ends of each box represent lower and upper quartiles, and bars at the ends of the whiskers represent lower and upper extremes. The individual data points outside the boxes are outliers. Baseline is defined as the last non-missing measurement prior to the start of study drug. Source: Module 5.3.5.1 CP-4-006 CSR Figure 14.2.6 (reference: Table 14.2.4.1)

IGF-1 SDS

IGF-1 SDS values approached 0 at 1-month post-baseline in the somatrogon group and remained in the target range up to 12 months, whereas in the somatropin group, IGF-1 SDS values remained near 0 at all post-baseline visits.

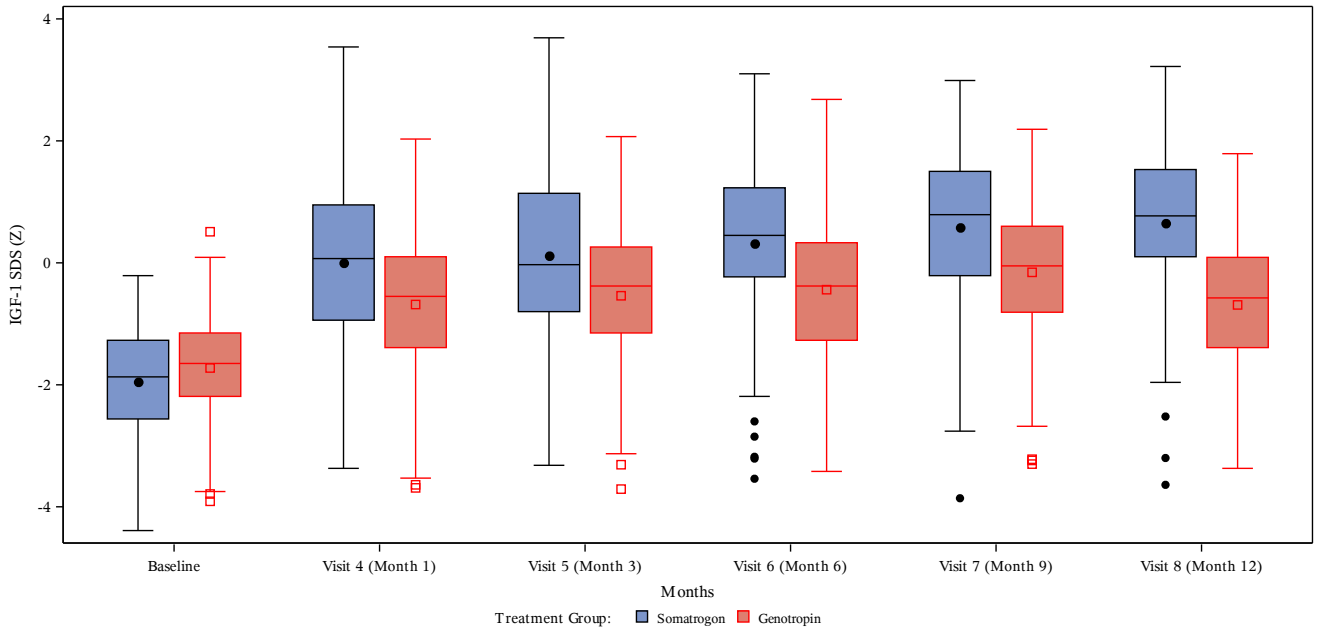
Serum IGF-1 concentrations were to have been measured on Day 3 or 4 post-dose, as this was determined to represent the best estimate of the mean IGF-1 SDS over the dosing interval.

Throughout the study, however, samples were obtained at variable timepoints post-dose, including some on Day 2 or 3 post-dose and other samples obtained on Day 5 or 6 post-dose. In order to be able to interpret the IGF-1 results, a *post-hoc* modelling analysis was performed in order to allow for the estimation of the mean IGF-1 SDS value over the dosing interval.

Consequently, results for IGF-1 and IGF- 1 SDS values are presented as both the raw study data (below), and modelled IGF-1 SDS values were presented.

Mean IGF-1 SDS values in the somatrogon group approached 0 as early as 1-month post-baseline and remained above 0 up to 12 months. Mean IGF-1 SDS values in the somatropin group remained near 0 SDS at all post-baseline visits, ranging from -0.69 SDS to -0.16 SDS.

Figure 11 CP-4-006, IGF-1 SDS through 12 Months, FAS population



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

Note: The closed circles inside boxes are means, lines inside boxes are medians. The ends of each box represent lower and upper quartiles, and bars at the ends of the whiskers represent lower and upper extremes. The individual data points outside the boxes are outliers. Baseline is defined as the last non-missing measurement prior to the start of study drug. Source: Module 5.3.5.1 CP-4-006 CSR Figure 14.2.6 (reference: Table 14.2.6.1)

Bone Maturation

The change in BM expressed as the change in bone age relative to the change in chronological age was similar in both the somatrogon and somatropin treatment groups at 12 months.

Table 14 Somatrogon protocol CP-4-006 (C0311009) summary of change in bone age relative to the change in chronological age at month 12 - full analysis set

	Somatrogon (N=109)	Genotropin (N=115)
Change in Bone Age Relative to the Change in Chronological Age		
N	104	102
Mean (SD)	1.07 (0.73)	1.12 (0.75)
Median	0.95	1.01
Range (min, max)	(0.00, 3.27)	(0.00, 3.16)
95% CI [a]	0.93, 1.21	0.97, 1.26

[a] The confidence interval is calculated using univariate methods.
Change in Bone Age (BA) relative to the change in Chronological Age(CA) at month 12 is (BA at month 12 - BA at baseline) divided by (CA at month 12 - CA at baseline). Chronological age was determined based on the assessment date. Source Data: 16.2.6.4.1

Other Efficacy-Related Endpoints

Quality of Life

QoL (as an exploratory endpoint) was assessed using the QoLISSY questionnaire. The raw scores were transformed to a scale of 0 to 100.

The QoLISSY questionnaire was completed in 8 countries (determined by the availability of the validated translated tools) at baseline and at 12 months. Two versions of the QoLISSY were used in a dyadic approach to assess the parent (children < 7 years) and child's (> 7 years of age) assessment of QoL.

Both the QoLISSY-CHILD and QoLISSY-PARENT demonstrated that both treatment groups had similar increases in core total scores and subscale scores from baseline at 12 months, indicating similar improvements in QoL following treatment with somatrogon administered once weekly or somatropin administered once daily.

Long-term efficacy

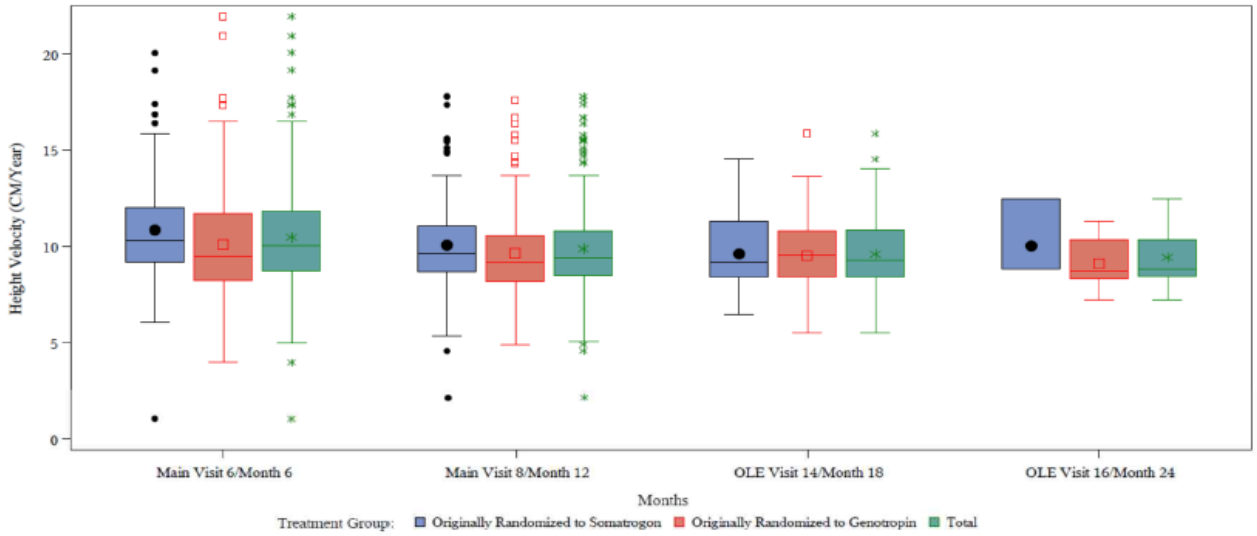
212 of 222 subjects who completed 12 months of the CP-4-006 main study period continued into the OLE period. As of the cut-off date of 01 November 2019, efficacy data was available for 94 subjects at Month 18 (6 months of OLE), and 9 subjects at Month 24 in the OLE period (12 months of OLE).

Patients who were receiving somatropin (Genotropin) were switched to weekly somatrogon.

Annualized HV with once weekly somatrogon treatment remained above baseline through the OLE period. The annualized HV for subjects who switched from somatropin to somatrogon at the beginning of the OLE period was consistent with subjects who received somatrogon during the main study and throughout the OLE period.

Given the cut-off date, no subject in the CP-4-006 OLE had achieved final height. as of the data cut-off date of 01 November 2019.

Figure 12 OLE annualised HV (cm/year), main study through OLE periods (FAS population)



	Main Visit 6/Month 6	Main Visit 8/Month 12	OLE Visit 14/Month 18	OLE Visit 16/Month 24
Treatment	**N**	**N**	**N**	**N**
Originally Randomized to Somatrogon	108	109	47	3
Originally Randomized to Somatropin	114	114	47	6
Total	222	223	94	9

Cut-off date for CP-4-006 OLE: 1 Nov 2019
Source Data: Table 14.2.2.1b

HT SDS values also improved with weekly somatrogon treatment in the main study period, and this trend was maintained over time in the OLE period. Improvements in change in HT SDS from baseline and HT SDS for subjects who switched from somatropin to somatrogon at the beginning of the OLE period were consistent with subjects who received somatrogon during the main study and throughout the OLE period.

IGF-1 SDS values with weekly somatrogon treatment approached 0 early in the main study period and remained in the target therapeutic range through the OLE period.

The trend in IGF-1 SDS values in subjects who switched from somatropin to somatrogon at the beginning of the OLE period was consistent with subjects who received somatrogon during the main study and throughout the reported OLE period.

Study CP-4-004 OLE

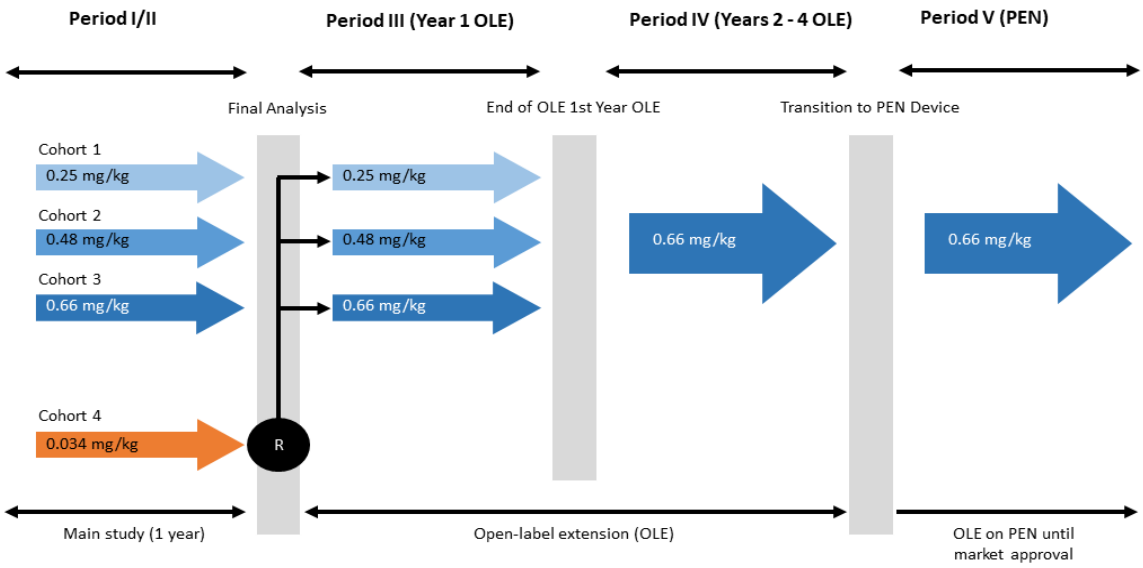
This was a safety and dose finding study of different MOD-4023 dose levels compared to daily r-hGH therapy in pre-pubertal growth hormone deficient children – open label extension.

Methods

This was a phase 2, open label, randomised, multi-centre, dose finding, and safety study of different somatrogon dose levels in pre-pubertal GHD paediatric subjects with yearly extension until marketing approval. The study consisted of a 6-week screening period, 2 active-controlled treatment periods, and 3 OLE periods.

The main study (Periods I and II) assessed treatment with 3 dose levels of somatrogon (0.25, 0.48, or 0.66 mg/kg/week) administered weekly via SC injection compared to the active control, daily SC injection of rhGH therapy (Genotropin 0.034 mg/kg/day) for up to 12 months.

Figure 13 Study diagram for CP-4-004 OLE and PEN periods



Subjects who completed 12 months of active treatment in the main study period, remained eligible for inclusion in the study, and consented to participate in the OLE Study continued with open label treatment until marketing approval. There were 3 defined OLE study periods:

- OLE period (Period III [Year 1 OLE]): This period lasted for 12 months post-completion of the main study. Subjects continued dosing with the 3 originally assigned dose levels of somatrogon (0.25, 0.48, and 0.66 mg/kg/week). Subjects originally assigned to daily somatropin in the main study were randomly re-assigned to 1 of the 3 somatrogon dose levels.
- LT-OLE period (Period IV [Years 2-4 OLE]): This LT-OLE period was planned to follow the 12 months in Period III (i.e., to start from second year of OLE and third year of the overall study). All eligible subjects were transitioned to receive somatrogon at a dose of 0.66 mg/kg/week.

- LT-OLE-PEN period (Period V [PEN]): Subjects were transitioned to somatrogon 0.66 mg/kg/week SC administration using a single subject, multi-dose, disposable pre-filled pen device and formulation. The Period V [PEN] duration will last until marketing approval.

- **Objectives and endpoints**

1. Safety evaluation

Monitoring and recording of all adverse events including serious adverse events, incidence of ADA formation, local injection site assessment, IGF-1 and IGF-1 SDS levels. monitoring of laboratory endpoints, regular monitoring of vital signs and physical condition.

2. Efficacy evaluation

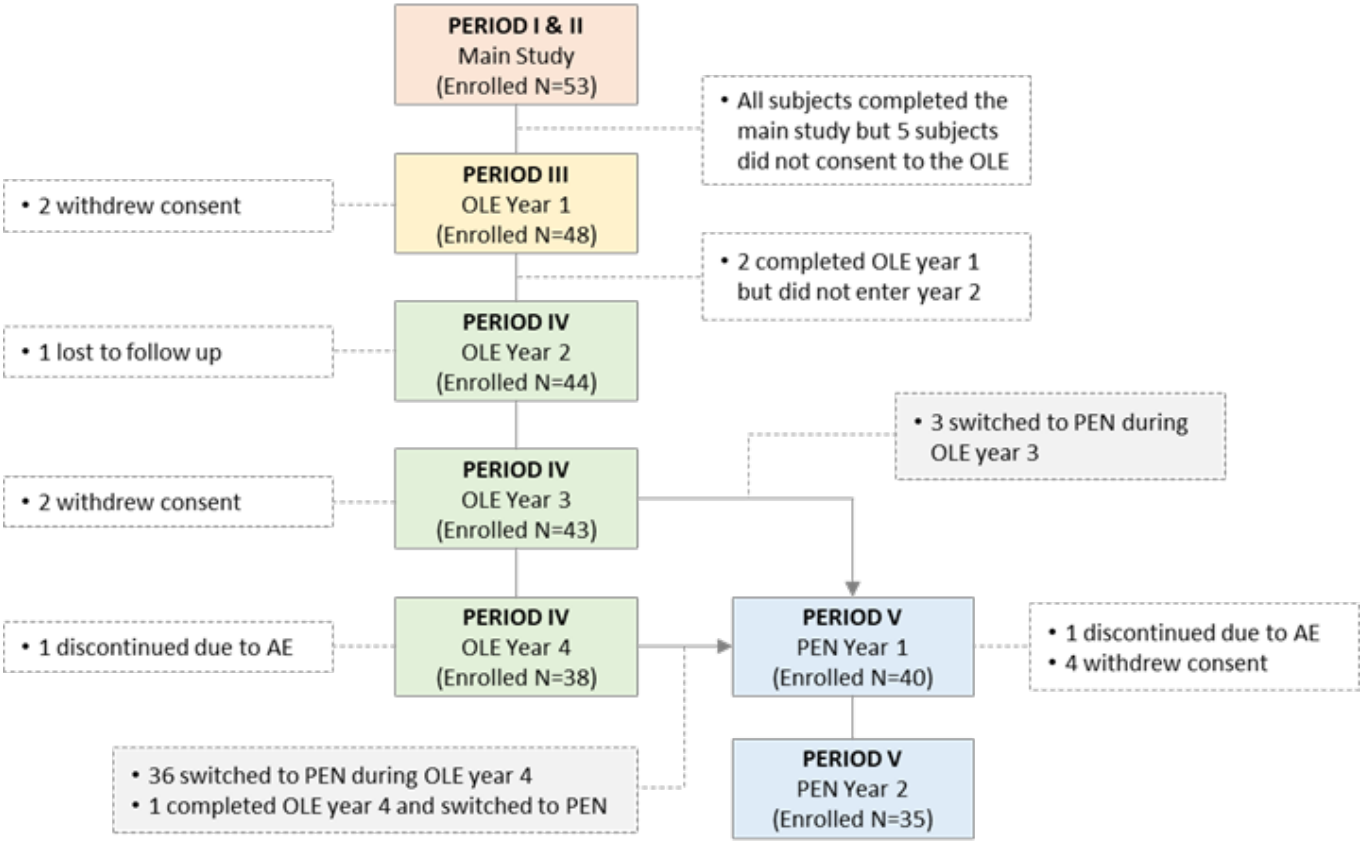
- Annual Height Velocity in cm/year at each 12 months interval
- Change in height SDS every 12 months
- Annual bone maturation

Results

- **Participant flow**

The disposition of subjects for Period III (Year 1 OLE), Period IV (Years 2-4), and Period V (PEN) is presented below.

