11 November 2021
EMA/706519/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lonapegsomatropin Ascendis Pharma

International non-proprietary name: lonapegsomatropin

Procedure No. EMEA/H/C/005367/0000

Note

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

Administrative information

Name of the medicinal product:	Lonapegsomatropin Ascendis Pharma
Applicant:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 12 2900 Hellerup DENMARK
Active substance:	lonapegsomatropin
International Non-proprietary Name/Common Name:	lonapegsomatropin
Pharmaco-therapeutic group (ATC Code):	Subject to final ATC code
Therapeutic indication(s):	Growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD])
Pharmaceutical form(s):	Powder and solvent for solution for injection
Strength(s):	3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg and 13.3 mg
Route(s) of administration:	Subcutaneous use
Packaging:	Dual-chamber cartridge (glass)
Package size(s):	4 cartridges + 6 needles

Table of contents

List of abbreviations

Abbreviations	Definition
ACP-001	TransCon mPEG80 hGH (predecessor molecule to lonapegsomatropin)
ACP-011	TransCon mPEG40 hGH, lonapegsomatropin
ADA	Anti-drug antibody
AHV	Annualised height velocity
AIEC	Anion Exchange Chromatography
ANCOVA	Analysis of covariance
AR	Assessment report
AUC, AUC0-168, AUC0-336, AUC0-inf	Area under the curve, from 0 to 168/336 h, or from 0 to infinity
BMI	Body mass index
CE	European Conformity
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum observed concentration
CQA	Critical quality attribute
CSR	Clinical study report
DCC	Dual-chamber cartridge
DOE	Design of experiments
DP	Drug product
DS	Drug substance
ECG	Electrocardiogram
ELISA	Enzyme linked immunosorbent assay
Emax	Maximum observed response
GH	Growth hormone
GHD	Growth hormone deficiency
GHR	Growth hormone receptor
hGH	human growth hormone, somatropin
HbA1c	Glycosylated hemoglobin, Type A1c
HPLC	High-performance liquid chromatography
HV	Height velocity
IBs	Inclusion bodies
ICH	International Council for Harmonisation
IGF-I	Insulin-like growth factor-1
IPC	In-process control
IPT	in-process test
ISO	International organisation for standardisation
ITT	Intent to treat
LLOQ	Lower limit of quantification
LOQ	Limit of quantification

Abbreviations	Definition
LS	Least squares
mPEG	Methoxypolyethylene glycol
OOS	Out of specification
PD	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics
PP	process parameters
PPQ	Process performance qualification
PRM	Primary reference material
RA	Risk assessment
RP-HPLC	Reversed-phase high performance liquid chromatography
SC	Subcutaneous
SDS	Standard deviation score
SRM	Secondary reference material
Tmax	Time to maximum plasma concentration
TSE	Transmissible spongiform encephalopathy
UCL	Upper confidence limit
UF/DF	Ultrafiltration/diafiltration
WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Ascendis Pharma Endocrinology Division A/S submitted on 8 September 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Lonapegsomatropin Ascendis Pharma, 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 2 October 2020.

Lonapegsomatropin Ascendis Pharma was designated as an orphan medicinal product EU/3/9/2213 on 17 October 2019 in the following condition: treatment of growth hormone deficiency.

The applicant initially applied for the following indication: growth failure in paediatric patients due to insufficient secretion of growth hormone, growth hormone deficiency, GHD.

The applicant later decided to withdraw the indication for the age group < 3 years and the final applied indication was as follows: growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD]).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lonapegsomatropin Ascendis Pharma 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/orphan-designations/eu-3-19-2213.

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 applicant's 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(s) P/0275/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0275/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0275/2020.

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 lonapegsomatropin 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
15 September 2016	EMA/CHMP/SAWP/588843/2016	Dr Kolbeinn Gudmundsson, Dr Elmer Schabel, Dr Peter Mol
9 November 2017	EMA/CHMP/SAWP/711581/2017	Dr Kolbeinn Gudmundsson, Prof. Minne Casteels

The Protocol assistance pertained to the following quality, non-clinical, and clinical aspects:

- Selection of starting materials for the drug substance
- Drug substance comparability testing to bridge manufacturing process changes, change in manufacturing sites, and change in manufacturing scale
- Adequacy of the proposed predefined drug product comparability testing for vial and dual-chamber cartridge presentations
- Classification of the TransCon hGH as a prodrug derivative of somatropin as the active substance
- Acceptability of the non-clinical safety programme
- Weight of evidence assessment for carcinogenicity obviating need for dedicated carcinogenicity studies
- Phase 3 clinical programme: dose regimen, weight based dosing increments, study population in/exclusion criteria, primary and secondary efficacy endpoints, non-inferiority margin, PK/PD profiling, ECG assessments, immunogenicity characterisation (assays and sampling time points), assessment of treatment adherence and preference vs. daily hGH administration, safety database,

adequacy of overall programme to support benefit/risk assessment

- Evidence generation plans to support registration of drug-device auto-injector and pen needle using dual-chamber cartridges

1.7. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	8 September 2020
The procedure started on	1 October 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	23 December 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 December 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	4 January 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	22 April 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	01 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 August 2021
Working Party experts from the Safety Working Party (SWP) and the Non-clinical Working Group (NcWG) of the PDCO were convened to address questions raised by the CHMP on The CHMP considered the views of the Working Party as presented in the minutes of this meeting.	23 July 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint	02 September 2021

Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	
Working Party experts from the Modelling and Simulation Working Party (MSWP) were convened to address questions raised by the CHMP on The CHMP considered the views of the Working Party as presented in the minutes of this meeting.	02 September 2021
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP second List of Outstanding Issues on	21 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	05 November 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 Lonapegsomatropin Ascendis Pharma on	11 November 2021
The CHMP adopted a report on similarity of Sogroya with Lonapegsomatropin Ascendis Pharma on (see Appendix on similarity)	11 November 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)	11 November 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Lonapegsomatropin Ascendis Pharma is proposed for growth failure in paediatric patients due to insufficient secretion of growth hormone, growth hormone deficiency, GHD.

Growth hormone deficiency (GHD) is characterised by too low systemic levels of growth hormone. Growth hormone (GH) is produced by the somatotroph cells of the anterior pituitary gland. The secretion of growth hormone from the pituitary gland is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, both of which are produced by the hypothalamus. Growth hormone deficiency (GHD) is often associated with defects arising in the pituitary gland or the hypothalamus.

The typical symptom of GHD in children is growth failure. Growth failure is suspected if the growth of paediatric subjects develops at a slower rate than would be expected based on the growth chart of the local geographic area. In this case, further diagnostic evaluations can be considered to find the cause of growth failure.[1]

2.1.2. Epidemiology and risk factors, screening tools/prevention

The incidence of short stature associated with GHD has been estimated to be approximately 1:4,000 to 1:10,000.[2,3] GHD may be isolated or may occur in association with deficiencies of other pituitary hormones.

GHD is the primary indication for growth hormone treatment in childhood.

2.1.3. Aetiology and pathogenesis

There are different causes of growth hormone deficiency, which can be categorized in different categories, namely:

- Congenital (organic causes such as pituitary aplasia, primary empty sella syndrome etc. or genetic causes including various mutations)
- Acquired (tumours of the hypothalamic-pituitary region, most commonly craniopharyngioma, head trauma, infection etc.)
- Idiopathic (no clear aetiology)

The aetiology of childhood GHD is usually hypothalamic in origin with impaired GHRH secretion, with the most common diagnosis being isolated idiopathic GHD (Cook 2009).

[1] Collett-Solberg et al. Diagnostics, genetics and therapy of short stature in children: a growth hormone research society international perspective. Horm Res Paediatr 2019; 92:1-14.
[2] Rona RJ, Tanner JM. Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch Dis Child. 1977 Mar;52(3):197-208.
[3] Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016 Jan; 101(1):96-100. Epub 2015 Jul 7.

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. A substantial reduction in growth rate may become apparent within the first few months of life (Huet 1999, Ogilvy-Stuart 2003, Ranke 2003). This is sometimes associated with a delay in fontanelle closure.

Signs

Although the most obvious feature of GHD may be short stature, the disease has broad health implications. Children with GHD may have a small midface, hands, and feet, excess subcutaneous truncal fat, reduced muscle mass, thin hair and nails, a high-pitched voice, delayed skeletal and dental maturation, and delayed puberty (Albanese 1994, Levy 1996). In addition, GHD can influence cognitive functions and the overall sense of well-being. When accompanied by other pituitary deficiencies, further clinical manifestations may be present.

2.1.5. Management

The typical symptom of GHD in children is growth failure, and consequently, the aim of treatment is to normalize the growth rate during childhood and attainment of normal adult height. For over 30 years, GHD has been treated with daily recombinant human growth hormone. The effects of human growth hormone replacement in children can be evaluated by assessing the increase in height velocity and related auxological parameters and bone maturation.

With current treatment algorithms paediatric recombinant human growth hormone doses 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.

While daily human growth hormone is both safe and effective, its frequency of administration can be burdensome for both children and their caregivers. Although children with GHD treated with daily growth hormone replacement can achieve normal adult height, real-world outcomes have not matched expectations. Due to nonadherence rates ranging from 5 to 82% (Fisher 2013), most GHD patients do not reach their target genetic height (Guyda 1999, Lustig 2004), leaving an opportunity to improve treatment outcomes in paediatric GHD.

While there are multiple therapeutic goals of human growth hormone therapy in treating GHD including achievement of normal growth patterns, lean/fat body composition, bone mass, glucose homeostasis, cognition and improved quality of life, the most readily measured indicator of efficacy is linear growth according to the applicant. In view of the applicant, a therapy that results in improved growth outcomes at the end of 52 weeks of treatment is expected to result in better clinical effects with long-term therapy.

For paediatric GHD patients, medicinal products for daily growth hormone supplementation are available (e.g. Omnitrope (EU/1/06/332), NutropinAq (EU/1/00/164)). A medicinal product for weekly growth hormone supplementation is available (Sogroya (EU/1/20/1501)) for adults GHD patients, apart from medicinal products for daily growth hormone supplementation.

2.2. About the product

Lonapegsomatropin is a long acting pegylated human growth hormone (somatropin). Lonapegsomatropin is designed to release somatropin with the same mode of action and distribution as daily somatropin, but with a once-weekly injection. Lonapegsomatropin consists of a parent drug, somatropin, which is transiently conjugated to a methoxypolyethylene glycol (mPEG) carrier (4 x 10 kDa mPEG) via a proprietary TransCon linker (Linker A). The carrier has a shielding effect that minimises renal excretion and receptor-mediated clearance of lonapegsomatropin. At physiologic pH and temperature, lonapegsomatropin releases unmodified and fully active somatropin via autocleavage of the linker in a controlled manner that follows first-order kinetics.

Human growth hormone (hGH) intermediate (with amino acid sequence identical to that of hGH of pituitary origin) is obtained from the fermentation of *E. coli* transformed with a genetically engineered plasmid containing the coding sequence for hGH.

Lonapegsomatropin Ascendis Pharma drug product is a powder and solvent for solution for injection presented in a dual-chamber cartridge (DCC), reconstituted utilizing a proprietary, non-integral, re-usable GH Auto-Injector. Clinical development was initiated with a hGH conjugated with an 80 kDa mPEG-Linker (ACP-001 – predecessor molecule), while current lonapegsomatropin is produced by conjugation of hGH with a 40 kDa mPEG-Linker (ACP-011). It presents a less frequent treatment option (once a week) for paediatric patients with growth failure due to insufficient secretion of growth hormone.