Figure 14 Disposition of subjects flow chart for study CP-04-004



- **Outcomes and estimation**

The secondary objective of the OLE Study was to evaluate the growth outcome of somatrogon LT treatment beyond the initial 12 months of the main study, including following the transition to PEN.

Annual Height Velocity

A summary of the annual HV at the end of Period III (Year 1 OLE) is provided in Table 6. The mean observed annual HV was similar between the 0.25 mg/kg/week and 0.48 mg/kg/week treatment groups but was higher in the 0.66 mg/kg/week treatment group.

Table 15 Annual HV 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)
Height Velocity at End of Year (cm/year)				
n	15	17	14	46
Mean (SD)	7.73 (1.89)	7.54 (1.28)	8.81 (1.12)	7.99 (1.54)
Median	7.33	7.22	8.86	7.84
Minimum, Maximum	5.51, 11.44	5.38, 9.99	7.19, 10.87	5.38, 11.44

Abbreviations: N = subjects that entered the study period; n = subjects with annual HV for the study period.
Source: Table 14.2.1.1

The mean annual HV was the greatest during Year 1 OLE and decreased with every subsequent year thereafter. The mean annual HV for subjects who received somatropin during the main study and were switched to somatrogon during Year 1 OLE was consistent with subjects who received somatrogon during the main study.

Annual Height SDS and Change in Height SDS

The observed mean annual height SDS was consistent across treatment groups. In general, the mean height SDS progressively increased from Year 1 through PEN.

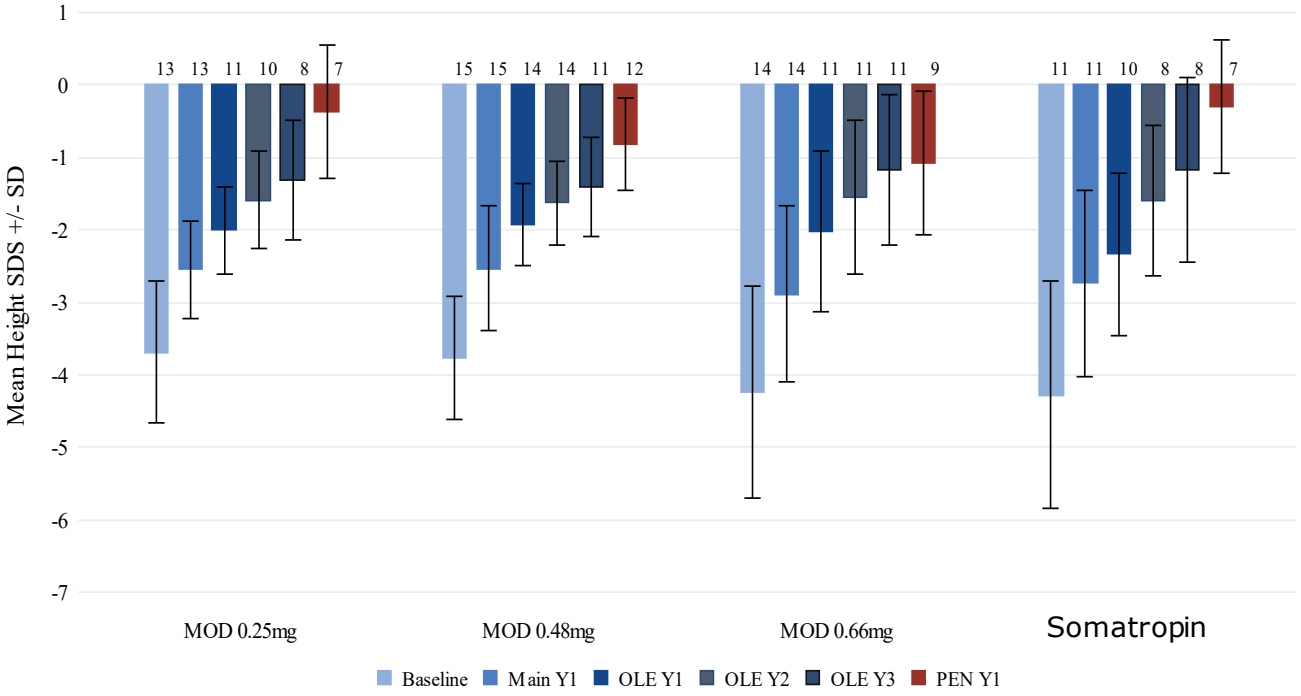
Table 16 Height SDS at End of Period III (Year 1 OLE): Full Analysis Set

	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)
Height SDS (Z) at End of Year				
n	15	17	14	46
Mean (SD)	-2.06 (0.77)	-1.92 (0.52)	-2.23 (1.21)	-2.06 (0.85)
Median	-1.95	-1.79	-1.81	-1.93
Minimum, Maximum	-4.02, -1.26	-3.35, -1.11	-4.51, -0.61	-4.51, -0.61

Abbreviations: N = subjects that entered the study period; n = subjects with Height SDS for the study period.
Source: Table 14.2.2.1

Mean height SDS continued to improve from the main study baseline (-3.98±SD 1.22) and was well into the normal range (-0.69±SD 0.87) at the end of PEN Year 1. Analysis of mean height SDS at the end of PEN Year 1 revealed no clinically meaningful differences by initial cohort assignment in the main study, including subjects initially randomised to somatropin treatment.

Figure 15 **Summary of height SDS by year of study and initial cohort assignment: full analysis set**



Note: Bar colors correspond to each year of the study.
All subjects who received somatropin during the main study were randomized to 1 of 3 doses of somatrogon for OLE Y1. All subjects received somatrogon 0.66 mg/kg/week during OLE Y2 and Y3.
Source data: Table 14.2.2.2

The mean change in height SDS was similar for the 0.25 mg/kg/week and 0.48 mg/kg/week treatment groups and was higher for the 0.66 mg/kg/week treatment group for Year 1 of OLE.

This is further reflected in the results of the mean change in height SDS for Years 2 and 3, and also in the change in height before and after transition to the prefilled pen device.

Table 17 **Change in height SDS at end of period IV (years 2-4 OLE): full analysis set**

	Year 2 (N=44)	Year 3 (N=43)	Year 4 (N=38)
Delta Height SDS (Z) at End of Year			
n	43	38	1
Mean (SD)	0.40 (0.28)	0.34 (0.28)	0.09 (-)
Median	0.34	0.29	0.09
Minimum, Maximum	-0.12, 1.03	-0.16, 1.31	0.09, 0.09

Abbreviations: N = subjects that entered the study period; n = subjects with Height SDS for the study period.
Note: Height Velocity for the 12-month interval in Years 2-4 used the last measure in each year with the measure at 12 months prior to the last measure as the reference.
Source: Table 14.2.3.1

Table 18 Change in height SDS at end of period V (PEN): full analysis set

	Annual Delta Height SDS at 12 Months Before First Pen Injection	Annual Delta Height SDS at 6 Months Before First Pen Injection	Annual Delta Height SDS at 12 Months After First Pen Injection
Statistic			
N	12	5	35
Mean (SD)	0.36 (0.14)	0.24 (0.25)	0.27 (0.25)
Median	0.39	0.15	0.25
Minimum, Maximum	0.19, 0.55	0.10, 0.69	-0.38, 0.82

Note: Height Velocity for the 6- and 12-month intervals started with the first Pen injection as the reference.
Source: Table 14.2.3.2

Table 19 Change in height 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)
Delta Height SDS (Z) at End of Year				
n	15	17	14	46
Mean (SD)	0.50 (0.38)	0.47 (0.29)	0.77 (0.25)	0.57 (0.34)
Median	0.40	0.36	0.78	0.54
Minimum, Maximum	-0.03, 1.16	-0.01, 0.99	0.35, 1.10	-0.03, 1.16

Abbreviations: N = subjects that entered the study period; n = subjects with Height SDS for the study period.
Note: Delta Height SDS for the 12-month interval in Year 1 started with the first injection in Year 1 as the reference.
Source: Table 14.2.3.1

The number of patients who transitioned from Genotropin to somatrogon was quite low, however, it was overall shown that patients treated with somatrogon maintained growth velocities in line with what would have been expected in this population taking other similar medicines.

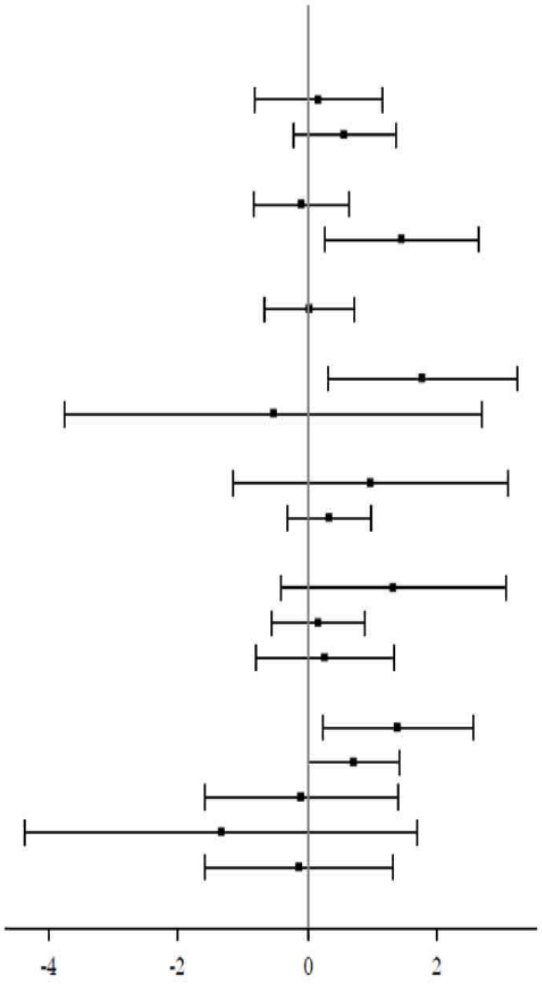
- **Ancillary analyses**

In CP-4-006, results of pre-specified subpopulation analyses comparing somatrogon and somatropin for the primary efficacy endpoint were generally consistent with the overall results of the primary efficacy endpoint analysis for:

Age group, Gender, Race, Ethnicity, Peak GH levels Region; and ADA status.

Figure 16 CP-4-006 Annual HV (cm/year) at 12 Months in Subpopulations

Group	Somatrogon LSM	Genotropin LSM	LSM Difference (95% CI)
Age Group			
>3 years to =<7 [43 , 47]	10.45	10.29	0.16 (-0.83, 1.15)
>7 years [65 , 66]	9.91	9.35	0.56 (-0.23, 1.36)
Gender			
Male [82 , 77]	9.88	9.98	-0.10 (-0.84, 0.63)
Female [26 , 36]	10.76	9.32	1.45 (0.26, 2.64)
Race			
White [80 , 85]	10.04	10.03	0.02 (-0.68, 0.71)
Black or African American [0 , 2]		10.06	
Asian [24 , 20]	10.80	9.03	1.77 (0.31, 3.24)
Other [4 , 6]	7.48	8.01	-0.53 (-3.76, 2.69)
Ethnicity			
Hispanic or Latino [11 , 13]	9.75	8.78	0.97 (-1.16, 3.10)
Not Hispanic or Latino [97 ,100]	10.18	9.85	0.33 (-0.32, 0.98)
Peak GH Level Group			
<=3 ng/mL [22 , 21]	12.70	11.38	1.32 (-0.42, 3.06)
>3 to <=7 ng/mL [52 , 55]	9.47	9.31	0.16 (-0.57, 0.88)
>7 to <10 ng/mL [34 , 37]	9.58	9.32	0.26 (-0.80, 1.33)
Region			
Region 1 [19 , 26]	10.27	8.88	1.39 (0.23, 2.56)
Region 2 [31 , 35]	9.85	9.14	0.71 (0.01, 1.42)
Region 3 [13 , 9]	9.15	9.26	-0.11 (-1.60, 1.39)
Region 4 [7 , 6]	8.80	10.14	-1.34 (-4.37, 1.69)
Region 5 [38 , 37]	10.84	10.98	-0.14 (-1.61, 1.32)



Note: [n1,n2] represent sample sizes for Somatrogon and Genotropin within each sub-group, respectively.
Region 1 - US and Canada
Region 2 - Europe (includes Bulgaria, Greece, Poland, Spain, UK, Belarus, Turkey, Israel)
Region 3 - Asia/ Pacific (includes Australia, New Zealand, Korea, Taiwan)
Region 4 - Latin America (includes Argentina, Columbia, Mexico)
Region 5 - Central Asia (includes Russia, India, Ukraine, Georgia).
Subjects age 7 years and 0 days are stratified into the >3 years to ≤7 years group.
'American Indian or Alaska Native(n=1)' and 'Native Hawaiian or Other Pacific Islander (n=1)' were included in 'Other' category.
Reference: Module 5.3.5.3 SCE Figure 14.2.5.1.1b (reference: Table 14.2.5.1.1b)

Efficacy by ADA Status

Somatrogon ADAs were reported in 10/42 (23.8%) somatrogon-treated subjects in Phase 2 of study CP-4-004 and in 84/109 (77.1%) somatrogon-treated subjects in phase 3 of study CP-4-006 during the first 12 months of treatment. ADAs first became detectable in most subjects after 6 months of treatment and generally persisted for at least 6 months thereafter.

In both studies, overall clinical findings for paediatric subjects who tested somatrogon ADA+ were

generally indistinguishable from those who tested ADA-.

Table 20 Somatrogon protocol CP-4-006 (C0311009) – OLE summary of annualized height velocity vs Anti-drug antibodies (ADA) status in study CP-4-006 LT-OLE – full analysis set parameter: height velocity (cm/year)

Visit		Originally Randomised to Somatrogon		Originally Randomised to Genotropin	
		ADA + (N=81) Observed Value	ADA - (N=23) Observed Value	ADA + (N=8) Observed Value	ADA - (N=100) Observed Value
OLE Month 3	N	66	15	8	82
	Mean (SD)	7.88 (2.88)	7.23 (2.77)	8.36 (1.75)	8.91 (3.09)
	Median	7.72	6.98	9.18	8.77
	Minimum, Maximum	0.00, 18.26	1.20, 13.43	5.62, 10.22	1.83, 17.49
OLE Month 6	N	40	6	8	38
	Mean (SD)	8.61 (2.13)	6.42 (1.69)	8.63 (1.92)	8.97 (2.58)
	Median	8.58	6.82	8.61	8.42
	Minimum, Maximum	2.95, 13.34	3.48, 8.33	6.46, 12.45	5.02, 14.14
OLE Month 9	N	12	6	3	21
	Mean (SD)	7.82 (1.57)	6.53 (1.42)	8.85 (0.45)	8.84 (2.10)
	Median	7.43	6.69	8.60	7.94
	Minimum, Maximum	5.46, 10.02	4.15, 8.05	8.57, 9.36	5.13, 12.66
OLE Month 12	N	2	1	1	5
	Mean (SD)	9.54 (0.72)	7.33	8.33	8.62 (2.57)
	Median	9.54	7.33	8.33	7.43
	Minimum, Maximum	9.03, 10.04	7.33, 7.33	8.33, 8.33	5.98, 12.14
OLE Month 15	N	0	0	0	2
	Mean (SD)				7.49 (0.26)
	Median				7.49
	Minimum, Maximum				7.31, 7.67
OLE EOS	N	2	0	1	1
	Mean (SD)	2.13 (3.90)		10.11	9.20
	Median	2.13		10.11	9.20
	Minimum, Maximum	-0.63, 4.88		10.11, 10.11	9.20, 9.20

	Originally Randomised to Somatrogon		Originally Randomised to Genotropin	
	ADA + (N=81)	ADA - (N=23)	ADA + (N=8)	ADA - (N=100)
Visit	Observed Value	Observed Value	Observed Value	Observed Value

OLE baseline is same as month 12 (visit 8) of the main study.
Categorization of positivity and negativity was assessed from the main study.
Source Data: Table 16.2.6.3.1c; Table 16.2.8.5.3.1

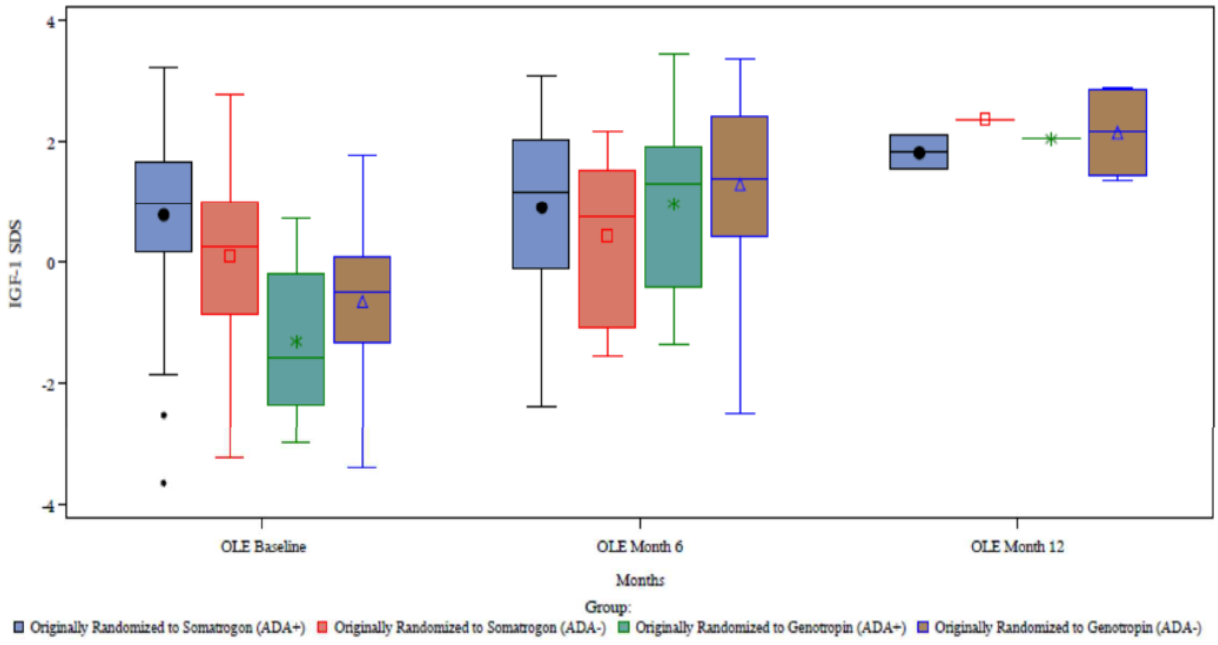
The available evidence suggests that the presence of ADAs in somatrogon-treated subjects does not compromise the efficacy of somatrogon with regard to IGF-1 levels or growth normalization.

Overall, somatrogon administered SC at a dose of 0.66 mg/kg/wk in a paediatric GHD population did not produce immunogenic effects that interfered with efficacy outcomes.

IGF-1 SDS Over Time

Testing ADA+ for somatrogon did not appear to affect IGF-1 profiles during the LT-OLE period. IGF-1 SDS by treatment randomization in the main study, time point through the first year of LT-OLE, and by ADA status is shown below.

Figure 17 IGF-1 SDS by Time Point by ADA Status in Study CP-4-006 LT-OLE



	OLE Baseline	OLE Month 6	OLE Month 12
Group	N	N	N
Originally Randomized to Somatrogon (ADA+)	80	40	2
Originally Randomized to Somatrogon (ADA-)	23	6	1
Originally Randomized to Genotropin (ADA+)	8	8	1
Originally Randomized to Genotropin (ADA-)	97	38	4

Cut-off date for CP-4-006 OLE: 1 Nov 2019
PFIZER CONFIDENTIAL SDTM Creation: 22JUN2020 (16:26) Source Data: Table 14.2.7.1.2c Output File: ./c0311009/006-OLE/advs_igfboxplot
Date of Generation: 21SEP2020 (17:46)

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 21 Summary of Efficacy for Trial CP-4-006

Title: A phase 3, open label, randomised, multicenter, 12 months, efficacy and safety study of weekly MOD-4023 compared to daily genotropin- therapy in pre-pubertal children with growth hormone deficiency			
Study identifier	CP-4-006 2016-003874-42 (EudraCT)		
Design	Phase 3, 12-month, open-label, multicentre, randomised, active controlled, parallel group study to compare the efficacy and safety of weekly somatrogon to daily GH in prepubertal children with GHD.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months Not applicable > 1 year
Hypothesis	Non-inferiority		
Treatments groups	Somatrogon		somatrogon 0.66 mg/kg/week. 12 months, N=109
	Genotropin		somatropin 0.034 mg/kg/day. 12 months, N=115
Endpoints and definitions	Primary endpoint	Annual HV	Annual height velocity after 12 months of treatment
	Secondary endpoint:	Annualized HV after 6 mo of treatment	Annualized HV after 6 months of treatment
	Secondary endpoint:	Δ Ht SDS at 6 and 12 mo	Change in height SDS at 6 and 12 months, compared to baseline
	Secondary endpoint:	Δ BM at 12 mo	Bone Maturation calculated as change in bone age from screening to the 12-month visit relative to the change in chronological age
	Secondary endpoint:	IGF-1 and IGF-1 SDS levels	Absolute IGF-1 and IGF-1 SDS levels on Day 4(-1) after somatrogon dosing across study visits
	Secondary endpoint:	IGFBP-3 levels and IGFBP-3 SDS	IGFBP-3 levels and IGFBP-3 SDS on Day 4(-1) after somatrogon dosing across study visits
	Other endpoint	Successful injections (PAT)	Proportion of successful single injections out of total number of single injections using the somatrogon single subject use, multidose, disposable prefilled pen (pen) in US subjects at Weeks 1, 2, 3, 4, 5, and 6, based on the PAT
	Other endpoint:	Successful injections (OAT)	Proportion of successful single injections out of total number of single injections using the somatrogon pen in US subjects at Week 1, based on the OAT
	Other endpoint:	QoLISSY	QoL core total score as measured by the Quality of Life in Short Stature Youth (QoLISSY) questionnaire at baseline and month 12 in specific countries
Database lock	Main study: 8 Oct 2019		

Analysis description	**Primary Analysis**			
Analysis population and time point description	All efficacy analyses were based on the FAS, defined as subjects who were randomised and have received at least one dose of study medication. Subjects were analysed according to the randomised treatment group for all efficacy endpoints. The aim of the study was to demonstrate that, in terms of the primary efficacy endpoint (Annual HV at 12 months), weekly somatrogon is non-inferior to daily somatropin (Genotropin) by a non-inferiority margin of 1.8 cm/year. Non-inferiority was to be concluded if the lower bound of the two-sided 95% CI for the mean treatment difference "somatrogon – somatropin", in the primary efficacy endpoint is ⩾-1.8 cm/year.			
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**	**Somatropin**	**Treatment Mean Difference**
	Number of subjects	109	115	
	ANCOVA			
	LS Means Estimate	10.1	9.78	0.33
	95% CI	--	--	-0.24, 0.89
	Observed			
	N	108	113	
	Mean (SD)	10.18 (2.42)	9.68 (2.46)	
	Median	9.66	9.21	
	Range (Min, Max)	4.57, 17.80	4.90, 17.60	
Analysis description	**Secondary Analysis** Annualized HV after 6 months of treatment			
Analysis population and time point description	The efficacy analysis was based on the FAS as defined above and subjects were analysed according to the randomised treatment group. The analysis conducted for the primary endpoint was repeated for the annual HV at 6 months also with no formal hypothesis testing.			
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**	**Somatropin**	**Treatment Mean Difference**
	Number of subjects	109	115	
	ANCOVA			
	LS Means Estimate	10.59	10.04	0.55
	95% CI	--	--	-0.13, 1.23
	Observed			
	N	108	114	
	Mean (SD)	10.86 (2.80)	10.12 (3.03)	
	Median	10.30	9.51	
	Range (Min, Max)	1.03, 20.06	3.97, 21.96	
Analysis description	**Secondary Analysis** Change in HT SDS at 6 and 12 months compared to baseline			
Analysis population and time point description	The efficacy analysis was based on the FAS as defined above and subjects were analysed according to the randomised treatment group. The analysis conducted for the primary endpoint was repeated for the Change in HT SDS at 12 and 6 months also with no formal hypothesis testing.			

Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**	**Somatropin**	**Treatment Mean Difference**
	Month 12 Results			
	Number of subjects	109	115	
	ANCOVA			
	LS Means Estimate	0.92	0.87	0.05
	95% CI	--	--	-0.06, 0.16
	Observed			
	N	108	113	
	Mean (SD)	0.93 (0.55)	0.84 (0.51)	
	Median	0.81	0.73	
	Range (Min, Max)	0.15, 3.92	0.03, 2.60	
	Month 6 Results			
	Number of subjects	109	115	
	ANCOVA			
	LS Means Estimate	0.54	0.48	0.06
	95% CI	--	--	-0.01, 0.13
	Observed			
	N	108	114	
	Mean (SD)	0.55 (0.33)	0.47 (0.31)	
	Median	0.46	0.40	
	Range (Min, Max)	-0.17, 2.45	-0.03, 1.68	

Analysis description	**Secondary Analysis** Change in BM at the end of 12 months		
Analysis population and time point description	The efficacy analysis was based on the FAS as defined above and subjects were analysed according to the randomised treatment group. Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.		
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**	**Somatropin**
	Bone Maturation at 12 Months		
	Observed		
	N	104	102
	Mean (SD)	0.72 (0.17)	0.72 (0.17)
	Median	0.73	0.72
	Range (Min, Max)	0.34, 1.13	0.37, 1.15
	95% CI	0.68, 0.75	0.68, 0.75
	Change in BA Relative to the change in CA		
	N	104	102
	Mean (SD)	1.07 (0.73)	1.12 (0.75)
	Median	0.95	1.01
	Range (Min, Max)	0.00, 3.27	0.00, 3.16
	95% CI	0.93, 1.21	0.97, 1.26

Analysis description	**Secondary Analysis** Absolute IGF-1 and IGF-1 SDS levels on Day 4(-1) after somatrogon dosing across study visits				
Analysis population and time point description	The efficacy analysis was based on the FAS as defined above and subjects were analysed according to the randomised treatment group. Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.				
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**		**Somatropin**	
		Observed	Change from Baseline	Observed	Change from Baseline
	IGF-1				
	Baseline				
	N	109		115	
	Mean (SD)	79.86 (46.46)		84.04 (41.21)	
	Median	77.00		84.00	
	Range (Min, Max)	15.90, 259.00		14.10, 201.00	
	Month 12				
	N	107	107	110	110
	Mean (SD)	263.76 (124.77)	183.66 (104.35)	154.56 (80.75)	70.68 (59.89)
	Median	246.60	174.00	139.50	62.00
	Range (Min, Max)	22.00, 649.00	4.00, 475.00	20.00, 495.00	-58.00, 329.00
	IGF-1 SDS (Z)				
	Baseline				
	N	109		115	
	Mean (SD)	-1.95 (0.89)		-1.72 (0.90)	
	Median	-1.87		-1.65	
	Range (Min, Max)	-4.39, -0.21		-3.91, 0.51	
	Month 12				
	N	107	107	110	110
	Mean (SD)	0.65 (1.32)	2.60 (1.26)	-0.69 (1.09)	1.02 (0.87)
	Median	0.77	2.59	-0.58	0.94
	Range (Min, Max)	-3.64, 3.22	-0.27, 6.11	-3.37, 1.79	-1.50, 3.15

Analysis description	**Secondary Analysis** Absolute IGFBP-3 and IGFBP-3 SDS (Z) levels on Day 4(-1) after somatrogon dosing across study visits				
Analysis population and time point description	The efficacy analysis was based on the FAS as defined above and subjects were analysed according to the randomised treatment group. Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.				
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon**		**Somatropin**	
		Observed	Change from Baseline	Observed	Change from Baseline
	IGFBP-3				
	Baseline				
	N	109		115	
	Mean (SD)	2468.85 (1046.50)		2574.24 (976.75)	

	Median	2455.00		2725.00	
	Range (Min, Max)	326.50, 4807.00		236.50, 4679.00	
	Month 12				
	N	108	108	111	111
	Mean (SD)	3879.29 (837.55)	1420.80 (888.77)	3262.40 (954.64)	688.45 (615.34)
	Median	4050.50	1294.50	3285.50	708.00
	Range (Min, Max)	1831.00, 5715.00	-607.00, 3740.00	641.00, 5710.00	-1027.0, 2620.00
	IGFBP-3 SDS (Z)				
	Baseline				
	N	109		115	
	Mean (SD)	-1.62 (1.24)		-1.46 (1.18)	
	Median	-1.44		-1.20	
	Range (Min, Max)	-4.84, 0.73		-4.66, 0.60	
	Month 12				
	N	108	108	111	111
	Mean (SD)	-0.02 (0.86)	1.62 (1.15)	-0.72 (1.04)	0.74 (0.77)
	Median	0.08	1.42	-0.52	0.74
	Range (Min, Max)	-2.19, 1.65	-0.93, 4.58	-4.05, 1.53	-1.30, 2.90

Analysis description	**Secondary Analysis** Summary of Successful Single Somatrogon Injections for the Period of the Participant Assessment Tool (PAT) Assessment
Analysis population and time point description	The analysis was based on the SAS defined as all subjects who received at least one dose of the study drug. Data was collected on PAT (n = 17) in the US subjects only at Weeks 1, 2, 3, 4, 5, and 6. Proportion of successful single injections was descriptively summarized for this endpoint with no formal hypothesis testing.

Descriptive statistics and estimate variability		Number of subjects who attempted dose administration and answered the PAT at the Week 1 visit and at home at Weeks 2, 3, 4, 5, and 6	Number of single injections required to complete a full dose administration	Successful Injection Attempts n (%)
	Week 1	17	17	15 (88.2)
	Week 2	17	17	15 (88.2)
	Week 3	17	19	17 (89.5)
	Week 4	17	21	20 (95.2)
	Week 5	17	19	17 (89.5)
	Week 6	15	15	14 (93.3)
	Overall		108	98 (90.7)

Analysis description	**Secondary Analysis** Summary of Successful Single Somatrogon Injections for the Observer Assessment Tool (OAT) Assessment at Week 1

Analysis population and time point description	The analysis was based on the SAS defined as all subjects who received at least one dose of the study drug. Data was collected on OAT (n = 17) in the US subjects only at Week 1. Proportion of successful single injections was descriptively summarized for this endpoint with no formal hypothesis testing.			
Descriptive statistics and estimate variability		Number of subjects who attempted dose administration at the Week 1 visit	Number of single injections required to complete a full dose administration	Successful Injection Attempts n (%)
	Overall Week 1	17	17	17 (100.0)
Analysis description	**Secondary Analysis** QoL core total score as measured by the QoLISSY questionnaire at baseline and month 12 in specific countries			
Analysis population and time point description	The efficacy analysis was based on the FAS, defined as subjects who were randomised and have received at least one dose of study medication. Subjects were analyzed according to the randomised treatment group. The QoLISSY questionnaire was intended to be only completed for the following countries using a validated translated tool: USA, Australia, New Zealand, Belarus, Russia, Ukraine, United Kingdom (UK), Spain. It includes three subscales (physical, social, emotional) and a total score. Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.			
Descriptive statistics and estimate variability	**Treatment group**	**Somatrogon (N=109)**	**Somatropin (N=115)**	
	Physical Baseline			
	N	54	63	
	Mean (SD)	59.57 (21.27)	55.49 (21.65)	
	Median	60.42	58.33	
	Range (Min, Max)	0.00, 95.83	4.17, 91.67	
	Physical Month 12			
	N	49	59	
	Mean (SD)	71.94 (19.61)	65.54 (22.09)	
	Median	75.00	70.83	
	Range (Min, Max)	8.33, 100.0	8.33, 95.83	
	Social Baseline			
	N	54	63	
	Mean (SD)	62.09 (22.14)	58.83 (21.18)	
	Median	65.63	59.38	
	Range (Min, Max)	0.00, 96.88	3.13, 96.88	
	Social Month 12			
	N	49	59	
	Mean (SD)	73.15 (19.04)	66.26 (23.41)	
	Median	78.13	71.88	
	Range (Min, Max)	18.75, 100.0	12.50, 96.88	
	Emotional Baseline			
	N	54	63	
	Mean (SD)	63.14 (24.46)	60.06 (24.24)	
	Median	65.63	59.38	

	Range (Min, Max)	0.00, 100.0	0.00, 100.0
	Emotional Month 12		
	N	49	59
	Mean (SD)	73.56 (19.52)	68.38 (22.40)
	Median	75.00	75.00
	Range (Min, Max)	6.25, 100.0	3.13, 100.0
	Total Baseline		
	N	54	63
	Mean (SD)	61.60 (20.56)	58.12 (20.00)
	Median	64.41	59.03
	Range (Min, Max)	0.00, 93.40	11.81, 93.75
	Total Month 12		
	N	49	59
	Mean (SD)	72.88 (17.52)	66.73 (20.93)
	Median	76.74	72.57
	Range (Min, Max)	12.15, 100.0	11.11, 96.53

Abbreviations: BA=bone age; BM=bone maturation; CA=chronological age; FAS=full analysis set; GHD=growth hormone deficiency; Ht SDS=height standard deviation score; HV=height velocity; IGF-1=insulin-like growth factor-1; IGF-1 SDS=insulin-like growth factor-1 standard deviation score; IGFBP-3=insulin-like growth factor-binding protein-3; IGFBP-3 SDS=insulin-like growth factor-binding protein-3 standard deviation score; max=maximum; min=minimum; OAT=Observer Assessment Tool; PAT=Participant Assessment Tool; QoL=quality of life; QoLISSY=Quality of Life in Short Stature Youth; SAS=safety analysis set; SD=standard deviation; SDS=standard deviation score.

2.6.5.3. Clinical studies in special populations

The clinical effects of somatrogon were evaluated in paediatric patients with growth hormone deficiency. No particular analyses were conducted in study patients with concomitant renal or hepatic impairment. This was found to be acceptable.

2.6.5.4. Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis or meta-analyses were conducted for efficacy. This was acceptable to the CHMP.

2.6.5.5. Supportive study

A phase 3, randomised, multicentre, 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. This name of this study was "Patient Perception of Treatment Burden in Weekly Versus Daily Growth Hormone Injections in Children With GHD".

The purpose of this study was to evaluate whether there is a benefit, defined as superior adherence and acceptance, of a once weekly injection schedule to support the benefit/risk profile of somatrogon, a long-acting rhGH for SC administration.

Subjects had been stable on treatment with daily somatropin for a minimum of 3 months prior to enrolment. They were then randomised in a 1:1 ratio to one of 2 sequences, either 12 weeks of treatment with daily somatropin 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 somatropin.

Control group

The active comparator (daily somatropin) and crossover study design were selected in order to test the hypothesis that, for children with GHD, a once weekly treatment schedule (once weekly somatrogon) has a treatment burden that is less than a daily treatment schedule (somatropin). There was no treatment washout period because these participants must take growth hormone continually.

The primary endpoint was treatment burden assessed as the difference in mean overall life interference total scores between weekly injection schedule and daily injection schedule as assessed by patient life Interference Questionnaire (DCOA) completed by the subject caregiver at baseline and after each treatment schedule experience.

The DCOA is a COA questionnaire specifically designed for self- or dyad-administration to measure the experiences of patients taking rhGH GHD injections in order to demonstrate significant benefit (in terms of better adherence and acceptance) of the weekly injection schedule compared with the daily schedule.

87 subjects were enrolled in the study. The number of participants who were randomised to both treatment sequences was comparable. All but 2 participants completed the study.

Efficacy results

Primary Endpoint Results - Treatment Burden: Difference in Mean Overall Life Interference Total Scores Between the Weekly Injection Schedule and the Daily Injection Schedule

This study met the primary endpoint by demonstrating the treatment burden, as evaluated by the Patient Life Interference questionnaire, of the once weekly somatrogon injection schedule was lower than that of the once daily somatropin injection schedule.

- The least squares mean of the Overall Life Interference total score was lower for the once weekly somatrogon injection schedule than for the once daily somatropin injection schedule.
- All scores were transformed from raw scores and converted to a 0 to 100 scale. Lower scores represent less life interference (better outcome).

- The mean difference (somatrogon-somatropin) was -15.49 (95% CI: -19.71, -11.27) (range 0-100).
- The difference in mean Overall Life Interference scores for somatrogon once weekly for 12 weeks, compared with administration of somatropin once daily for 12 weeks, was statistically significant ($p<0.0001$).