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 development

In the quality development of lonapegsomatropin, 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.

Clinical development

Five clinical development studies were conducted with lonapegsomatropin: two phase 1 (healthy adult volunteers) and three phase 3 studies (children with growth hormone deficiency). In total, across these studies, 379 subjects have been exposed to lonapegsomatropin: 306 children with GHD and 73 healthy adults. In the pivotal study CT-301, the proposed dosage of 0.24 mg hGH/kg/week was studied.

Overall, the scientific advice was followed by the applicant.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as powder and solvent for solution for injection containing 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg or 13.3 mg of somatropin equivalent to 8.6 mg, 10.3 mg, 12.3 mg, 14.8 mg, 18 mg, 21.7 mg, 25.9 mg, 31.4 mg or 37.9 mg, respectively, of lonapegsomatropin as active substance.

Other ingredients are: succinic acid, trehalose dihydrate, trometamol (as powder) and water for injections (as solvent).

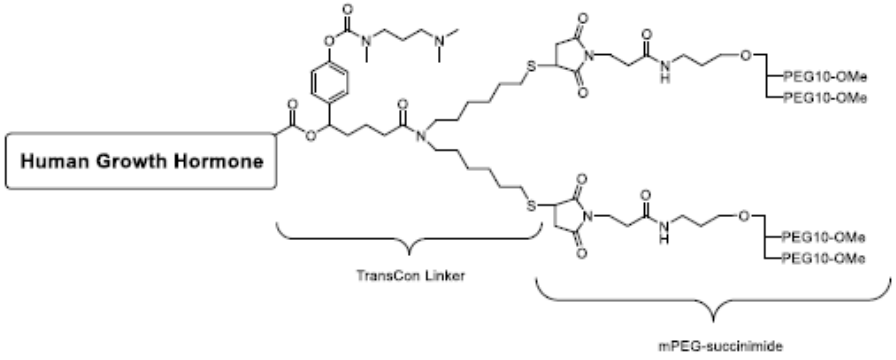
The product is available in a glass cartridge (Type I glass) with two chambers separated by a rubber stopper (bromobutyl). The cartridge is closed by a rubber stopper (bromobutyl) in one end and by a rubber closure disc (bromobutyl) in the other end. The cartridge is mounted in a plastic needle adaptor. Each pack contains 4 single-use dual-chamber cartridges packed in individual blisters and 6 disposable injection needles 0.25 mm x 4 mm (31G x 5/32”). Each dual-chamber cartridge has a specific label with assigned two-colour coding ribbons that is only used by the Auto-Injector to select the correct reconstitution settings. Strength colours are indicated on the carton and blister foil and should be used to differentiate the individual strengths.

2.4.2. Active substance

2.4.2.1. General information

Lonapegsomatropin is a recombinant human growth hormone (hGH) transiently conjugated to a methoxypolyethylene glycol carrier consisting of 4 × 10 kDa mPEG chains (mPEG-Linker). The hGH intermediate is obtained from fermentation of a strain of *E. coli* transformed with a genetically engineered plasmid containing the coding sequence for hGH. The mPEG-Linker is generated by conjugation of mPEG-maleimide to Linker A (proprietary TransCon linker), converting mPEG-maleimide to mPEG-succinimide. At physiologic pH and temperature, lonapegsomatropin is designed to release (via autocleavage of the linker) somatropin with the same mode of action and distribution as daily somatropin, but with a once-weekly injection. The structure of lonapegsomatropin is provided in Figure 1 below.

Figure 1. Lonapegsomatropin structure



The hGH intermediate is a 191 amino acid residue protein with a molecular weight of approximately 22.125 Da. The amino acid sequence of hGH is provided in the dossier. Cysteine residues Cys53 and Cys165 are

linked by an intra-molecular disulfide-bond as are cysteine residues Cys165 and Cys189. The amino acid sequence, the N-terminus and the disulfide-bonds of hGH intermediate are identical to that of hGH of pituitary origin. There are no post-translational modifications of the hGH.

Lonapegsomatropin active substance is produced through chemical conjugation of hGH intermediate to the mPEG-Linker. The average molecular weight of lonapegsomatropin is approximately 63 kDa.

2.4.2.2. Manufacture, process controls and characterisation

The sites employed in the manufacture of the hGH Intermediate and in the manufacture of active substance are detailed in the submission dossier. Lonapegsomatropin active substance is manufactured at FUJIFILM Diosynth Biotechnologies UK Limited, Belasis Avenue, Billingham TS23 1LH, United Kingdom and packaged, stability tested and quality-control tested in accordance with good manufacturing practice (GMP).

Description of manufacturing process and process controls

Lonapegsomatropin active substance is manufactured by conjugation of hGH Intermediate and mPEG-Linker.

Sufficiently detailed description of the manufacturing process has been provided, including a flow diagram, information on media and buffers used, the objective of the process steps and a short narrative of how each step is performed. To ensure process consistency, process parameters with associated ranges have been presented and critical process parameters (CPPs) impacting critical quality attributes (CQAs) or important parameters have been identified. The information has been presented clearly and in sufficient detail.

<u>hGH Intermediate</u>

The hGH used for manufacture of lonapegsomatropin active substance is expressed by *E. coli* cells as inclusion bodies (IBs), which are then harvested, dissolved, refolded, modified and purified to yield hGH intermediate.

The upstream process starts with the thawing of one vial of Working Cell Bank (WCB) in a shake flask followed by further propagation in the production bioreactor. The fermentation is terminated at the end of the production phase. The cells are harvested, separated from the fermentation media by centrifugation, followed by a homogenisation, recovery and storage of the IBs until the purification process starts. The upstream process is adequately described. As regards to the downstream manufacturing process, it includes: dissolution, refolding and modification of the IBs, chromatography steps and ultrafiltration/diafiltration.