Secondary endpoints

Treatment Experience: Difference in Mean Scores Between the Weekly Injection Schedule Experience and Daily Injection Schedule Experience – DCOA 1 Questionnaire

The estimated mean score differences for most variables within the DCOA 1 questionnaire showed an improvement (i.e., negative estimated mean difference) during the once weekly somatrogon injection schedule compared with the once daily somatropin injection schedule and these differences were statistically significant, except for the following:

- The point estimate of the mean satisfaction with the overall treatment experience score was lower (ie, improved) for participants in the once weekly somatrogon injection schedule than for participants in the once daily somatropin injection schedule; however, the estimated mean difference was not significant (p=0.0739).
- Overall mean scores for injection signs and symptoms (for participants 8 years and above) and the assessment of signs (as reported by the caregiver for the children aged <8 years) were similar between both injection schedules.

Proportion of Participant/Caregiver Dyads Responding to the DCOA 2 Questionnaires at Week 24

The majority of participant/caregiver dyads preferred the once weekly somatrogon injection schedule compared with those who preferred the once daily somatropin injection schedule or expressed no difference/no preference between injection schedules for most variables within the DCOA 2 questionnaire, except for:

- Pen ease of use : Although the majority of participant/caregiver dyads reported the somatrogon pen was easier to use based on preparing the pen, less than half of them indicated the somatrogon pen was easier to use for setting the dose, injecting the medicine, and storing the pen.
- Most of the participant/caregiver dyads responded it would be extremely or very beneficial to take injections less often.

Patient Global Impression at Week 12 and Week 24

The once weekly somatrogon injection schedule had less impact on the daily activities than the once daily somatropin injection schedule based on the lower overall mean PGIS-IDA score.

Overall conclusion on efficacy

The results of study C0311002 indicate a preference for weekly injection schedule, based on the patient reported outcomes gathered in this study.

2.6.6. Discussion on clinical efficacy

The clinical efficacy of somatrogon in paediatric patients with growth hormone deficiency (GHD) was evaluated in one phase 2 dose-finding study (CP-4-004 + OLE), a pivotal phase 3 study (CP-4-006 +OLE) and an additional phase 3 patient preference study (C0311002).

The applicant also submitted studies in adult patients with GHD, however as an indication in this population is not requested, these were not further discussed. The dose finding study, which is described in detail in the above sections, showed that the 0.66 mg/kg/week selected was appropriate to bring forward for phase 3 development.

Design and conduct of clinical studies

Study CP-4-006 was a pivotal, 52-week, randomised, open-label, phase 3 clinical study in paediatric GHD patients. The study was designed to test that somatrogon 0.66 mg/kg/wk was non-inferior to daily treatment with somatropin (Genotropin) 0.034 mg/kg/day at 52 weeks. The applicant received advice from the SAWP on the development programme, which was followed for the most part. Patients were randomly assigned in a 1:1 ratio and were stratified based on GH level, chronological age (CA) and region.

Both the phase 2 study (CP-4-004) and the pivotal phase 3 study (CP-4-006) had OLE periods designed to gather further safety and efficacy data.

The second phase 3 study (C0311002) was a randomised, multicentre, open label cross over study. It was designed to assess subject perception of treatment burden with use of weekly growth hormone compared to daily Genotropin in children with GHD.

Study population

In the pivotal study, the patients enrolled were prepubertal aged 3 to <11 years (females) and < 12 years (males). The patients had either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiencies. They were also treatment naïve. Similar to the phase 2 dose finding study, subjects had a HV below the 25th percentile for CA and gender. Baseline IGF-1 levels were at least 1 SD below the mean IGF-1 standardised for age and sex.

In the additional phase 3 study (C0311002), children aged ⩾3 years old and <18 years were enrolled and were currently on either Genotropin Pen, Genotropin GoQuick Pen, HumatroPen (USA only), or Omnitrope Pen (USA only) ⩾3 months and complaint. They were also required to have an IGF-I SDS <2.

Comparator

In the phase 2, and pivotal phase 3 study (CP-4-006), Genotropin was included as a comparator arm at a dose of 0.034 mg/kg/day which is in line with the posology licensed for its use.

Endpoints

For the pivotal phase 3 study, the primary efficacy endpoint was annualised HV at 12 months cm/year. The key secondary endpoints were HV at 6 months, change in HT SDS at 6 and 12 months compared to baseline. Change in BM at 12 months compared to screening BA. Absolute IGF-1 and IGF-1 SDS levels on day 4 and IGFBP-3 and IGFBP-3 SDS on day 4 were also measured. These were considered by the CHMP to be appropriate endpoints and they were previously endorsed by the SAWP advice and are also in line with similar applications.

Primary endpoint results

The aim of the study was to demonstrate that, in terms of the primary efficacy endpoint (Annual HV at 12 months), weekly somatrogon is non-inferior to daily somatropin by a non-inferiority margin of 1.8 cm/year. Non-inferiority was to be concluded if the lower bound of the two-sided 95% CI for the mean treatment difference "somatrogon – somatropin", in the primary efficacy endpoint is ≥-1.8 cm/year.

Somatrogon demonstrated a HV of 10.1 cm/year compared to somatropin 9.78 cm/year at 12 months. The LS mean difference -0.33 (-0.24-0.89) was in favour of somatrogon.

Secondary endpoints

HV at 6 months was 10.59 cm/year for somatrogon and 10.04 cm/year for somatropin, LS mean difference 0.55 (-0.13, 1.23). Change in HT SDS at 12 months was 0.92 and 0,87 and 0.54 and 0.48 at 6 months for somatrogon and somatropin respectively.

Change in BM at 12 months was mean 0.72 (SD 0.17) and 0.72 (SD 0.17) for somatrogon and somatropin respectively.

Absolute IGF-1 levels on Day 4(-1) mean (SD) 263.76 (124.77) and 154.56 (80.75) for somatrogon and somatropin respectively. This translated into a change from baseline of 183.66 (104.35) and 183.66 (104.35) respectively.

IGF-1 SDS (Z) at 12 months were 0.65 (1.32) for somatrogon and -0.69 (1.09) for somatropin. The change form baseline was 2.60 (1.26) and 2.60 (1.26) for somatrogon and somatropin respectively.

Absolute IGFBP-3 levels on Day 4(-1) after somatrogon at month 12 was observed mean 3879.29 (837.55) and 3262.40 (954.64) for somatrogon and somatropin. The change from baseline was 1420.80 (888.77) and 688.45 (615.34) respectively.

IGFBP-3 SDS (Z) change from baseline at 12 months was reported as 1.62 (1.15 SD) and 0.74 (0.77 SD) for somatrogon and somatropin respectively.

Therefore, it was demonstrated that the effects of somatrogon are not inferior to somatropin for the secondary endpoints. In some respects, even higher numerical results were shown. BM was similar between both medicinal products.

Subgroup analyses

Results of the prespecified subgroup analyses comparing somatrogon and somatropin based on stratification factors (age group, gender, peak GH levels, and region) were generally consistent with the overall results of the primary efficacy endpoint.

The change in bone age relative to the change in chronological age from baseline to the 12-month visit was comparable between both treatment groups.

In both the phase 2 study (CP-4-004) and phase 3 study (CP-4-006), the overall clinical findings for paediatric subjects who tested somatrogon ADA+ were generally indistinguishable from those who tested ADA. This suggests that the presence of ADAs in somatrogon-treated subjects does not compromise the efficacy of somatrogon with regard to IGF-1 levels or growth normalization.

Longer term efficacy

Both the phase 2 and pivotal phase 3 studies had OLE periods.

In the pivotal phase 3 study, 212 of 222 subjects who completed 12 months of the CP-4-006 main study period continued into the OLE period. As of the cut-off date of 01 November 2019, efficacy data was available for 94 subjects at month 18 (6 months of OLE), and 9 subjects at month 24 in the OLE period (12 months of OLE). The Annualised HV for patients on somatrogon at months 18 and 24 were slightly lower to the results reported at month 12, however demonstrated continual effect on growth.

The annualized HV for subjects who switched from somatropin to somatrogon at the beginning of the OLE period was consistent with subjects who received somatrogon during the main study and throughout the OLE period.

Change in HT SDS from baseline demonstrated sustained improvement with weekly somatrogon in the main study period, and this improvement continued over the OLE period. Improvements in change in HT SDS from baseline and HT SDS for subjects who switched from somatropin to somatrogon at the

beginning of the OLE period were consistent with subjects who received somatrogon during the main study and throughout the OLE period.

The results from the OLE part of study CP-4-004 were broadly in line with those seen in the Phase 3 pivotal study. Patients were initially either maintained on their initially assigned treatment dose, with patients receiving somatropin being randomised to one of the three cohorts. Following the assessment of the initial phase data, all patients were transitioned onto the final dose of 0.66mg/kg/day, where they remained for the remaining periods.

The height velocity profiles of patients who were initially assigned to the lower dose cohorts but later transitioned to the final 0.66mg/kg/day dose were similar to those in patients who had received that dose from the beginning, although it is unclear whether patients experienced a catch-up phase in their growth once the dose change occurred.

A comparative analysis between the OLE phase of study CP-4-004 and historical data was requested in a Scientific Advice. The applicant has presented an analysis of the data generated as part of their clinical development, compared with matched historical controls from disease registries. This supports the conclusion that the final height anticipated for the patients treated with somatrogon are likely to be similar to other similar treatments already on the market.

The analysis lends support to the applicant's claim of efficacy for their product.

Treatment burden

Treatment burden was studied in a phase 3, randomised, multicentre, 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 (study C0311002).

The purpose of this study was to evaluate whether there is a benefit, defined as superior adherence and acceptance, of a once weekly injection schedule to support the benefit/risk profile of somatrogon.

The primary endpoint of treatment burden was assessed using the Patient Life Interference Questionnaire component of DCOA 1 and was completed by the participant/caregiver (dyad questionnaire) as an ePRO using a computer tablet.

87 patients were enrolled (43 somatropin, 44 somatrogon) 85 patients completed the study (97.7% completion).

The least squares mean of the Overall Life Interference total score was lower for the once weekly somatrogon injection schedule than for the once daily somatropin injection schedule. The mean difference (somatrogon-somatropin) was -15.49 (95% CI: -19.71, -11.27).

The difference in mean Overall Life Interference scores for somatrogon once weekly for 12 weeks, compared with administration of somatropin once daily for 12 weeks, was statistically significant ($p<0.0001$).

2.6.7. Conclusions on the clinical efficacy

Submitted clinical studies support that somatrogon is non inferior to somatropin in the treatment of paediatric GHD patients who have or have not received prior growth hormone treatment.

As the population included in the main studies was limited from 3 years to prepubertal, additional longer-term efficacy data was provided by the applicant to allow for extrapolation of data into older population. This was also in line with previously authorised medicinal products used for the treatment of this condition. CHMP agreed with an indication for use from 3 years to adolescents with GHD.

Overall, the applicant has provided a comprehensive clinical efficacy package, and, in addition, long-term efficacy data will be collected as secondary endpoints in the non-interventional study to be performed in the post-authorisation setting.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Two hundred and sixty-nine (269) paediatric subjects were exposed to somatrogon (vial and prefilled pen presentations). 257 subjects were exposed to the dose and pen presentation of somatrogon intended for registration of whom 147 subjects were treated for >12 months and 5 were treated for >24 months. Limited long-term exposure up to 5 years is available for children (n=35) who were treated with the vial formulation. These subjects then switched to somatrogon in the pen presentation (n = 35) for 12 months and additional exposure up to 01 November 2019 in Period V of the phase 2 OLE. No safety data are available for children <3 years of age.

2.6.8.2. Adverse events

In the controlled phase 3 pivotal study CP-4-006, the most frequently reported all-causality TEAEs that occurred in both somatrogon and somatropin treatment group were: injection site pain (39.4% vs 25.2%), nasopharyngitis (22.9% vs 25.2%), headache (16.5% vs 21.7%), pyrexia (16.5% vs 13.9%).

There was some variability in the incidence of AEs between the somatrogon and somatropin group. However, differences were generally small apart from increased reports of TEAEs in the General Disorders and Administration Site Conditions SOC in the somatrogon vs the somatropin group (46.8% vs 33% respectively).

Injection site pain (39.4% vs 25.2%), injection site erythema (8.3% vs 0.0%), injection site pruritus (5.0% vs 0.0%), injection site swelling (4.6% vs 0.0%) and injection site induration (3.7% vs 0.0%) were all reported more frequently in the somatrogon group compared to the somatropin treated group.

Most of the AEs were mild to moderate in severity. Of note, there were more reports of severe injection site pain in the somatrogon group (4.6%) compared with the somatropin group (2.6% subjects). In addition, there was one report each of severe injection site erythema and severe injection site haemorrhage in the somatrogon group.

Common treatment-related AEs by PT that occurred in $\geqslant$2% of subjects in the somatrogon treatment group were: injection site pain (39.4%), injection site erythema (8.3%), injection site pruritus (5.5%), injection site swelling (4.6%), injection site induration (3.7%), hypoinsulinemia (3.7%), headache (3.7%) and anaemia (3.7%).

In the CP-4-006 OLE period, 58% of study subjects reported AEs. The overall incidence of TEAEs was lower than in the main study period. Subjects who were originally randomised to somatropin in the main study experienced a higher incidence of TEAEs than subjects originally randomised to somatrogon (68.5 vs 47.1%) respectively. The TEAES reported in the open label arm were similar to the main study. The most common TEAEs were injection site pain (22.6%), nasopharyngitis (13.7%), pyrexia (7.1%), and headache (7.5%). All of these TEAEs were similar to or more commonly reported in

subjects who were previously treated with somatrogon, apart from injection site pain which was reported by 33% of subjects originally randomised to somatropin, compared to 18.3% of subjects treated with somatrogon. In this OLE, four subjects reported increased levels of IGF-1 as AEs (all previously treated with somatropin). Six subjects (2.8%) had treatment related severe TEAEs. There were five reports of severe injection site pain and 1 report of injection site deformation. Five of the reports were in subjects who received somatropin in the main study period and switched to somatrogon in the OLE.

Adverse event (AE) data from phase 2 CP-4-004 supports a similar short-term safety profile of somatrogon with that reported in CP-4-006. No new safety concerns were identified in the AE longer-term safety data from the extension study CP-4-004 OLE other than one report of serious scoliosis. This was reported as related to study drug but is likely to be due to exacerbation of existing scoliosis due to a rapid phase of growth and has been previously described with GH therapy.

In the follow-on open label extension, a slightly higher proportion of the study population (81.3%) reported AEs. Most were mild or moderate in intensity and were considered unrelated to study treatment. No new or unexpected safety signals were identified. Of note two reports of scoliosis (1 in year 3 and 1 in year 4) and 2 reports of insulin like growth factor increased (1 in year 2 and one with PEN) were reported as related to study drug. One subject each had dose reductions due to Scoliosis and Keeled chest acquired during Period IV (Year 4 OLE). All were considered to be possibly or definitely related to study treatment. Two subjects were withdrawn due to Osteochondrosis during Period V (pen) and Scoliosis during Period IV (Year 4). These AEs were reported after long-term treatment with somatrogon. These conditions are most common in adolescence but could have been exacerbated during rapid bone growth with GH treatment.

The applicant has provided updated tabulated summaries of TEAEs, (all cause and treatment related) SAEs and AESIs according to treatment exposure and ADA status up to the data cut-off date of 21 December 2020. These data are presented according to initial randomization groups i.e. those originally randomised to somatrogon and for those originally randomised to somatropin. The safety profile of the pooled safety data is similar to the safety data described for the individual studies in the original application. Injection site pain, nasopharyngitis, headache and pyrexia were the most common all causality reported TEAEs reported in the pooled analysis. Injection site pain was the most frequently reported TEAE overall (5.0/PY). The rate of injection site pain reported per patient year was slightly lower in subjects originally randomised to somatrogon vs those originally randomised to somatropin (adjusted Rate/PYs 4.75 vs 5.25 respectively). In patients originally treated with somatrogon TEAEs were reported more frequently in the ADA+ subgroup. However, in subjects originally randomised to somatropin, TEAEs were more frequently reported in the ADA- subgroup. There is no clear pattern of association between the TEAEs reported and the ADA status.

The most commonly reported treatment related TEAEs were injection site reactions: injection site pain, pruritus, swelling and erythema.

The applicant has identified a number of additional TEAEs that may be causally linked to treatment with somatrogon which have been added to the SmPC Section 4.8 as adverse drug reactions (anaemia, eosinophilia, arthralgia, pain in extremities, hypothyroidism, adrenal insufficiency, headache, pyrexia, conjunctivitis allergic, rash generalized). Other TEAEs of interest that were reported as being treatment related were 4 reports of eosinophilia in the group originally randomised to somatrogon and 3 in the group originally randomised to somatropin.

Although it is recognised that a number of adverse reactions related to growth hormone class effects (i.e. diabetes mellitus type 2, paraesthesia, benign intracranial hypertension, pancreatitis) have not been identified in this clinical development program, these are well-described side effects and were

also included in Section 4.8 as class effects under the subheading 'Description of selected adverse reactions'.

Overall, apart from increased reports of local injection site reactions and concerns regarding increased levels of IGF-1 (see AESI ISR and IGF-1 discussed below), the short-term safety profile suggests that the safety of somatrogon is comparable to daily hGH therapy.

Adverse Events of Special Interest

AESIs were based primarily on the class-based important potential identified risks associated with treatment with somatropin-containing products. Injection site reactions, glucose metabolism impairment, thyroid function impairment, immunogenicity, elevated pancreatic enzymes (e.g. amylase or lipase) or diagnosis of acute or chronic pancreatitis, cortisol changes, intracranial hypertension, malignant neoplasia, intracranial haemorrhage, intracranial aneurysm, and slipped capital femoral epiphysis and other musculoskeletal, nonserious adverse events, were evaluated as adverse events of special interest (AESIs). With regard to the AESIs, the incidences in most of the categories were low and similar between treatment groups in the CP-4-006 and CP-4-004 main study periods, and in the respective OLE periods, apart from the categories of injections site reactions and immunogenicity (see section on immunogenicity).

In the Phase 3 main study, injection site reactions AEs were more commonly reported with somatrogon compared to somatropin. (43.1% during somatrogon treatment vs. 25.2% during somatropin treatment). Injection site pain was the most frequent injection site reaction. Other reported injection site reactions (erythema, pruritus, swelling, induration, bruising) was also higher in the somatrogon group than the somatropin group. There were no reports of lipoatrophy. Five subjects treated with somatrogon reported severe injection site pain.