At the end of the manufacturing process, the hGH intermediate is filtered through the 0.2 µm filter and stored. There are no reprocessing steps during the manufacture of hGH intermediate.

<u>mPEG-Linker</u>

The manufacturing process for the mPEG-Linker consists of coupling of the mPEG-maleimide to Linker A. All starting materials for the synthesis process of mPEG-Linker are justified and adequately described in the dossier. There are no reprocessing steps during the manufacture of mPEG-Linker.

<u>Lonapegsomatropin</u>

Lonapegsomatropin active substance is manufactured through chemical conjugation of hGH intermediate to mPEG-Linker. The process includes UF/DF, conjugation reaction of hGH Intermediate with mPEG-Linker, chromatographic purification of lonapegsomatropin, buffer exchange and concentration by UF/DF, followed by final 0.2 µm filtration and filling.

The overall description of manufacturing process and controls for the hGH intermediate and lonapegsomatropin active substance is considered acceptable, appropriately detailed and adequate analytical data for IPTs is provided. Typical process and maximum hold times are stated. Re-use of columns and membranes is monitored and evaluated continuously. Process parameters and in-process tests are well defined and controlled within appropriate ranges as well as in-process test controlled by action limit or acceptance criteria.

The batch numbering system is adequately presented. Ranges or typical batch sizes for hGH intermediate and lonapegsomatropin active substance are stated. Pooling strategies for hGH intermediate and lonapegsomatropin active substance are adequately presented.

Adequate specifications have been proposed for the container closure system for lonapegsomatropin active substance. Both primary container and closure comply with relevant standards and are commonly used for pharmaceutical products. The containers are sterilized by gamma irradiation. A safety evaluation on the extractables was performed by the applicant and concluded that none of the identified extractables were found in levels exceeding a safety limit of 1.5 µg/patient/day and that no class I, II or III elemental impurities according to ICH Q3D were found in levels above the reporting limit.

Overall, the active substance manufacturing process is considered acceptable.

Control of materials

Sufficient information on raw materials used in the active substance manufacturing process has been submitted. Raw materials used in the manufacture of hGH intermediate and lonapegsomatropin active substance are either of compendial quality or released using in-house specifications/methods. Specifications and acceptance criteria for quantitative analysis of non-compendial material are provided. No materials of human or animal origin are used in the manufacturing process. Adequate information on filters and membranes is included in the dossier.

<u>hGH intermediate manufacturing process</u>

Information provided for Master Cell Banks (MCBs) and WCBs follows in general ICH Q5B and ICH Q5D guidelines. The species, strain and known characteristics of the host organism (*E. coli*) as well as cultivation history and genetic manipulation are described. The nucleotide sequence in the expression plasmid coding for the protein was synthesised de novo. Component parts of the expression construct and their function are described. The nucleotide sequence of vector is determined. Analytical methodologies are considered validated for the intended purpose of confirmation of the nucleotide sequence.

Transformation methodology as well as criteria used to select cell clone for production is adequately described. The cell line history and production of the cell banks are described in sufficient detail. Cell banks are adequately characterised. Descriptions of analytical methods for cell bank testing are provided. Based on characterisation results, MCBs and WCBs are considered appropriate for their use in the manufacturing process.

The genetic cell bank stability of the production cell line was investigated. The protocol for the establishment of future WCBs is provided and assessed as acceptable.

<u>mPEG-Linker manufacturing process</u>

mPEG-Linker manufacturing process is schematically presented in the dossier. A Major Objection was raised requesting re-definition of the starting material since Linker A was not considered suitable. The re-defined starting material, proposed by the applicant, has been identified as an appropriate starting material fulfilling

all the ICH Q11 general principles. For all starting materials, general information (structure and properties) and characterisation data has been provided, as well as information on manufacturers, summary of the manufacturing processes, synthesis scheme and specifications with batch analysis data.
Impurities that have a potential impact on the quality of lonapegsomatropin active substance, are controlled by adequate specifications. The impurities that do not have an impact on the quality of lonapegsomatropin active substance are adequately discussed and their control strategy is justified by the applicant. It is confirmed by the applicant that the analytical procedures have been validated. Re-test period and storage conditions have been proposed for both starting materials, based on stated stability protocol.

Control of critical steps and intermediates

Acceptable information has been provided on the control system in place to monitor and control the active substance manufacturing process with regard to critical, as well as non-critical operational parameters and in-process tests.

Control of hGH intermediate and lonapegsomatropin active substance manufacturing process

An overview of critical process parameters, in process hold-times and critical in-process tests (used actively to control the process) is presented by the applicant. Additionally, a microbial control strategy is adequately defined and microbial limits will be reviewed periodically. Analytical procedures for critical in-process tests have been shown to be suitable for the intended use.

Control of mPEG-linker intermediates

No critical in-process tests have been identified in the manufacturing process of chemical intermediates. Impurities that have a potential impact on the quality of the lonapegsomatropin active substance are included in the respective specification, except for one impurity for which an impurity removal study was conducted. The impurities that do not have an impact on the quality of the lonapegsomatropin active substance are adequately discussed and their control strategy is justified by the applicant. Specifications for all intermediates have been provided, along with a description and validation summary for the non-compendial methods.

Batch data for representative intermediates batches manufactured at commercial scale comply with the proposed specifications. The specifications are based on representative batches and ICH Q6A/Q6B guidelines covering control parameters for appearance, identification, purity, impurities and physiochemical properties. Justifications of proposed specifications are considered acceptable. Proposed shelf-life for the chemical intermediates is adequately justified by the provided stability data.

Process validation

Process validation of the mPEG-Linker and intermediates, hGH intermediate and lonapegsomatropin active substance manufacturing processes has been adequately conducted. Studies performed for the process validation, together with commercial-scale data were used to define the process parameters and their ranges, to implement suitable in-process tests throughout the manufacturing process and to set the acceptance criteria or acceptable ranges. Designation of parameters and in-process tests as critical or non-critical for the commercial process has been performed following principles of ICH guidelines.

Hold times for in-process materials in lonapegsomatropin active substance manufacturing process were established based on experimental data. Overall data confirms that all proposed hold times for manufacturing of hGH intermediate and lonapegsomatropin active substance in commercial scale were justified by small-scale data and/or manufacturing data at scale, and yield a product that meet all specification limits. In

support to the established hold times, microbial hold studies were also performed, results of which, together with data from historical GMP batches, show that the process consistently operates with low amounts of endotoxins and bioburden.

Clearance validation studies for certain impurities introduced or formed during the hGH intermediate manufacturing process have been conducted, demonstrating that the hGH intermediate purification process is capable of efficiently removing these process impurities to consistently low levels.

In addition, regarding the lonapegsomatropin active substance manufacturing process, depletion studies were conducted and adequately demonstrated removal or reduction of impurities that are not controlled by the lonapegsomatropin specification, but which can impact the impurity profile of the active substance. Fate and purge of other impurities originating from chemical starting materials and from mPEG-Linker degradation and their potential impact on the quality of the active substance are also adequately discussed and respective control strategy is considered acceptable. The potential impact of each impurity on the quality of the lonapegsomatropin active substance has been assessed using impurity thresholds from ICH Q3A and ICH Q3B as an additional measure to ensure product quality. None of the impurities are considered mutagenic based on toxicological evaluations.

PPQ campaigns covering the manufacturing of IBs, hGH intermediate, lonapegsomatropin active substance, as well as for mPEG-Linker intermediates were performed and the data for several PPQ active substance batches is provided in the dossier. All parameters, in-process controls and measures of product quality are consistently within the acceptable ranges and acceptance criteria demonstrating effective control of the process over all process steps. Batch release testing results comply with the release specification acceptance criteria at the time of testing. Deviations were investigated and determined to have no impact on the acceptability of the PPQ or the quality of the product. Results demonstrate that the process can operate effectively and reproducibly and within the specified ranges and acceptance criteria to produce a product meeting its predetermined specifications and quality attributes.

Process is maintained in a validated state by continued monitoring and trending of process parameters, in-process tests, CQAs and release data. The lifetime of the resins and UF/DF membranes is confirmed by monitoring and evaluating performance parameters as part of concurrent process validation at the commercial scale. All results fulfil the release criteria. The protocol for validation of resins / membranes life span on commercial scale, is provided and considered acceptable. A maximum number of cycles was set for the resins and membranes. A protocol for cleaning of resins in between lonapegsomatropin active substance batches has been provided by the applicant.

Shipping qualification

The shipping configuration of lonapegsomatropin active substance is described in the shipping protocol. The use of a qualified shipping system and defined shipping lanes ensures that there is no risk to product quality during shipping of the active substance.

Manufacturing process development

Development history is presented in an adequate manner covering sufficient information of all processes and all changes introduced. hGH intermediate and lonapegsomatropin materials generated by different processes were investigated either by comparison of batch release, characterisation and stability data, or by head-to-head analytical comparability. The results indicate these changes had no significant influence on the quality profile of hGH intermediate and lonapegsomatropin active substance materials produced via the different process versions.

Lonapegsomatropin active substance clinical development was initiated with hGH intermediate conjugated with an 80 kDa mPEG-Linker (ACP-001 – lonapegsomatropin predecessor molecule) while current lonapegsomatropin is produced by conjugation of hGH with a 40 kDa mPEG-Linker (ACP-011). Lonapegsomatropin produced by the commercial process was used in long-term safety and efficacy extension study.

Characterisation

Both hGH intermediate and lonapegsomatropin active substance have been sufficiently characterised by physicochemical and biological state-of-the-art methods revealing that the active substance has the expected structure.

Primary, secondary and tertiary structure, purity, impurities, high molecular weight species (HMWS), product variants, immunological identity and biological activity were studied in PPQ batches in order to characterise hGH intermediate and lonapegsomatropin active substance. It should be noted that the protein concentration is expressed as the content of hGH and not as the content of lonapegsomatropin. This is acceptable since a correlation was established between hGH content and lonapegsomatropin, in order to calculate the equivalence of lonapegsomatropin content and this is deemed acceptable.

Presented results have confirmed the identity, structure and physical characteristics of hGH intermediate and lonapegsomatropin active substance. Results of hGH intermediate and hGH released from lonapegsomatropin are in a good correlation.

The biological activity assay for hGH intermediate consists in a cell proliferation assay which is in line with the Ph. Eur. monograph 950. The biological activity is quantified relative to an in-house reference material, which is endorsed.

Biological activity for lonapegsomatropin active substance is determined by the use of the same biological activity assay as for the hGH intermediate. The biological activity is measured for the liberated hGH.

Control strategy for product related substances / impurities and process-related impurities is acceptable. Relevant species and substances are controlled by both the specification of hGH intermediate and/or lonapegsomatropin active substance or just by lonapegsomatropin active substance specification. Other impurities are either controlled as part of total impurities and/or have been proven to be reduced to low / below LOQ / negligible levels. Potential impurities originating from polymers in contact with intermediate and active substance materials are evaluated by risk assessment and by an extractable study performed by the manufacturer, followed by safety evaluation by the applicant. The approach is endorsed.

Specification

Release and shelf-life specification for hGH intermediate and for lonapegsomatropin active substance are provided in the dossier. hGH intermediate specification is predominantly based on the Ph. Eur. and USP somatropin monographs. The proposed hGH intermediate specification was considered acceptable, after the applicant was requested to provide additional information. Additionally, tightening of acceptance criteria for several test parameters was requested during assessment. The proposed specification covers all relevant characteristics of somatropin molecule. The acceptance criteria stated in the monographs were applied for testing the hGH intermediate with the compendial methods. The justification of the analytical procedures and acceptance criteria for the test parameters which are not described in the somatropin monographs is provided.