In the OLE 26.9% of subjects reported ISRs. 12.5% in the group originally randomised to somatrogon compared with 40.7% in the group originally randomised to somatropin. The most frequently reported AE was injection site pain (22.6%%) the incidence was higher in the group originally randomised to somatropin (33.3%) compared to the group originally randomised to somatrogon (11.5%). Other injection site reactions reported were injection site erythema and injection site pruritus, both reported at higher incidences in subjects originally randomised to somatropin than subjects originally randomised to somatrogon. There were 5 reports (2.4%) of severe injection site pain and one severe report of injection site deformation.

One patient discontinued from phase 3 study due to AEs of Injection site erythema and injection site induration. In the phase 3 OLE, 4 subjects had study drug withdrawn due to moderate injection site reactions of pain, erythema and pruritus.

In a heat map analysis of severity and duration of injection site pain, injections site pain were most commonly reported in the first 6 months of treatment but most subjects reported multiple episodes of injection site pain with 4 subjects treated with somatrogon reporting between 22 to 51 painful injection events. Injection site pain including severe events was most commonly reported for injections to the arm (left and right). The incidence rate for injection site pain was higher in males compared to females and in Asian subjects compared to White.

An analysis of all injection site reactions by self-reported patient assessment (regardless of whether they met the criteria for an AE as determined by the investigator) indicated 89.0% of the subjects (97 of 109) in the somatrogon group and 88.7% of the subjects (102 of 115) in the somatropin group experienced at least one injection site reaction. The incidence of subjects with the most severe (self-

reported) pain score (5= ”hurts worse”) was 29.9% in the somatrogon group compared with 13.7% in the somatropin group.

In the Phase 2 CP-4-004 Main Study Period one subject in the 0.66 mg/kg/week dose group experienced 5 moderate injection site reactions (injection site erythema, injection site hematoma, injection site pain, injection site pruritus, and injection site swelling). No subject reported an AE of injection site reaction during years 1-4 of the OLE period. 7.5% (3 subjects) reported injection site reactions during Period V (pen).

In the pooled safety analysis, a review of AESIs based primarily on the class-based important potential identified risks relating to somatropin-containing products is presented by PT and SOC rather than grouped together under specific headings like ‘injection site reactions’. Nonetheless, it is apparent that similar to the original safety analysis, injection site reactions are the most frequently reported AESI category in both treatment groups (subjects originally randomised to somatrogon and somatropin).

2.6.8.3. Serious adverse event/deaths/other significant events

No fatal cases were reported during the clinical development plan for somatrogon.

In the phase 3 study, 2.2% (5 subjects) in the somatrogon group reported serious adverse events, none are considered related to the drug trial. None led to permanent discontinuation from study treatment. In the phase 3 OLE, 3.3% (seven) subjects reported 10 SAEs. None of these SAEs was related to study medication. There were no subjects that discontinued due to an SAE. In phase 2 CP-4-004 study; there were no reports of SAEs in either the somatrogon group or somatropin group. In CP-4-004 OLE Period, 3 subjects (6.3%) reported at least 1 SAE. One serious case of idiopathic scoliosis was considered to be related to study medication by the investigator but not by the applicant.

In the analysis of pooled data, 10 subjects in the group originally randomised to somatrogon reported SAEs compared to 5 subjects originally randomised to somatropin. The only SAE reported in more than one subject in the group originally randomised to somatrogon is pneumonia which is reported twice. Two other SAEs of note in this subgroup were one serious report of Schwannoma and one serious reaction of urticaria.There was one report of Kawasaki disease. There were no serious injection site reactions. None of the SAEs were reported in the ‘related to study treatment’ analysis.

The only SAE reported in more than one subject in the group originally randomised to somatropin was appendicitis which was reported twice. Overall, 10 subjects in the group originally randomised to somatrogon reported SAEs compared to 5 subjects originally randomised to somatropin.

The only SAE reported in more than one subject in the group originally randomised to somatrogon is pneumonia which is reported twice. Two other SAEs of note in this subgroup were one serious report of Schwannoma and one serious reaction of urticaria.

There was one report of Kawasaki disease. There were no serious injection site reactions. None of the SAEs were reported in the ‘related to study treatment’ analysis.

2.6.8.4. Laboratory findings

The haematology parameters for the majority of subjects were generally within normal limits during the main study period in CP-4-006. A majority of the clinically significant haematology shifts to out of range values were mild and transient and were not considered treatment related. There were 7 reports of clinically significant anaemia. There were 2 reports of eosinophilia. None of the events required any dose modifications. Overall, none of these deviations in hematologic parameters from normal were considered clinically significant. A similar trend in hematologic were noted during the CP-4-006 OLE

period. During the phase 2 study, CP-4-004 e8 subjects had anaemia recorded as an AE, 11 subjects (26.2%) receiving somatrogon had absolute eosinophil counts above the normal range.

Clinical laboratory including glycaemic, hormonal, and lipid parameters were generally stable throughout somatrogon treatment. The clinical laboratory profile in CP-4-006 showed no glucose metabolism abnormalities in the somatrogon treatment group. There was no new onset of diabetes or hyperglycaemia in any subject treated with somatrogon. No clinically meaningful differences between treatment groups were observed for thyroid function or lipids.

IGF-1

Twenty-two (22) subjects had at least 1 out-of-range IGF-1 value. Clinically significant IGF-1 values were only recorded as an AE if the change in IGF-1 was associated with signs or symptoms.

CP-4-006 main study period: 29 subjects (26 in somatrogon and 3 in somatropin) had an IGF-1 SDS >2 at any time during study CP-4-006. The proportion of somatrogon treated patients with IGF-1>2SDS increased from 4.7% at month 1 to 13.1% at month 12. 14 subjects experienced persistent IGF-1 levels >2 SDS (i.e., 2 consecutive SDS>2 measurements), resulting in dose modification for 12 of these subjects. Eight of these subjects reported other AESIs (injection site reactions n=8, vomiting n=4, nausea n=1, abdominal pain n=3 hypothyroidism n=1).

A *post hoc* population PK/PD analysis was performed using 535 post dose IGF-1 samples collected from 109 subjects in the somatrogon group to determine and evaluate individual mean IGF-1 SDS over the dosing interval. The incidence of individual observed IGF-1 SDS values >2 was larger compared to individual modelled IGF-1 SDS values. At 1 month, the IGF-1 SDS modelled mean [SD] over the dosing interval was -0.32 [0.94] (median: -0.3) and observed IGF-1 SDS mean was 0.00 [1.38] (median: 0.07). At 12 months, the IGF-1 SDS modelled mean [SD] over the dosing interval was 0.25 [0.97] (median: 0.28) and observed IGF-1 SDS mean was 0.66 [1.30]) (median: 0.77).

CP-4-006 OLE period: 18 subjects (8.5%) with levels of IGF-1 >2.0 SDS had protocol-specified somatrogon dose reductions. Two IGF-1 related AEs were reported. One subject had an increase that required a dose reduction, was mild in severity and related to study treatment. Another subject reported an AE of headache.

Study CP-4-004: No subjects in 0.25 mg/kg/week group or 0.48 mg/kg group had levels of IGF-1 SDS >2 at any time point during the 12 months safety analysis period. Only 1 subject in 0.66 mg/kg/week had levels of IGF-1 SDS >2 at 5 visits that required dose reduction. In the OLE mean IGF-1 SDS for all cohorts in Year 1 and subjects in Year 2 were similar and increased at Year 3 and the end of Period V (pen). A total of 7 subjects (15.9%) in year 2, 7 (16.3%) in year 3 and 1 (2.6%) in year 4 had IGF-1 SDS (Z) >2 of whom 2 subjects (4.5%), 2 subjects (4.7%) and 2 subjects (5.3 %) respectively required dose reduction.

2.6.8.5. In vitro biomarker test for patient selection for safety

No such tests were performed, which is acceptable.

2.6.8.6. Safety in special populations

There were no remarkable differences between the various age groups, genders or regions with respect to demographics, incidence of treatment-emergent adverse events, or laboratory test results. It should

be kept in mind that the indication applied for is for children only. Therefore, no information on the elderly (over the age of 65) was included in this assessment.

Animal reproduction studies have not shown evidence of harmful effects on the foetus. There are, however, no adequate and well controlled studies in pregnant women. There have been no studies of somatrogon in pregnant or lactating women.

2.6.8.7. Immunological events

The total incidence of subjects with AEs related to immunogenicity/hypersensitivity was 18.3% (20 subjects) in the somatrogon group and 7.8% (9 subjects) in the somatropin group. In the somatrogon group, the most frequent events were conjunctivitis allergic (2.8%), rash generalized (2.8%), and rhinitis allergic (2.8%). In the somatropin group, the most frequent event was rash (2.6%). All other individual PTs were reported in <2% (≤ 2 subjects) in each treatment group. Two events of eyelid oedema in 1 subject in the somatrogon group and 1 event of urticaria in a subject in the somatropin were treatment related. In the OLE 5.2% of subject reported AEs related to immunogenicity/hypersensitivity.

In the updated pooled analysis, AESIs relating to immunogenicity/hypersensitivity are presented by SOC rather than as grouping of immunogenicity related AEs. Similar to the original analysis, most of the immunogenicity related AESIs are reported in the skin and subcutaneous disorders SOC. The overall safety profile is similar to that reported in the original analysis of studies CP-4-004 and CP-4-006. Only one report of idiopathic urticaria is reported as treatment related.

During the OLE period of the main study, the percentage of subjects reporting AEs related to immunogenicity/hypersensitivity was lower than the main Phase 3 study at 5.3%. Eczema, which had an incidence of 1.9%, was the only AE reported in more than one subject. There were increased reports of Immunogenicity AESIs in the 3-7 years age group, in male and Asian children.

In the supportive Phase 2 study the incidence of TEAEs related to immunogenicity/hypersensitivity in the somatrogon groups were low and comparable across the treatment groups. In the phase 2 OLE (37.5%) tested ADA+ for somatrogon at any time during the OLE period. Three somatrogon subjects were newly reported ADA+ in the OLE period.

In the phase 3 study CP-4-006, 77.1% subjects tested ADA+ for somatrogon compared to 15.7% for somatropin treated subjects at any time during the main study. Two somatrogon-treated subjects tested positive for NAbs: 1 subject at month 6 (Week 26) and both subjects at month 12 (Week 52). Median time to the first ADA+ result was 6 months, and 98.8% had persistent ADA+ results. The incidence of injection site reactions was numerically higher in ADA+ subjects compared to ADA- subjects and 6 of the 7 subjects with severe injection site reactions in the somatrogon group, tested ADA+. In the OLE 65.8% tested ADA+ at Month 6 in the OLE. Most subjects who tested ADA+ showed specificity to hGH, 5 subjects showed specificity to CTP.

Within the phase 2 study CP-4-004 among 42 somatrogon-treated subjects, 10 subjects (23.8%) tested ADA+ for somatrogon at 6 months (Week 26), and 5 of these subjects (11.9%) tested ADA+ at 12 months (Week 52), suggesting that transient anti-somatrogon antibodies had developed. No subjects receiving the lowest dose (0.25 mg/kg/week) developed ADAs. Testing ADA+ for somatrogon had no overall effect on incidence of treatment emergent adverse events during the 12-month main study period. In the registration study CP-4-006, 84/109 patients (77.1%) were tested ADA+ for somatrogon at any time during the main study. The applicant stated that median time to the first ADA+ result was 6 months, and 83/84 subjects had persistent ADA+ results. The tolerability of somatrogon seems to be partially better in patients tested negative for ADA, particular regarding immunogenicity (21.4% vs

8.0%), injection site reactions (46.4% vs 32.0%) and abdominal symptoms. (13.1% vs 4.0%). Some have been further discussed by the applicant (see the discussion on clinical safety).

2.6.8.8. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been conducted with somatrogon. This is acceptable and no AEs were reported related to drug-drug interactions. Literature reports were used to describe potential interactions. Somatrogon may be considered a weak inducer of CYP3A4.

The impact of GH on insulin activity is complex but is generally antagonistic to insulin. Studies have not been performed to assess the effects of somatrogon on blood sugar control in subjects with diabetes, either type 1 or type 2, controlled with either insulin or oral glucose lowering drugs.

2.6.8.9. Discontinuation due to adverse events

In the phase 3 study, 2.8% (3 subjects) of subjects treated with somatrogon had their study drug dose reduced or temporary discontinuations due to an AE. All events were mild to moderate in intensity and resolved (pyrexia, synovitis, Henoch–Schönlein purpura). Only 1 event synovitis (somatrogon treatment group), was considered by the Investigator to be possibly treatment related.

One subject from the somatrogon group permanently discontinued the study drug and from the study due to injection site erythema and injection site induration.

In the CP-4-006 OLE period, 1.4% (3 subjects) experienced TEAEs that led to either a dose reduction or dose interruption. 2.4% (5 subjects) had TEAEs that led to study drug withdrawal and discontinuation, 4 subjects withdrew due to injection site reactions (erythema, pruritus, 2 cases of injection site pain; all related to study drug). One subject withdrew due to increasing anxiety, not considered related to study drug.

In CP-4-004 OLE Period, 4 subjects (8.3%) had dose reductions due to a TEAE. Two subjects had dose reductions due to IGF-1 increase. One subject each had dose reductions due to scoliosis and keeled chest acquired during Period IV (Year 4 OLE). All were considered to be possibly or definitely related to study treatment. Two subjects were withdrawn due to osteochondrosis during Period V (pen) and scoliosis during Period IV (Year 4).

2.6.8.10. Post marketing experience

Somatrogon was approved in Canada on 27 October 2021 for the long-term treatment of paediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (growth hormone deficiency). This approval occurred after the cut-off date for the safety report included in this application, and no post-marketing data are yet available.

2.6.9. Discussion on clinical safety

Exposure

The safety assessment information comprised data from a single-phase three study, a supportive phase 2 study with their respective OLEs in children with GHD (CP-4-006 and CP-4-004 and their OLE periods). Some additional safety data regarding injection site reactions was provided from a 'Perception of

Treatment Burden' study C0311002. GH treatment naive children between the ages of 3 and 11 were recruited to the phase 2 and 3 studies.

The safety assessment is mainly focussed on studies CP-4-006 and CP-4-004 and their OLE periods. Safety data has not been integrated so studies have been reviewed separately. Across these studies, 269 subjects were exposed to the vial and pen presentations of somatrogon at all dose levels. The combined total exposure to somatrogon in these studies was 476.8 patient-years. The median duration of exposure was 14.9 months. Of these 269, 257 subjects were treated using the PEN presentation (0.66 mg/kg/week) intended for commercialisation with a total exposure of 272.4 patient years and a median duration of exposure of approximately 14.7 months. Of these 147 subjects were treated for > 12 months and 5 were treated for ≥ 24 -30 months. 37 subjects received 0.66 mg/kg/week (vial presentation), the dose intended for registration of somatrogon for up to 5 years. 119 subjects who were initially treated with somatropin switched over to somatrogon in the OLE phases of CP-4-006 (n=108) and CP-4-004 (n=11).

The applicant has provided a pooled safety analysis with exposure adjusted analyses for patients across Phase 2 (CP-4-004) and Phase 3 studies (CP-4-006) along with their ongoing OLE periodsup to the data cut-off date of 21 December 2020The mean weekly dosage of somatrogon in the main treatment period for the pivotal study CP-4-006 (using the pen presentation) tended to be higher compared to patients treated with somatropin (0.65 mg/kg/week for somatrogon vs. 0.24 mg/kg/week somatropin). In the extension treatment period, mean study treatment doses of somatrogon in patients who were previously treated with somatrogon and those previously treated with Genotropin were comparable (0.63mg/kg/week and 0.66mg/kg/week). The clinical relevance of this observed increase in weekly exposure between the somatrogon and somatropin treated patients with respect to long-term safety of paediatric GHD treatment is unclear and further supports the need for the proposed PASS.

The exposure data partially fulfils the requirements of ICH-E1 guideline on the extent of population exposure to assess clinical safety (CPMP/ICH/375/95). However, GH is a well-known active substance and the safety population could be sufficient to determine the short comparative safety profile with somatropin over 1 year.

The potential impact from the novel molecular structure needs to be carefully evaluated over longer term exposure. The safety of long acting somatropin (the mechanism by which GH action is prolonged and the duration of prolongation) will be further evaluated in a post marketing safety study to address the long-term safety of somatrogon.

IGF-1 SDS >2

Most subjects in both study CP-4-006 and CP-4-004, main and OLE periods, had IGF-1 SDS values within normal limits. The proportion of study participants reporting an IGF-1 level >2 SDs at any time during the CP-4-006 main study was noticeably higher in the somatrogon group compared to somatropin and the proportion of subjects in the somatrogon group with IGF-1 level >2 SDs increased across all treatment cycles. A total of 14 Subjects had sustained levels (>2 consecutive visits which lasted at least 13 weeks). Twelve of these subjects required dose modification. Eight subjects reported other AESIs. However, none was attributed to the high IGF-1 levels. Only two AEs were considered related to somatrogon (ISR and hypothyroidism) and are expected with hGH therapy. No subjects reported IGF>3SDS.

One explanation of the high levels (IGF-1 SDS >2) was that samples were collected earlier in the dosing interval than outlined in the protocol (before 72 hours post dose, rather than at the suggested 4 days post dose). *Post hoc* population PK/PD modelling showed that although the mean and median IGF-1 levels were< 2SDS, there was a trend towards increased levels across the repeat doses in the main study.

In the phase 2 study CP-4-004 OLE the proportion of subjects with IGF-1 >2 was significant and fluctuated over the 5-year period of the study. (15.9% in year 2, 16.3% in year 3 2.6% in year 4 and 27.5% in PEN (year 5).

There were no reports of malignancy in the phase 2 study. No clinically meaningful changes in glucose metabolism, including insulin sensitivity, were observed in the phase 2 OLE. Although the observed mean blood glucose values and HbA1c remained within normal, mean blood glucose values did tend to increase during the PEN phase.

Out-of-range IGF-1 laboratory results that were deemed clinically significant without an associated AE were not recorded as an AE because IGF-1 values were not intended to be monitored for clinical significance nor as an AE, unless the change in IGF-1 was associated with signs or symptoms. Serum IGF-I levels in themselves are a measure of safety. The sustained high level of IGF-1 (IGF-1 SDS > 2) above the physiological range in patients treated with somatrogon compared to daily dose of somatropin in study CP-4-006 is a concern. High normal IGF-I levels have been associated with an increased risk of multiple forms of cancer. IGF-1 has been associated with glucose intolerance and may have a role in tumorigenesis. The risks related to non-pulsatile physiological levels and sustained high IGF-1 levels above the physiological range over longer-term exposure with somatrogon needs to be carefully evaluated. The applicant has provided details of a suitable PASS to address this issue. Malignancy and glucose intolerance (type 2 diabetes) have been included as important potential risks in the RMP. The SmPC has been updated to include information regarding IGF-1 monitoring and the need for GH dose adjustments.