Proposed lonapegsomatropin active substance specification is, in general, in line with ICH Q6B guideline and covers most of the relevant characteristics of the molecule. Parameters covered include appearance, identification, quantity, purity and impurities and contaminants. Comprehensive justification of specification limits for parameters stated in the active substance specification is provided. Even though the proposed lonapegsomatropin specification is considered acceptable, since limited number of batches are taken as base for establishing acceptance criteria, the applicant is recommended to re-evaluate the current acceptance criteria for several specification parameters once data from a larger number of commercial process batches will be available (Recommendation).

Analytical methods

Description and system suitability criteria of non-compendial analytical procedures for hGH intermediate and for lonapegsomatropin active substance are provided in the dossier and are considered adequate. Summary of development history of analytical procedures is provided and found acceptable.

Most of the analytical methods have been validated, and validation summaries are provided except for the bioburden and endotoxin compendial methods. The approach is considered acceptable. Since validations were performed in accordance with ICHQ2 (R1) and predetermined validation acceptance criteria were met, analytical methods are considered validated for their intended use.

Batch analysis

Analytical testing results for hGH intermediate batches used to manufacture lonapegsomatropin active substance for nonclinical studies, development studies, clinical studies, reference materials, stability testing and PPQ have been provided. Additional information on the manufacturing process, manufacturer, date of manufacturing, batch size, quality (GMP / non-GMP) and use is indicated. Additionally, brief descriptions of analytical procedures used only during the development and summaries of their respective validations, if applicable, are also provided. The results are within the specifications and confirm consistency of the manufacturing process. The provided information is considered adequate.

Reference materials

For hGH intermediate, the current Ph. Eur. Chemical Reference Substances are used for identification and purity/impurity. For biological activity, WHO Somatropin International Standard was used until 2019, when it has been replaced by an in-house hGH Primary Reference Material (PRM). The PRM was calibrated against the WHO International Standard and was derived from a hGH intermediate development batch, used in the clinical study. A summary report for calibration of PRM against WHO standard is provided. A protocol for qualification and re-qualification of hGH PRMs and SRMs has been provided and is considered acceptable. Acceptance criteria for release of PRM and SRM are mostly aligned with the release specification for hGH intermediate and are considered acceptable. Additional characterization studies as those performed for the current PRM are added to the protocol for qualification of future RM. Proposed acceptance criteria for RMs stability testing are considered acceptable and adequate stability data for PRM has been provided in the dossier.

For lonapegsomatropin, a two-tier in-house reference standard (PRM and SRM) has been established. The history of the establishment of reference standards used throughout the development is provided. The current PRM and SRM are derived from the active substance batches used in clinical studies. The production and testing of the current PRM and SRM are, in general, sufficiently described and considered adequate. Some differences between the PRM and SRM specifications and the current active substance specifications are observed and are considered appropriately justified by the applicant.

Stability data are presented for all lonapegsomatropin in house reference materials established so far. The proposed shelf-life is considered acceptable. The protocol for the establishment of future lonapegsomatropin reference materials is provided. The PRM and SRM will be prepared from batches representative of a commercial process, which will be tested according to the provided specification. Acceptance criteria will be the same as for the release specification of lonapegsomatropin active substance. Additionally, a stability protocol for the future reference standards has been provided.

Stability

For hGH intermediate, stability data have been provided for long-term and accelerated conditions.

Stability testing is identical to release testing for the hGH intermediate, except for some quality attributes not expected to change during shelf-life. The methods used for PPQ batches stability testing are identical to the ones used for hGH intermediate release. The Applicant has evaluated the data obtained during the long-term conditions stability program against stability acceptance criteria in place at the time of the studies. Results were within the acceptance criteria and no significant changes have been observed. Additionally, all results provided are within the proposed commercial stability acceptance criteria.

Increase in the percentage of impurities at accelerated conditions is discussed and the justification provided is endorsed.

Adequate post-approval stability information is presented and acceptable handling of any confirmed OOS is proposed. In conclusion, based on the stability data provided, the proposed shelf-life for the hGH intermediate is endorsed.

For lonapegsomatropin active substance stability data has been provided for long-term, accelerated and stress conditions. The batches for stability studies were stored in a container closure representative of the commercial containers. The long-term stability program is designed and performed according to ICH guidelines.

Methods used for stability testing of PPQ batches are identical to the ones used for lonapegsomatropin active substance release. The stability-indicating properties of several analytical procedures have been investigated through forced degradation studies. Stability testing is identical to release testing for the lonapegsomatropin active substance, except for some quality attributes not expected to change during shelf-life. Long-term stability results, except for one test parameter for one batch, are within the commercial acceptance criteria, and no significant changes have been observed. For the noncompliant results, the explanation provided by the applicant is considered acceptable.

Results from accelerated conditions studies remained within the acceptance criteria through the testing period. No significant changes have been observed. Results from stress conditions studies demonstrate a clear trend of autocleavage for lonapegsomatropin and an increase in impurities. Forced degradation studies demonstrate that the lonapegsomatropin active substance is sensitive to light exposure, heat, oxidation, acidic conditions (low pH), basic conditions (high pH) and agitation. Light exposure study, as part of the forced degradation study, was designed in accordance with ICH Q1B guideline. Results on confirmatory photostability testing for lonapegsomatropin active substance are not provided, but a confirmatory study is provided for the finished product. Based on the provided stability data, the proposed container for the active substance provides adequate protection. Freeze/thaw studies were performed and the provided results support the proposed number of freeze/thaw cycles for hGH intermediate and for lonapegsomatropin active substance.

Adequate post-approval stability protocol information is presented and acceptable handling of any confirmed OOS is proposed.