Adverse events

In the integrated summary of TEAEs of pooled safety data from studies 004 and 006 up to 21 Dec 2020 (main study period and OLE for both studies) a total of 216 subjects reported an adverse event in this analysis.

The safety profile of the pooled safety data is similar to the safety data described for the individual studies. Injection site pain, nasopharyngitis, headache and pyrexia, are the most common all causality reported TEAEs reported in the pooled analysis. Injection site pain is the most frequently reported TEAE overall (overall adjusted rate 5.0/PY). There is no clear pattern of association between the TEAEs reported and ADA status.

The incidence of serious adverse events (SAEs) was low across all studies. All were considered unlikely to be related to study treatment except one report of scoliosis.It is agreed with the applicant that this is more likely to have been caused by a good growth response to somatrogon, which potentially resulted in worsening of the scoliosis. The adjusted rates for SAEs are similar across both groups (somatrogon and somatropin originally randomised treatment groups,) and in each strata (ADA+ and ADA-). None of the SAEs were related to study treatment.

With consideration of possible class effects, a number of additional ADRs have been identified. In addition to the ADR of 'injection site reaction' which includes reports of injection site pain, erythema, pruritus, swelling, induration, bruising, haemorrhage, warmth, hypertrophy, inflammation, deformation and urticaria, a number of additional TEAEs were identified. These may be causally linked to treatment with somatrogon (anaemia, eosinophilia, arthralgia, pain in extremities, hypothyroidism, adrenal insufficiency, headache, pyrexia, conjunctivitis allergic, rash generalized). These have been added to the SmPC Section 4.8 as adverse drug reactions.

As somatrogon has a similar side effect profile to somatropin, it is also anticipated that it will share many of the known side effects of daily rhGH. GH therapy class effects have been added as adverse reactions in Section 4.8 under the sub-heading 'Description of selected adverse reactions'. Adverse reactions

described in section 4.4 or known to result from conditions mentioned here have also be included in section 4.8.

The overall incidence of AESIs was higher in the somatrogon group compared to somatropin in both the phase 3 and phase 2 studies. In most of the categories, the incidences of AESIs were low and similar between somatrogon and somatropin treatment groups across all studies. Injection Site Reactions (ISRs) and Immunogenicity had the highest incidence of any AESI categories in both treatment groups in the phase 3 Study CP-4-006 main study period. In regard to the pooled safety data review, the adjusted rates for AESIs were similar across both groups (somatrogon and somatropin originally randomised treatment groups,) and in each strata (ADA+ and ADA-).

Injection site reactions

In the phase 3 Study CP-4-006 main study period, almost twice as many patients in the somatrogon group vs somatropin (43.1% vs 25.2%) reported injection site reactions as AESIs. Over the OLE, 26.9% reported ISRs. However, of note in the OLE the proportion of subjects previously treated with somatropin had a much higher rate of ISRs (51.9%) compared with subjects previously treated somatrogon (12.5%).

Injection site pain was the most common injection site reaction. These reactions were mainly reported as mild to moderate in severity, but 5 cases of severe AEs were reported in the main phase 3 study and a further 5 in the OLE. Reports of painful injections were consistently more frequently reported for somatrogon compared to somatropin, despite the fact that one was weekly and the other a daily injection. The methodology for assessing and recording injection site reaction AEs in particular injection site pain impacted on the interpretation of the results from the various studies, and the incidence of injection site pain between the two treatment groups is thus difficult to compare.

The higher rate of painful injection site reactions in the somatrogon group did not result in significant levels of withdrawal of treatment (13 patients overall) or dose adjustments.Injections into the arms were more painful than other sites in the body. Severe reactions were most commonly reported in the arm. There was a disparity between the number of reports of injection site pain reported as AEs and severe AEs across the different analyses in the Phase 2 and Phase 3 paediatric GHD studies, asa result of the difference in how AEs were recorded in the two studies.

Children who switched from Genotropin treatment to somatrogon treatment experienced rates of ISRs similar to starting somatrogon treatment *de novo*, which could be due to the way in which ISR AEs were reported or could suggest that the ISRs experienced with somatrogon were more painful.

Further information on injection site reactions was also collected in the tolerability study (C0311002).. All reported Injection site reactions were recorded as AEs. There was no minimum severity score required for these injection site reactions and there was no limit to the number of injection site reactions that could be recorded as AEs per week. In this study 21.8 % of the somatrogon group vs 16.3% of once daily somatropin group reported ISR AEs. However, the different reporting methodology and crossover study design makes it difficult to interpret this data.

Although injection site reactions were commonly reported with somatrogon, and in some cases these reactions persisted over longer-term treatment, it is not possible to accurately compare the rate of injection site reactions with somatrogon and somatropin. The relative tolerability of these treatments in terms of ISRs is difficult to determine, due tothe difference in how AEs were recorded across studies. The reason for the increase in injection site pain observed with somatrogon compared to somatropin is not clear, althoughseveral possible causes were explored: needle features, injection volume, injection solution temperature, injection site, osmolality, pH, excipients and injection technique. The only difference of note was that subjects administering somatrogon injected an average volume 4-5x that of somatropin. However, the severity of pain does not appear to correlate with an increasing volume within

each cohort. The wording in section 4.2 of SmPC thus recommends rotating the site of injections to minimise the risk of a painful injection.

The information provided in the subsection on injection site reactions under the heading 'Description of selected adverse reactions' in section 4.8 has been expanded to provide information on the time to onset, duration of and persistence of injection site reactions with somatrogon treatment.

With the expectation of better tolerability of weekly somatrogon over daily hGH dosing, the applicant was requested to further discuss the clinical implications of the observed high reporting rates of painful injections. No literature evidence has been identified by the applicant that suggests repeated painful injections have a lasting impact on the child's pain responses. Although there are no reports in patients following daily growth hormone injections, reports of needle procedures in other settings (vaccination, hospital settings) report that injections are highly feared by many children (*Hart & Bossert, 1994; Taddio 2012*) and are often accompanied by significant pain and distress for both children and their parents, which, in turn, can lead to the development of significant needle fears which can persist into adulthood (*McMurtry 2015b*). This can contribute to medical non-adherence (*Pate 1996*).

Immunological events

Most AEs were mild or moderate in severity and most events were grade as not related to study treatment by the investigators. There were no systemic hypersensitivity reactions (anaphylaxis, angioedema, and immune complex disorders). The applicant has further discussed the immunogenicity AEs in more detail, particular the relatedness to treatment and has added conjunctivitis allergic, rash generalized (local to injection site reaction), pyrexia, and section 4.8 of the SmPC was informed accordingly. There are no reports of severe systemic hypersensitivity in the somatrogon clinical trials. Side effects due to the presence of the C-terminal peptide (CTP) of the hCG beta-subunit have been discussed by the applicant. No new side effects or concerns relating to immunogenicity associated with the CTP have been identified.

In relation to the anti somatrogon antibodies, it seems that not all patients have complied with all visits respectively blood sampling for antibody titres. The original protocol for the CP-4-006 main study included testing for ADA not earlier as 6 and 12 months after study start. This was amended later on, but by the time of implementation at all study sites, many subjects had already completed the Day 10, Month 1, and Month 3 visits per the original Protocol. In addition, samples were collected at Visits 3 and 4, which were close in timing, and all results were negative for ADA, so that it is agreed that combining both groups does not change the outcome of the findings or report.

In relation to the presence and impact of the ADA status on the safety profile of somatrogon, there is not a temporal relationship with onset of injection site reactions and ADA. Although injection site reactions may persist, most occur early in treatment and subside as the study continues. In contrast (temporary), although some individuals tested positive for ADA at 3 months after study start, most of those who ultimately tested positive among treatment naïve individuals tested positive 6 months after study start.

There was no clear pattern of ADA positivity being associated with severe injection site reactions and immunogenicity is included as an important potential risk in the safety specification of the RMP.

Almost all individuals who tested positive for ADA showed persistent ADA. As almost all individuals who tested positive for ADA showed persistent ADA, no further comparison of patient characterises based on persistent ADA response is possible (age, sex, weight, GHD severity, dose adjustments and final dose of somatrogon as well as number and timing of the blood samplings for antibody titres, titre values in the course of the study as well as the incidence /severity of related adverse events and IGF-1 level).

Reports of injection site reactions was numerically higher in ADA+ subjects compared to ADA- subjects and 6 subjects with severe injection site reactions in the somatrogon group, tested ADA+. The applicant states that a higher rate of injection site reactions within the first few months of treatment, prior to the emergence of ADAs at 6 months undermines a potential relationship between ISRs and ADA positivity. However high rates of ISRs were reported throughout the main study. Further details of the ADA profile of these cases of severe ISR have been provided for review. In all cases of severe ISR, ADA positivity was first detected at 6 months. In three cases ADA positivity was sustained across 24 + months. The ADA titres fluctuated across all time points with titres ranging from 250 to >6250 detected at varying time points. There was no clear pattern of ADA positivity identified in these cases of severe ISR including time to onset of ADA positivity, duration of positivity, ADA titres.

The long-term clinical relevance of sustained ADA positivity needs to be carefully evaluated. "Immunogenicity specifically related to the long-term clinical impact on lack of efficacy and safety (especially in relation to severe injections site reactions)" has been included as a safety concern in the RMP.

Further events of special interest

The incidence of AEs related to potential signs and symptoms of abdominal pain was low overall and similar across the somatrogon and somatropin groups. No subjects had AEs related to elevated pancreatic enzymes. Additionally, no subjects had AEs indicative of a diagnosis of pancreatitis. In the somatrogon group, the most frequent events were vomiting (7.3%), abdominal pain (3.7%) and nausea (2.8). A warning has been included in the SmPC somatrogon regarding severe abdominal pain and the risk of pancreatitis during treatment.

Although the effect was small in the paediatric population the data presented confirmed that somatrogon might impair the glucose tolerance as well as the thyroid and adrenal cortical function. As the clinical experience of somatrogon is low, a warning was included section 4.4 of the SmPC, in line with the other growth hormone medicinal products. More data on the long-term safety is to conclude on a possible induction of type 2 diabetes mellitus.

With regard to the data provided until now, no AEs related to intracranial haemorrhage, aneurysm, or hypertension as well as to epiphyseal disorders were reported. As the clinical experience with somatrogon is limited, the warnings in the SmPC were adapted to those of other growth hormone medicinal products.

The incidence of AEs related to benign neoplasia was low overall, similar in the somatrogon and somatropin groups, and limited to the events of skin papilloma and melanocytic naevus. A warning regarding the risk of neoplasia has been added to section 4.4. In addition, it should be kept in mind that, the data for the long-term safety is considered insufficient, as there is an ongoing discussion of a long-term carcinogenic effect of GH (and/or IGF-I).

The potential impact on glycaemic control and tumorigenesis in children will be evaluated in a phase 4, open-label post marketing safety study. Malignancy and diabetes mellitus type 2 have been included as important potential risk information in the safety specification of the RMP.

Most TEAEs that were reported were mild to moderate in severity and were graded as not related to study treatment. Following a review of TEAEs arthralgia, pain in extremity have been added to section 4.8 as ADRs.

Subgroups

There were some differences between the various age groups, genders or regions with respect to incidence of TEAEs. Immunogenicity reactions was reported in the somatrogon subgroup: >3 years =<7 compared to >7 years. (30.2% vs 10.6%). The immunogenicity events reported by more than one subject were rash, rash generalised and conjunctivitis allergic. The incidence of injection site pain was

higher in males (34.8%) than females (25.4%) and White subjects (30.2%) compared to Asian subjects (4.8%). The higher number of reports of immunogenicity reactions in the younger age group in the somatrogon cohort has not been clearly explained. Immunogenicity is included as an important potential risk in the safety specification It is agreed that the higher reporting of injection site pain in White subjects vs Asian subjects administering somatrogon and somatropin most likely relates to geographical variation and does not appear to carry any clinical meaningfulness.

Laboratory findings

Two significant errors regarding reporting and data handling of laboratory results were identified Further clarification regarding the extent, root cause and resolution of these errors has been provided. and GCP inspections were conducted for the somatrogon clinical CP-4-006 by the FDA in 2021. Six clinical trial sites, 4 in the US and 2 in the European Union, namely Spain and Poland were inspected. There were no findings of note. In view of the existing information it is agreed that it is unlikely that the omitted data would have impacted the safety evaluation.

Glucose metabolism, thyroid function and cortisol levels

Laboratory parameters related to glucose metabolism, thyroid function and cortisol levels, all of which were AESIs, were generally within normal limits.

However, glucose intolerance is a well-described side effect of growth hormone treatment and section 4.4 of the SmPC includes a warning to that effect.

Mean FT4 and TSH levels remained consistent over time and comparable for both treatment groups during the main period and OLE periods. No significant change from baseline of the mean values of FT4, T3 or TSH parameters was observed in somatrogon or somatropin treated patients although there were occasional increases or decreases noted for individual subjects.

In the phase 3 study, 6.4% of the somatrogon group compared with 2.6% of the somatropin group reported AEs of hypothyroidism. Two subjects reported an AE of Thyroxine free decreased. None of these events was considered related to study medication. Treatment with daily rhGH may unmask previously undiagnosed or subclinical central hypothyroidism. Growth hormone replacement therapies are well known to be associated with potential decreased levels of FT4. Section 4.4 of the SmPC includes a warning regarding suboptimal response to GH treatment with undiagnosed/untreated hypothyroidism. A warning regarding impact of GH on conversion of T4 to T3 has been included in section 4.4. Hypothyroidism has also been included as an ADR in section 4.8.

The incidence of AEs related to cortisol changes in study CP-4-006 and study CP-4-004 (main study and OLE periods) was low, the events were mild or moderate, and none was reported as possibly related to study treatment.

The potential for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism has been described for patients on daily growth hormone therapy who have or are at risk for pituitary hormone deficiency(s). Patients with known hypoadrenalism may need to adjust their dose of glucocorticoid. Section 4.4 includes a warning to this effect. The need for careful monitoring of glucocorticoid dosing is also included as a warning in section 4.5. Adrenal insufficiency is included as an ADR in section 4.8.

Haematology & blood chemistry

Haematology parameters for majority of subjects were generally within normal limits during the main study period in CP-4-006. Most were mild and transient and were not considered treatment related and no new safety concerns identified. increased blood creatine phosphokinase levels were found, even if however, there was no clinical impact of increased blood creatine phosphokinase (CK) and this shift had

a higher incidence in the somatropin group , and this information was not listed as ADR, which was agreed on..A higher proportion of subjects treated with somatrogon compared with somatropin shifted from normal to high eosinophils levels in the phase 3 study (29.4% somatrogon group vs 12.2% somatropin group).The majority of these also had above normal eosinophil readings at screening/baseline visits. Many were transient. Eosinophilia was included as an ADR in the SmPC section 4.8.

Most of the mean blood chemistry values were within normal limits and showed no significant changes during the course of the study. Of note, a higher proportion of the somatrogon population had clinically significant out-of-range IGF-1 value compared to somatropin (see discussion of IGF-1 levels). Change from baseline of increase of phosphate levels, a known effect of GH therapy, was more common in the somatrogon group compared to daily somatropin. A shift from normal to high values of phosphate (known effects of GH therapy) was reported for more subjects in the somatrogon group than in the somatropin group. There was no clinical impact of the shift from normal to high values of the phosphate and the observed shift is consistent with the known effect of GH therapy. Further details of the case of elevated LDH >600 for subject (226-134) including a causality assessment has been provided for review.

The changes in the lipid parameters (cholesterol, triglycerides, free fatty acids, HDL cholesterol, and LDL cholesterol) were generally small and consistent between both treatment groups.

Drug-drug interactions

There were no clinical trials conducted with somatrogon to directly test for drug-drug interactions. In study CP-4-006, CP-4-004, and their respective OLE no AEs were reported related to drug-drug interactions. However, regarding glucose metabolism (insulin sensitivity) and different endocrine aspects (adrenal function, thyroid function, oestrogens) respectively the according concomitant hormonal therapies, there are some known interactions and section 4.5 of the SmPC has been updated in line with other GH products.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Overall, the most notable safety findings from the review of the adverse event data were the increased reports of painful injection site reactions in subjects treated with somatrogon and in subjects that switched from somatropin to somatrogon and increased immunogenicity reactions (all mild to moderate local hypersensitivity reactions). The percentage of study participants testing ADA+ for somatrogon at any time during the CP-4-006 main study was considerably higher compared with somatropin treated subjects. The proportion of study participants reporting an IGF-1 level >2 SDs at any time during the CP-4-006 main study was noticeably higher in the somatrogon group compared to somatropin and the proportion of subjects in the somatrogon group with IGF-1 level >2 SDs increased across all treatment cycles.

Otherwise, weekly dosing of somatrogon administration across over the short to medium term was generally well tolerated and similar to somatropin.

The CHMP considers the following measures necessary to address issues related to safety:

A category 3 PASS is planned for the post-authorisation setting. This will be an active surveillance study to monitor the real-world long-term safety of somatrogon among paediatric patients in Europe

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns

Important identified risks	None
Important potential risks	Benign and malignant neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour)
	Diabetes mellitus type 2
	Medication errors (resulting in under or overdosing of this long-acting formulation)
	Immunogenicity specifically related to long term clinical impact on lack of efficacy and safety (especially in relation to severe injections site reactions)
Missing information	None

2.7.2. Pharmacovigilance plan

Ongoing and Planned Additional Pharmacovigilance Activities

Study	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None	Not applicable	Not applicable	Not applicable	Not applicable
Category 3 - Required additional pharmacovigilance activities (by the competent authority)				
An Active Surveillance Study to Monitor the Real-World Long-term Safety of Somatrogon Among Paediatric Patients in Europe Planned	• Estimate the incidence rates of neoplasms, diabetes mellitus type 2, and the clinical endpoints related to immunogenicity, and medication errors in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care. • Evaluate long-term efficacy by measuring IGF-1 levels, and height in paediatric patients treated with somatrogon, and	• Benign and malignant neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour). • Diabetes mellitus type 2. • Immunogenicity specifically related to long term clinical impact on lack of efficacy and safety (especially in relation to	Interim results of the study will be submitted every 2 years and a final study report will be generated.	Final study report planned for submission 10 years after somatrogon approval.