In conclusion, the stability results indicate that the active substance is sufficiently stable and justify the proposed shelf-life in the proposed container.

2.4.3. Finished medicinal product

2.4.3.1. Description of the product and Pharmaceutical development

Lonapegsomatropin powder and solvent for solution for injection are presented in a dual-chamber cartridge (DCC):

- Chamber 1 containing a lyophilized cake prepared from different fill volumes of an aqueous compounded solution of lonapegsomatropin, succinic acid, trehalose dihydrate and tromethamine.
- Chamber 2 containing different volumes of diluent (WFI) for reconstitution.

The primary packaging is a glass cartridge (Type I glass) with two chambers separated by a rubber stopper (bromobutyl). The cartridge is closed by a rubber stopper (bromobutyl) in one end and by a rubber closure disc (bromobutyl) in the other end. Injection needles with the dimensions 0.25 mm x 4 mm (31G x 5/32”) are supplied co-packed with the finished product.

Following reconstitution utilizing a proprietary, non-integral, re-usable Auto-Injector medical device, lonapegsomatropin finished product will be presented as a single-use, sterile solution for subcutaneous (s.c.) administration.

To accommodate dosing of the intended patient group, the finished product is supplied in nine strengths containing different amounts of lonapegsomatropin and based upon variable fill volume, two solution strengths are obtained (i.e., 11.0 mg hGH/mL and 22.0 mg hGH/mL). There is no overage in the lonapegsomatropin finished product formulation. An overfill is included in chamber 1 to compensate for loss in the DCC headspace. The volume in chamber 2 is based on calculations of the DCC bypass volume loss and volume expansion during reconstitution of the dry matter in the lyophilized cake.

The composition of the finished product is sufficiently described. All excipients are of pharmacopoeial grade (Ph. Eur./USP), non-animal origin and commonly used in parenteral formulations. There are no novel excipients used in the finished product formulation.

Pharmaceutical development

During the clinical phases, the formulation has been adjusted for the intended purpose, while assuring quality, safety and efficacy of the finished product.

The compatibility of lonapegsomatropin active substance with the excipients listed above has been discussed by the applicant, as well as the choice of excipients, their concentration and characteristics that can influence the finished product performance. Lonapegsomatropin is shown to be sufficiently compatible with the excipients during long-term storage conditions and accelerated storage conditions.

A brief summary describing the development of the finished product formulation as well as the differences between clinical formulations and proposed commercial formulation is provided and discussed. A predecessor ACP-001 molecule (containing 80 kDa mPEG carrier) was utilized in early development and clinical phase 2,

whereas clinical phase 3 studies were conducted with lonapegsomatropin (containing 40 kDa mPEG carrier) in DCC or vials. The final formulation is shown to be robust with regards to variations in protein concentration, excipient concentrations, pH and residual moisture in the lyophilized product. The results of the DoE and humidity studies performed with lonapegsomatropin finished product to investigate the formulation robustness are submitted.

Differences introduced during development are presented in sufficient detail in the dossier. In clinical development, finished product was first delivered as lyophilized powder of predecessor ACP-001 or lonapegsomatropin in vials, with WFI in PFS. To provide a more patient convenient container closure system (CCS), single-use DCC and a re-usable Auto-Injector were developed for lonapegsomatropin administration. Besides changes in the CCS, there have been additional manufacturing changes introduced (minor adjustment due to introduction of DCC), as well as site transfer from development site to the proposed commercial site. Following the changes in the primary container, dosing system and manufacturing process, adequate comparability study have been performed. Supporting data was also provided from an in-use stability study comparing the quality profile of the reconstituted finished product in vials and in DCC over 4 hours. In conclusion, finished product program development is presented in sufficient detail.

Container closure system

The primary and secondary packaging of the finished product consist of the following parts:

- dual chamber cartridge (borosilicate glass type I, Ph. Eur., USP, siliconized)
- two rubber stoppers and rubber closure disc (bromobutyl grey, Ph. Eur., USP, siliconized)
- polypropylene snap-on cap (secondary packaging material, not in the contact with product)
- stainless-steel needle, CE marked, 0.25 mm x 4 mm (31G x 5/32”).

The primary packaging components description, including test procedures and specifications for incoming primary packaging components are adequately presented in the dossier. Compliance with the relevant USP and Ph. Eur. monographs is stated for contact packaging materials. Short description of secondary packaging components is also provided. To justify the appropriateness of the container closure system, an extractable study was performed with the rubber material (bromobutyl grey) used for stoppers and closure disc. In addition, results of the leachables studies on brombutyl grey siliconized stoppers were provided.

Following reconstitution utilizing the proprietary Auto-Injector device, lonapegsomatropin finished product will be presented as a single-use, sterile solution for subcutaneous administration, to be automatically dosed by the Auto-Injector as a single dose empty-all concept injection. The Auto-Injector provides a well-controlled reconstitution of the lyophilized finished product in which an automatic mixing step controlled by the device is followed by a manual mixing step.

The Auto-Injector, provided separately, is a CE marked, re-usable, polypropylene electronic medical device, with a needle adaptor and a strength specific two-colour coding DCC label. Analysis of the testing data confirms that the Auto-Injector and DCC combination product meets the dose accuracy and precision requirements of ISO 11608-1, delivering the labelled dose (mg hGH) within the targeted limits. Dose accuracy testing also confirmed that proposed fill volumes are appropriate to deliver the labelled amount of product.

The compatibility of the finished product with the injection needle and reconstitution diluent (WFI) has been demonstrated during stability studies.

Overall, the container closure system is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

Lonapegsomatropin finished product is manufactured, packaged, stability tested and quality control tested in accordance with good manufacturing practice (GMP). The manufacturer responsible for the batch release of the finished product is: Ascendis Pharma A/S, Tuborg Boulevard 12, DK-2900 Hellerup, Denmark.