Ongoing and Planned Additional Pharmacovigilance Activities

Study	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	paediatric patients treated with once daily somatropin, in the course of routine clinical care. • Estimate the hazard ratios of the neoplasms, diabetes mellitus type 2, and the clinical endpoints related to immunogenicity, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.	severe injections site reactions). • Medication errors (resulting in under or overdosing of this long-acting formulation).		

2.7.3. Risk minimisation measures

Summary Table of Risk Minimisation Activities by Safety Concern

Safety Concern	Risk Minimisation Measures
None	None
Benign and malignant neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour)	Routine risk minimisation measures: Proposed SmPC Section 4.3 and 4.4. Proposed PL Section 2. Additional risk minimisation measures: No risk minimisation measures.
Diabetes mellitus type 2	Routine risk minimisation measures: Proposed SmPC Section 4.4. Proposed PL Section 2. Additional risk minimisation measures: No risk minimisation measures.
Medication errors (resulting in under or overdosing of this long-acting formulation)	Routine risk minimisation measures: Proposed SmPC Section 4.2. Proposed PL Section 3. Proposed labelling Section 5 (carton) and Section 2 (pen). Instructions for Use. Additional risk minimisation measures: No risk minimisation measures.
Immunogenicity specifically related to long term clinical impact on lack of efficacy and safety (especially in relation to severe injections site reactions)	Routine risk minimisation measures: Proposed SmPC Section 4.8 Undesirable effects. Additional risk minimisation measures: No risk minimisation measures.

Safety Concern	Risk Minimisation Measures
None	None

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.5 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 27.10.2021 The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Ngenla (somatrogon) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Somatrogon (Ngenla) is indicated for the long-term treatment of paediatric patients with growth disturbance due to insufficient secretion of growth hormone.

In children, GHD is primarily manifested as abnormal linear growth. GHD also impacts bone, lipid, protein, and glucose metabolism in children, with findings that include decreased bone mineral density, decreased lean body mass, and increased fat mass. The incidence of growth failure associated with GHD has been estimated to be approximately 1:4000 to 1:10.000.

Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes for congenital malformation include pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions and genetic abnormalities. Aetiology for acquired GHD includes brain tumours in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation and surgical intervention.

In children the growth attenuation and short stature resulting from GHD begins in early childhood and continues through attainment of final adult height, which can lead to a reduced QoL. This is confounded by delayed puberty and deficits in facial, dental and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycaemia, particularly in infancy. The inability to achieve normal growth and attainment of age and gender appropriate height can lead to early onset of severe psychosocial problems directly related to short stature including behavioural and cognitive disturbances.

3.1.2. Available therapies and unmet medical need

The current standard of care for paediatric GHD is daily SC injection of rhGH.

hGH replacement therapy of recombinant DNA origin (somatropin) has been used for over 30 years. Treatment response is assessed by measurements of height and growth velocity and is generally continued until final height, epiphyseal closure, or both have been recorded.

Early intervention produces the most optimal outcome as growth potential decreases overtime.

For the currently available rhGH products, daily SC injections are necessary to achieve efficacy and maintain IGF-1 blood levels within the target therapeutic window, in the normal age and sex-adjusted range for safety reasons. Injection frequency has been found to be positively correlated with growth response and final height among children with idiopathic GHD treated with rhGH.

Non-compliance/ non-adherence with treatment is a common problem. Non-adherence rates vary widely depending on study methodology and non-adherence/ compliance definitions but have been reported to be 36% to 49% across a variety of studies.

One approach to improving adherence to treatment has been the development of long-acting GH formulations that would require less frequent injections.

Several different technological approaches have been evaluated including sustained-release preparations that utilize microsphere encapsulation (Nutropin Depot, LB03002), pegylated formulations (Jintrolong), non-covalent albumin binding (somapacitan), prodrugs (TransCon31), and Fc GH fusion formulations (GX-H9, albutropin). There are currently no approved long-acting GH formulations on the

market in EU.

3.1.3. Main clinical studies

The applicant conducted a phase 2 dose finding study (**CP-4-004**). This study investigated three dose levels of somatrogon 0.25 mg/kg/week, 0.48mg/kg/week and 0.66 mg/kg/week. In the fourth arm patients were administered somatropin 0.034 mg/kg/day. Patients were randomised 1:1:1:1. The trial had 4 periods. Patients who completed periods I and II were enrolled into an OLE for 12 months (period 3), to continue into a longer term OLE period (period 4), and ultimately into a period where patients used the final pre-filled pen formulation (Period 5).

The main evidence of efficacy submitted is from a single 52-week, phase III multicentre, randomised, open-label study (**CP-4-006**). Patients were randomised in 1:1 ratio to somatrogon 0.66 mg/kg/week or somatropin 0.034 mg/kg/day.

Patients enrolled were prepubertal (Tanner stage 1) and were aged 3 to <11 years (females) and < 12 years (males). The patients had either isolated GHD, or GH insufficiency as part of multiple pituitary hormone deficiencies and were naïve to GH treatment.

224 patients were treated, 109 received somatrogon and 115 somatropin. There was a high completion rate of 99.1% of subjects. The mean age was 7.72 years, 40.2 % were aged between 3 and 7 years, with 59.8% older than 7 years of age. 71.9% were males and 28.1 % females. The majority of patients were Caucasian (71.9%) followed by Asians (20.1%) with very small percentages from other races.

During the open label extension period, patients receiving somatropin were switched to somatrogon and continued weekly SC administration of somatrogon 0.66 mg/kg/week. The study is still ongoing.

An additional 24-week phase study (**C0311002**) was conducted, this was a cross over design study to examine perception of treatment burden with use of weekly growth hormone (somatrogon) versus daily growth hormone (Genotropin) injections in children with growth hormone deficiency. 87 patients were enrolled (43 somatropin, 44 somatrogon) 85 patients completed the study (97.7%).

3.2. Favourable effects

Phase 2 dose finding study (CP-4-004)

At 12 months the mean HV in the FAS population for somatrogon 0.66 mg/kg/week was 11.4 (95% CI: 9.2, 13.7) cm/year. The mean HV for the Genotropin group was 12.5 cm/year (95% CI: 11.0-13.9 cm/year).

The mean HV at six months for somatrogon 0.66 mg/kg/week was 13.0 (95% CI: 9.9, 16.0) cm/year and for the somatropin cohort was 15.0 (95% CI: 13.1, 16.9). The 95% CI for all MOD-4023 cohorts overlaps the somatropin CI.

At 12 months, the mean change in HT SDS for the somatropin cohort was 1.51 (range 0.82, 2.38). and 1.35 (range 0.06, 2.47) for 0.66 mg/kg/week. Therefore, it is agreed that the 0.66 mg/kg/week selected was appropriate to bring forward for phase 3 development.

Open-label extension (OLE) phase of study CP-4-004

The mean observed annual HV at the end of Year 1 was similar between the 0.25 mg/kg/week and 0.48 mg/kg/week treatment groups but was higher in the 0.66 mg/kg/week treatment group. The mean annual HV was the greatest during Year 1 OLE and decreased with every subsequent year thereafter.

The observed mean annual height SDS was consistent across treatment groups. The analysis of mean height SDS at the end of PEN Year 1 revealed no clinically meaningful differences by initial cohort assignment in the main study, including subjects initially randomised to somatropin treatment.

The small number of patients transitioned from somatropin were initially insufficient to support the use of somatrogon as a substitution treatment for somatropin. However, additional supportive data from patient registries have supported the longer-term efficacy profile of the product. The assessment of long-term efficacy was added to the non-interventional PASS as a secondary endpoint, as recommended by PRAC and supported by the CHMP.

Pivotal phase 3 study (CP-4-006)

Somatrogon demonstrated a HV of 10.1 cm/year compared to somatropin 9.78 cm/year at 12 months. The LS mean difference -0.33 (-0.24-0.89) was in favour of somatrogon.

HV at 6 months was 10.59 cm/year for somatrogon and 10.04 cm/year for somatropin. LS mean difference 0.55 (-0.13, 1.23).

Change in HT SDS at 12 months was 0.92 and 0.87 and at 6 months it was 0.54 and 0.48 for somatrogon and somatropin respectively.

Change in BM at 12 months was mean 0.72 (SD 0.17) and 0.72 (SD 0.17) for somatrogon and somatropin, respectively.

IGF-1 SDS (Z) at 12 months were 0.65 (1.32) for somatrogon and -0.69 (1.09) for somatropin. The change form baseline was 2.60 (1.26) and 2.60 (1.26) for somatrogon and somatropin, respectively.

IGFBP-3 SDS (Z) change from baseline at 12 months was reported as 1.62 (1.15 SD) and 0.74 (0.77 SD) for somatrogon and somatropin, respectively.

The pivotal phase 3 study demonstrated that somatrogon was non-inferior to daily somatropin at 12 months in terms of HV, HT SDS or change in BM.

24-week phase study (C0311002) examining perception of treatment burden

The least squares mean of the Overall Life Interference total score was lower for the once weekly somatrogon injection schedule than for the once daily somatropin injection schedule.

The difference in mean Overall Life Interference scores for somatrogon once weekly for 12 weeks, compared with administration of somatropin once daily for 12 weeks, was statistically significant ($p<0.0001$).

3.3. Uncertainties and limitations about favourable effects

The results of HV in the somatropin arm in the pivotal study seem to be lower than that reported in the phase 2 CP-4-004 study, however it was agreed that non-inferiority was demonstrated.

The applicant was initially seeking a broad indication for long-term treatment of paediatric patients

with growth disturbance due to insufficient secretion of growth hormone. However, the population enrolled were prepubertal, treatment naïve and aged > 3 years.

There was no efficacy seen in patients < 3 years, in treatment experienced patients and only limited efficacy seen in older patients > 12 years of age. Furthermore, there is very limited data with longer term treatment which is considered insufficient to support the indication. Accordingly, the applicant has amended the indication to be restricted to children and adolescents > 3 years of age.

3.4. Unfavourable effects

Adverse events

In the pivotal phase 3 study TEAEs overall were reported more frequently in the somatrogon group compared to the somatropin treated group (84.45 vs 78.3%). The most frequently reported AEs that occurred in both somatrogon and somatropin treatment groups respectively were injection site pain (39.4% vs 25.2%), nasopharyngitis (22.9% vs 25.2%), headache (16.5% vs 21.7%) and pyrexia (16.5% vs 13.9%). Most of the AEs reported in the somatrogon and somatropin groups were of mild to moderate severity. In the CP-4-006 OLE period, 58% of study subjects in the OLE reported similar AEs to the main study. The overall incidence of AEs was lower than in the main study period. Injection site pain, nasopharyngitis, headache and pyrexia, were the most common all causality reported TEAEs reported in the pooled analysis. Injection site pain was the most frequently reported TEAE overall.

Other treatment related adverse events of note in somatrogon vs. somatropin treated subjects were: hypoinsulinemia (3.7% vs 2.6%), headache (3.7% vs 2.6%), anaemia (3.7% vs 1.7%), free fatty acids increased (3.7% vs 0.9%), blood creatine phosphokinase increased (1.8% vs 2.6%), and pain in extremity (2.8 vs 0.9%). These AEs are associated with GH replacement therapy. The majority of these treatment related adverse events were mild to moderate in severity and were reported more frequently in the somatrogon group compared to the somatropin treated group.

After review of the pooled safety analysis and review of the additional open-label extension data with data cut-off of 21 December 2020, all relevant TEAEs have been added to the SmPC Section 4.8. It is expected that somotrogon will share all of the known risks of daily rhGH and section 4.8 'Description of selected adverse reactions' has been updated with known class effects of growth therapy.

In the pivotal phase 3 study, 3 subjects had TEAES leading to study drug reduction or interruption (pyrexia, Henoch-Schönlein Purpura, synovitis). All events were mild to moderate in severity. Only synovitis was considered by the investigator to be possibly related to study drug.

AESIs

The percentage of subjects reporting AESIs was higher during treatment with somatrogon administered once weekly (26.4%) than during treatment with somatropin administered once daily (18.6%). This difference was mainly due to increased incidence of injections site reactions and immunogenicity reactions in the somatrogon group.

Injection site reactions

Injection site reaction was the most commonly reported AESI. Injection site pain was the most frequently reported event, 39.4% in the somatrogon group compared with 25.2% in the somatropin group. Injection site erythema and injection site pruritus were the next most frequently reported ISRs in the somatrogon group. Severe injection site reactions were reported more frequently in the somatrogon compared to the somatropin group (6.4% vs 3.5%). The incidence of ISR in the OLE was

26.9%. Subjects previously treated with somatropin reported a higher rate of ISRs (40.7%) compared with subjects previously treated with somatrogon (16.3%).

Injections site pain were most commonly reported in the first 6 months of treatment, but most subjects reported multiple episodes of injection site pain. The incidence rate for injection site pain was higher in males compared to females and in Asian subjects compared to White subjects and in younger patients (>3 years to =<7) and across peak GH level categories in the somatrogon group compared to somatropin Section 4.8 has been updated to include this information on time to onset and duration of injection site reaction.

Immunogenicity

In the Phase 3 main study 18.3% in the somatrogon group and 7.8% in the somatropin group reported AEs related to immunogenicity/hypersensitivity. In the somatrogon group, the most frequent events were conjunctivitis allergic (2.8%), rash generalized (2.8%), and rhinitis allergic (2.8%). Most events were mild or moderate in severity. Two reports eyelid oedema and 1 report of idiopathic urticaria were related to somatrogon.

In somatrogon treated patients, the incidence of AESIs in the immunogenicity category were higher overall in the Asian population compared to the White population, in the male population compared to the female population in the subgroup: >3 years to =<7 w compared to the somatropin treated populations.

Within the phase 2 study CP-4-004 among 42 somatrogon-treated subjects, 10 subjects (23.8%) tested ADA+ for somatrogon at 6 months (Week 26), and 5 of these subjects (11.9%) tested ADA+ at 12 months (Week 52), suggesting that transient anti-somatrogon antibodies had developed. No subjects receiving the lowest dose (0.25 mg/kg/week) developed ADAs. Regarding the data presented so far for the phase 2 study (CP-4-004), testing ADA+ for somatrogon does not seem to have an overall effect on the incidence of TEAEs, SAEs, or AESIs throughout the study.

In the registration study CP-4-006, 84/109 patients (77.1%) tested ADA+ for somatrogon at any time during the main study. Median time to the first ADA+ result was 6 months, and 83/84 subjects had persistent ADA+ results. The tolerability of somatrogon seems to be partially better in patients tested negative for ADA, particular regarding immunogenicity (21.4% vs 8.0%), injection site reactions (46.4% vs 32.0%) and abdominal symptoms (13.1% vs 4.0%).

The incidence of injection site reactions was numerically higher in ADA+ subjects compared to ADA- subjects and 6 of the 7 subjects with severe injection site reactions in the somatrogon group, tested ADA+. Most subjects who tested ADA+ showed specificity to rhGH. Four subjects who tested ADA+ showed specificity to CTP. Two somatrogon-treated subjects tested positive for somatrogon NAbs during the main study.

Further adverse event of special interest

Although the effect was small in the paediatric population, the data presented confirmed that somatrogon might affect the glucose tolerance as well as the thyroid and adrenal cortical function.

The incidence of AEs related to benign neoplasia was low overall, similar in the somatrogon and somatropin groups, and limited to the events of skin papilloma and melanocytic naevus.

Other AESI categories for which events were reported, included adrenal cortical hypofunction, arthralgia and pain in extremity. No subjects reported elevated pancreatic enzymes (eg, amylase or lipase) or had a diagnosis of acute or chronic pancreatitis.

In the Phase 3 OLE, 34.4% of subjects reported AESIs. Events were more commonly reported in subjects originally randomised to somatropin. Most were mild to moderate in severity and were not

related to study medication. The incidences in most of the categories were low and similar in CP-4-004 main study period and OLE periods as well.

IGF-1

During the main study period of the phase 2 study CP-4-004, no subjects in the 0.25 mg/kg/week group or 0.48 mg/kg group had levels of IGF-1 SDS >2 at any time point during the 12 months safety analysis period. Only one subject in 0.66 mg/kg/week group had levels of IGF-1 SDS >2 at 5 visits. At Visit 12, the subject's IGF-1 values tested within normal range. The subject's dose was reduced from 0.66 mg/kg/week (Cohort 3 dose) to 0.48 mg/kg/week prior to Visit 6 (Week 14). No other AEs were reported in this subject, including those known to be related to high IGF-1 levels in adult subjects (such as headache or oedema).

In the pivotal phase 3 study the proportion of study participants reporting an IGF-1 level >2 SDs was higher in the somatrogon group compared to somatropin and increased across all treatment cycles. 12.8% of somatrogon treated compared with 0.9% treated with somatropin had sustained levels (>2 consecutive visits which lasted at least ~ 13 weeks). The incidence of subjects in the somatrogon group with IGF-1 SDS >2 increased over the time. Of the 26 subjects in the somatrogon group with elevated IGF-1 SDS>2, twenty-three (23) subjects had at least 1 of their IGF-1 samples obtained 2- or 3-days post dose, rather than 4 days post dose. In the somatrogon group, 14 subjects experienced persistent IGF-1 levels >2 SDS (ie,2 consecutive SDS>2 measurements) resulting in dose modification for 12 of these subjects. The other 2 subjects had their persistent IGF-1 levels above 2 SDS at 9 and 12 months; therefore, their dose was not reduced during the 12-month study). Eight of these subjects reported other AESIs (injection site reaction, vomiting/nausea, abdominal pain, hypothyroidism). Modelled mean and median values although falling below the >2SDS threshold increased over the 12-month duration of the phase 3 pivotal study. In the phase 2 OLE the proportion of subjects with IGF-1 >2 fluctuated (15.9% in year 2, 16.3% in year 3, 2.6% in year 4.

Scoliosis

Two subjects reported scoliosis, 1 subject reported mild scoliosis during Period IV (Year 3 of OLE) that was deemed possibly related to the study treatment and 1 subject reported an SAE of severe scoliosis during Period IV (Year 4 of OLE), which was considered probably related to study treatment.

Laboratory findings

Haematology test results were generally stable and comparable between the treatment groups. However, the number of subjects who shifted from normal to high eosinophils at 12 months was higher for the somatrogon group than for the somatropin one. In addition, clinically relevant mild to moderate anaemia was reported. Chemistry test results were generally stable and comparable between the treatment groups as well. However, a shift from normal to high values of phosphate (known effects of GH therapy) was reported for more subjects in the somatrogon group than in the somatropin group. The changes in the lipid parameters (cholesterol, triglycerides, free fatty acids, HDL cholesterol and LDL cholesterol) were generally small and consistent between both treatment groups.

Vital Signs

Subjects treated with somatrogon reported an increase in BMI across repeat treatment cycles, however those treated with somatropin showed a reduction in BMI during the main period of both studies followed by increases in BMI after switching to somatrogon during the OLE periods.

3.5. Uncertainties and limitations about unfavourable effects

The number of patients (N=269) is limited for a safety database and does not fully fulfil the requirements of the ICH-E1. However, the safety profile of somatropin in the paediatric population is well described in the literature and in other GH formulations approved for use in this population. The safety database is considered sufficient to compare the short-term safety profile with the known profile of GH. The applicant has also provided an updated pooled safety analysis up to the data cut-off date of 21 December 2020, with exposure adjusted analyses for patients across Phase 2 (CP-4-004) and Phase 3 studies (CP-4-006) along with their ongoing OLE periods.

Although 35 subjects have been treated with somatrogon for up to 5 years, the safety database is insufficient to fully characterise the long-term safety of non-physiological GH profile. The mean and median levels of IGF-1 levels (observed and modelled) although within normal range increased over the 12 months of the phase 3 study. The proportion of subjects with IGF values>2 also increased over this period. A higher proportion of the somatrogon population had clinically significant out-of-range IGF-1 value compared to somatropin.

Some subjects may have had IGF-1 SDS >2 because the samples were collected earlier in the dosing interval than the optimal 96-hour timepoint outlined in the protocol. The SmPC states that dosage may be adjusted as necessary, based on growth velocity, body weight and serum insulin-like growth factor 1 (IGF-1) concentrations, and additional guidance on how to titrate somatrogon in response to an IGF-1 level that falls outside the target range (upper normal range not exceeding 2 SDS) was also included.

For patients with IGF-1>2SDS a tabulated summary of demographic details, actual dose administered dose of somatrogon and extent of dose adjustment, duration of IGF-1 >2SDS, due high level of IGF has been presented by the applicant. No obvious pattern is identifiable in terms of dose administration, time to onset of elevated IGF-1 value, incidence /severity of related adverse events or ADA status that would help characterise patients with IGF-1 > 2SDS. The rationale presented by the applicant in support of measurement of mean instead of peak IGF-1 levels is accepted.

The applicant's comment that the transient increase in IGF-1 is not associated with an adverse safety profile and therefore does not merit inclusion of IGF-1 as an ADR in section 4.8 is accepted.

The tumorigenic potential of IGF-1, a key mediator of GH activity and secreted in response to GH receptor activation is well established. The impact of higher IGF-1 levels on long term safety profile of somatrogon has not been fully evaluated. The applicant has proposed a non-interventional 10yr PASS study as an additional pharmacovigilance measure to further characterize malignancy and diabetes. Risk of malignancy and diabetogenic potential have also been included as important potential risks in the RMP.

With the expectation of better tolerability of weekly somatrogon over daily hGH dosing the clinical implications of the observed high reporting rates of painful injections in the somatrogon group is a concern. The different methodologies used for collecting injection site reactions in somatrogon and somatropin treated populations makes it difficult to compare the incidence of ISRs across treatment groups.

Severe ISRs were reported more frequently in the somatrogon treated population (mostly ADA+). There was no clear pattern of ADA positivity identified in these cases of severe ISR. The disparity between the number of reports of injection site pain reported as a severe AEs across different analyses (e.g. AESI ISR and Injection site reactions by site of injection analyses) and the high numbers of patients self-reporting pain score above or equal 4 which described the highest level of pain experienced by children is a concern. The validity of the injection site assessment (local reactions)

has not been discussed by the applicant. The pain assessment scale, the FACES Pain Rating Scale is based on the established Wong-Baker FACES scale and is a widely accepted and reliable tool used in routine practice and clinical research. The applicant has reviewed and discussed any risk factors that could have contributed to the incidence of ISR. No other measures other than rotating the site of injection can be recommended to reduce the pain. Advice to users regarding rotation of injection sites is included in section 4.2. The wording in Section 4.2 has been revised to be consistent with the language in Section 6.6 (Special precautions for disposal and other handling).

Two significant anomalies regarding reporting laboratory results were identified but further details including root causes analyses have been provided regarding these errors. Details of an FDA GCP inspection that took place during the Phase 3 studies has also been provided for review, with no findings of note.

The laboratory parameters were stable and were mainly in the normal range. Abnormal values for several parameters were revaluated by the applicant. Anaemia and eosinophilia have been added to section 4.8 as ADRs.

There is a tendency for greater weight gain and increase in BMI in subjects treated with somatrogon compared to those treated with somatropin. Subject treated with somatropin reported a decrease in BMI during the main period of both studies followed by increases in BMI after switching to somatrogon during the OLE periods.

These changes, particularly for somatrogon, likely represent increases in weight and BMI related to the changes in body composition associated with increases in HV and Height SDS.

The incidence of anti-hGH antibody formation was noticeably higher in the somatrogon compared to the somatropin population in both studies. Antibody formation was more persistent in patients treated with somatrogon. A small number of antibodies to somatrogon were identified as nAbs. AEs related to immunogenicity/hypersensitivity were reported in 18.3% in the somatrogon group and 7.8% in the somatropin group.

There were considerable inconsistencies regarding immunological events within the dossier, however the applicant has provided information to show that this does not change the outcome of the findings or report.

Within the ADA-positive subgroup exposure ranges were huge with up to 96-fold for Cmin and prolonged half-life up to 56 hours. ADA impact on PK has not yet been sufficiently investigated and several issues are raised: e.g. to detail whether also PD markers such as IFG-1, IGF 1 SDS were differently affected by different ADA titers, to simulate how PK parameter develop after change to pen for both ADA positive and negative patients. "Worst case scenarios" for exposure and PD considering combined intrinsic factors, like light young female patient with ADAs vs. older heavier male without ADAs, are requested. In summary, Immunogenicity particularly in relation to severe injections site reactions will be further characterised in the post authorisation setting. Immunogenicity was included as an important potential risk in the RMP.

3.6. Effects Table

Table 22. Effects Table for Somatrogon for paediatric patients with GHD (Data cut off 1st November 2019).

Effect	Short Description	Unit	Somatrogon	Genotropin	Uncertainties/ Strength of evidence	References
Favourable Effects						
AHV	Annual height velocity after 12 months of treatment observed	cm/year	10.18	9.68	Ls mean difference 0.33 (95% CI -0.24, 0.89) at 12 months	CP-4-006
Δ Ht SDS at 6 and 12 mo	Change in height SDS at 6 and 12 months, compared to baseline	NA	0.55 (6 months) 0.92 (12 months)	0.47 (6 months) 0.87 (12 months)	LS mean difference 0.06 (95% CI, -0.01, 0.13) LS mean difference 0.05 (95% CI, -0.06, 0.16)	CP-4-006
Δ Ht SDS at 3 years	Change in height SDS at 6 and 12 months, compared to baseline	NA		0.34 (3 years)	Mean, min, max 0.34, -0.16, 1.31,	CP-4-003 (OLE)
BM at 12 mo	Bone Maturation at 12 months and Change in Bone age relative to chronological age	NA	Bone maturation mean (SD) 0.72 Change in BA Relative to the change in CA Mean (SD) 1.07 (0.73)	Bone maturation mean (SD) 0.72 Change in BA Relative to the change in CA Mean (SD) 1.12 (0.75)	Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.	CP-4-006
IGF-1 and levels	Change from baseline IGF-1 levels on Day 4(-1) after somatrogon dosing across study visits month 12	NA	Mean (SD) 183.66 (104.35)	70.68 (59.89)	Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.	CP-4-006
IGF-1 SDS levels	IGF-1 SDS levels on Day 4(-1) after somatrogon dosing across study visits month 12	NA	Mean (SD) 2.60 (1.26)	Mean (SD) 1.02 (0.87)	Descriptive analysis was conducted for this endpoint with no formal hypothesis testing.	CP-4-006
Treatment burden	Life interference total scores	NA	Mean (SD) 8.4 (11.0)	Mean (SD) 24.1(20.0)	Treatment difference -15.49 (95% CI -19.71, -11.27) P< 0.0001	C0311002
Unfavourable Effects						

Effect	Short Description	Unit	Somatrogon	Genotropin	Uncertainties/ Strength of evidence	References
Injection site reaction Injection site pain			43.1% (n= 47) 39.4% (n=43])	25.2% (n=29) 25.2% (n=29).	Safety data base of 225 children with GH exposed to somatrogon for 12 months. The analysis of injection site reactions is confounded by the methodology used to record ISRs. Injection site pain reactions on the Patient Diary Card were only filled out once a week, thus capturing the once weekly somatrogon injection but only 1 of 7 daily Genotropin injections.	Phase 3 Study CP-4-006 cut-off 1 Nov 2019
Immunogenicity AEs			18.3% (n=20) Among 109 somatrogon-treated subjects, 84 subjects (77.1%) tested ADA+	7.8% (n=9) Among 115 Genotropin-treated subjects, 18 subjects (15.7%) tested ADA+ for hGH	In the somatrogon group, the most frequent events were Conjunctivitis allergic (2.8%), Rash generalized (2.8%), and Rhinitis allergic (2.8%). No reports of anaphylaxis or serious hypersensitivity reactions.	Phase 3 Study CP-4-006 cut-off 1 Nov 2019

Effect	Short Description	Unit	Somatrogon	Genotropin	Uncertainties/ Strength of evidence	References
Long term safety IGF-1 SDS >2	Missing data		The percentage of children with IGF-I SDS>2 levels increased over time with somatrogon. 4.7% had IGF-1 SDS > 2 at month 1 compared with 13.1% at month12 12.8% had persistent IGF-1 levels >2 SDS: 2 consecutive SDS>2 measurements		Supra-physiological IGF-I levels between injections could increase the risk of iatrogenic acromegaly, neoplasia and glucose intolerance	Phase 3 Study CP-4-006

Abbreviations:
Notes: AHV= Annual height velocity, HT= height, SDS= standard deviations, BM= bone maturation, Δ= delta, MO= months.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The aim of treatment is replacement of GH in patients with GDH deficiency, to enable normal adult height. Furthermore, GHD also impacts on bone, lipid, protein and glucose metabolism in children, with findings that include decreased bone mineral density, decreased lean body mass and increased fat mass.

Currently the treatment is rhGH therapy administered by daily SC injections. The rationale for developing long lasting GH formulations is that patients would require less frequent injections which may improve compliance.

Two paediatric studies, a phase 3 registration study (CP-4-006) and a supportive Phase 2 dose finding study (CP-4-004), were conducted in support of long-term treatment of paediatric patients with GHD. Both studies enrolled similar patient populations prepubertal, GH treatment-naive children with a verified diagnosis of GHD. The applicant received CHMP SA and followed this in their development programme for the most part.

The phase 3 study demonstrated that the annual 12-month HV with somatrogon administered once weekly in the Phase 3 registration study was non-inferior to Genotropin administered once daily. The study met its primary objective.

Weekly somatrogon treatment produces catch-up growth and height normalization, as reflected by HV, change in HT SDS and HT SDS. The change in HT SDS in the Phase 3 registration study was numerically higher compared to daily somatropin.

Bone maturation values demonstrated that growth improvement was not associated with accelerated BA advancement relative to CA.

Therefore, it can be concluded that over 12 months, treatment with somatrogon was not inferior to daily somatropin therapy.

Additional guidance is given in section 4.2 of the SmPC on how to titrate somatrogon in response to an IGF-1 level outside the target range. In patients whose serum IGF-1 concentrations exceed the mean reference value for their age and sex by more than 2 standard deviation score (SDS), the dose of somatrogon should be reduced by 15%. More than one dose reduction may be required in some patients. Routine monitoring of serum IGF 1 SDS levels throughout the course of treatment is recommended, especially during puberty.

The supportive Phase 2 dose finding study (CP-4-004) was conducted in two parts, an initial dose finding part which confirmed the appropriateness of the 0.66mg/Kg/day dose, and a subsequent Open Label Extension (OLE) part. Of the two, the OLE part is more significant, as it provided some evidence regarding the efficacy profile of the medicine when used over an extended period (3 years). The data from the OLE were similar to growth profiles for patients treated with other GH products for whom data was captured in patient registries.

The overall safety database is small. From the data available the short-term safety profile of somatrogon is generally in line with the safety profile of the comparator somatropin with two exceptions, Injection site reactions, and antibody formation. Long term safety, particularly with the pen presentation intended for authorisation, is limited. The incidence of subjects in the somatrogon group with IGF-1 SDS >2 increased over time. The impact of transient elevations of serum IGF-I and supra-physiological IGF-I levels between injections over the longer term is unclear. IGF-1 has been associated with glucose intolerance and may have a role in tumorigenesis. The risks related to non-pulsatile physiological levels and sustained high IGF-1 levels above the physiological range over longer term exposure with somatrogon will be evaluated in a non-interventional PASS. Other known adverse events associated with GH treatment will also be evaluated in the post authorisation safety study.

Long-term efficacy of somatrogon, specifically height velocity (HV), height SDS (Ht SDS), change in Ht SDS and final height have been included as secondary endpoints in the active surveillance study to monitor the real-world long-term safety of somatrogon among paediatric patients in Europe.

Reports of treatment related TEAES generally were higher in somatrogon compared to somatropin treatment groups. This was mainly due to reports of injection site reactions (ISRs) in particular injection site pain. The majority of the reactions were mild to moderate in severity. Severe reactions were reported more frequently with somatrogon. These reactions decreased over subsequent months but a number of children in the studies reported multiple painful injections. Switching from somatropin to somatrogon in the phase 3 OLE was also associated with an increase report of painful ISRs. The methodologies used to collect data on ISRs makes it difficult to compare rates of ISRs across treatment groups. Uncertainties remain regarding the rates of injections site reactions, in particular in regard to the determination of severity of injection site pain between patients treated with somatrogon and somatropin. The majority of severe ISRs (6/7) were ADA+, although the applicant argues that most ISRs occurred within 6 months of treatment and ADA positivity wasn't established until around 6 months after treatment started. In three cases ADA positivity was sustained across 24 + months. Five subjects withdrew from pivotal study/OLE because of an ISR (pain, erythema, induration, pruritus). The development of long-acting HGH analogues that allow for decreased injection frequency come with

the expectation of better tolerability of weekly over daily HGH dosing. The clinical implications of the observed higher reporting rates of painful injections in the somatrogon group is a concern. Painful invasive procedures in young children are associated with stress, and anxiety and can affect compliance with treatment.

No measures have been identified other than injection site rotation that can reduce the pain associated with injection.

Immunogenicity of somatrogon is clearly increased compared to daily somatropin and appears to lead to increased exposure to somatrogon and consequently IGF-1 levels and may also be associated with immune-mediated adverse effects. Indeed, IGF-1 levels increased over time. Recommendations for IGF-1 monitoring 96 hours after injection of somatrogon along with a recommendation that dose adjustments should be made as necessary, based on growth velocity, body weight and serum insulin-like growth factor 1 (IGF-1) concentrations have been substantiated by the applicant and additional wording has been included in section 4.2. A target IGF-1 SDS in the upper normal range not exceeding 2 SDS is also included in section 4.2.

The impact of persistent high levels of antibodies on the clinical effects of somatrogon is unclear. Although there were no reports of serious hypersensitivity reactions, there were more reports of local skin, eye and upper respiratory hypersensitivity reactions in the somatrogon group. Of note the majority of subjects with sever ISRs were ADA+. The ADA titres fluctuated across all time points with titres ranging from 250 to >6250 detected at varying time points. There was no clear pattern of ADA positivity identified in these cases of severe ISR. 'immunogenicity specifically related to long term clinical impact on lack of efficacy and safety (especially in relation to severe injections site reactions)'. is included as an important potential risk in the safety specification of the RMP.

A number of laboratory data handling and processing errors were identified during the conduct of the pivotal phase 3 study. This is an application with one pivotal trial and both these errors occurred in the pivotal trial. 7 sites were involved in the second error which suggest a systemic failure rather than just difficulty at one site. The applicant has provided further information, including root cause analyses for the laboratory data handling and processing errors. This has addressed any concerns relating to the conduct of the trial and data integrity. The applicant has also indicated that GCP inspections were conducted for the somatrogon clinical CP-006 and there were no findings of note.

3.7.2. Balance of benefits and risks

The study results of conducted clinical studies supports that efficacy of once-weekly somatrogon in treatment naïve prepubertal GHD children (3-11 years) is non inferior to daily somatropin treatment.

Patients treated up to 5 years showed that somatrogon was effective and further data should be available in relation to longer term use in the planned non interventional PASS. Patients switched from somatropin to somatrogon in the OLE phase (after 12 months in the phase 3 DBP) showed that patients achieved benefit.

The treatment burden study conducted demonstrated that the majority of patients preferred once-weekly treatment compared to daily injections. Therefore, beneficial effects have been demonstrated in the population enrolled into the clinical development programme.

The applicant has provided an updated analysis of pooled data (TEAEs, SAEs, AESIs, ADA status etc.) with exposure adjusted analyses for patients across Phase 2 (CP-4-004) and Phase 3 studies (CP-4-006) along with their ongoing OLE periods, including data collected following the initial submission cut-off

point of 01 November 2019 up to the data cut-off date of 21 December 2020. Integration of the safety data from the four studies has resulted in a more robust estimate of the AE frequency and identification of a number of additional ADRs. . Concerns remain regarding the long-term safety implications of increased levels of IGF-1 including the potential for neoplasia (benign and malignant) and impaired glucose tolerance. The impact of immunogenicity over the longer term is also a concern. These issues will be followed-up in a planned active surveillance study to monitor the real-world long-term safety of somatrogon in paediatric patients.

3.7.3. Additional considerations on the benefit-risk balance

Somatropin Biopartners was another long-acting growth hormone-containing product approved by CHMP. Post authorisation safety studies were agreed to characterise the long-term risks of exposure to non-physiological growth hormone and IGF-I. The marketing authorisation ceased to be valid due to the sunset clause.

A PASS is proposed to assess long-term safety (neoplasm, diabetes mellitus, and other known side effects of GH treatment) of somatrogon in children with growth hormone deficiency. Long-term efficacy of somatrogon, specifically height velocity (HV), height SDS (Ht SDS), change in Ht SDS and final height have been included as secondary endpoints in the PASS.

3.8. Conclusions

The overall benefit/risk balance of Ngenla is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ngenla is not similar to Sogroya within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Ngenla is favourable in the following indication(s):

Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that somatrogon is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).