Separate batch formulae for excipients and diluent are provided. The batch formula for lonapegsomatropin compounded solution is presented in formulae for calculations of required amounts. The batch formula and batch size for the intended commercial finished product batch size expressed in mass units is also stated. The maximum number of active substance batches that can be pooled for commercial finished product manufacturing, confirmed during process validation of PPQ batches, has been stated by the applicant. The approach is endorsed. The manufacturing process and process controls are sufficiently described in the dossier and start with the preparation of equipment, primary packaging components and succinic acid solution, which is sterile filtered through one 0.22 µm filter. Components of the finished product are mixed and sterile filtered through a 0.22 µm filter. On the filling line, the lonapegsomatropin compounded solution is in-line sterile filtered through one 0.22 µm filter and filled by weight into cartridges. Diluent (WFI) is prepared by distillation, filtered through a sterile 0.22 µm filter into a break tank and in-line sterile filtered through a 0.22 µm filter. WFI is then filled by weight into the cartridges. The filled DCCs are visually inspected and secondary packed. Operational and performance parameters are described. Primary packaging components are depyrogenated in a dry heat tunnel or sterilized in an autoclave under Ph. Eur. conditions and in line with the Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container. The overall description of the manufacturing process and controls in considered acceptable.

For process justification, technical and GMP batches manufactured in the commercial facility were investigated for selected process parameters, which were challenged to investigate the potential contribution of process variability to product quality and robustness of the manufacturing process. Data gathered during process justification have demonstrated a robust manufacturing process for lonapegsomatropin finished product.

Process and hold times have been set through the entire manufacturing process. Steps that could potentially increase degradation were challenged at maximum or above proposed process/hold times. Other manufacturing steps were investigated below proposed process/hold times with explanation that these are unlikely to affect the quality of lonapegsomatropin finished product. Proposed hold times are appropriately justified and supported by data.

A list of CQAs, indicating their potential impact on safety and efficacy, and associated controlled strategy has been provided. Most CQAs are controlled in the specifications or as IPCs. The criticality assessment and the justifications provided are considered appropriate. Overall, the control strategy is appropriately designed to ensure that each CQA is within the appropriate range, limit or distribution to assure the quality of lonapegsomatropin finished product.

For PPQ, adequate bracketing concept was used. The PPQ covers all unit operations. All results obtained for the PPQ batches show that the manufacturing process of lonapegsomatropin finished product and the control strategy is suitable, by demonstrating the reproducibility, performance, consistency and robustness of the manufacturing process within pre-defined limits and specified conditions. Validation of aseptic processing included results of the three most recent media fills. All acceptance criteria are met. Adequate bracketing approach was also applied for the filter validation. The investigations and validations performed on the sterilizing filter have shown that the filter is capable of retaining bacteria and is compatible with the

lonapegsomatropin compounded solutions, placebo and WFI. Based on the results from the extractables studies, the risk for patients due to potential leachables from the filter used for the manufacture of the lonapegsomatropin finished product is negligible. In conclusion, the sterilizing filter can be used to supply sterile lonapegsomatropin finished product to the patient. In order to further substantiate conclusions on sterilizing filter validation studies, a summary of results of extractables and leachables studies, with presented calculations of worst-case exposure of potential substances with regards to compound-specific permitted daily exposure levels are provided. Additionally, adequate data in support to transport validation are provided and is considered sufficient.

In conclusion, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification

Lonapegsomatropin finished product specification is provided in the dossier. Parameters covered include the following aspects: appearance for the diluent; appearance, reconstitution time and residual moisture for the lyophilized powder; appearance, general tests (osmolality, subvisible particles, pH), identification, protein content, uniformity of dosage units expelled volume, biological activity, linker cleavage, purity and impurities and contaminants for the reconstituted solution. The release and end of shelf-life testing specification for lonapegsomatropin finished product is provided. Wider limits for the end of the shelf-life are proposed for some QAs, which is considered acceptable.

Revision/tightening of several specifications was requested during assessment. Even though the proposed lonapegsomatropin finished product specification is considered acceptable, since limited number of batches is taken as base for establishing acceptance criteria, the applicant is recommended to re-evaluate the current acceptance criteria once data from a larger number of commercial process batches will be available (Recommendation).

Specifications are set taking into account release and stability results for finished product batches. Several clinical, PPQ and technical batches have been considered for establishing the specification. Overall, finished product acceptance criteria at release and during shelf-life are considered acceptable.

No new impurities are formed during the finished product manufacturing process. A risk assessment performed in accordance with ICHQ3D on elemental impurities in the finished product is provided and deemed acceptable. Based on the risk assessment, it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

Initially, the applicant has provided a risk evaluation concerning the presence of nitrosamine impurities in lonapegsomatropin active substance and in the finished product. However, an updated risk assessment, including an evaluation of probability of contamination with nitrosamines during the manufacture of starting materials, was requested as a Major Objection. The requested risk evaluation has been performed, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Description and system suitability criteria of non-compendial analytical procedures for the finished product are provided in the dossier and are considered adequate. For residual moisture for lyophilized powder, appearance (clarity and colour) of the reconstituted solution, visible particles, bacterial endotoxins, sterility, osmolality, sub-visible particles and pH, reference to Ph. Eur. and/or USP is given, which is considered acceptable. The biological activity of the finished product is determined using a cell proliferation assay, in line with the Ph. Eur. monograph 950.

The validation for in-house methods is performed according to ICHQ2 (R1) and validation summaries (validated parameters and results) are provided. Provided summaries for all non-compendial methods show that all predetermined validation acceptance criteria were met and that all methods are considered validated for their intended use. Basic analytical procedures (residual moisture, clarity, colour, visible particles, osmolality, sub-visible particles and pH) have been verified and demonstrated to be suitable for the intended use. Procedures for bacterial endotoxins and sterility have been validated in accordance with the harmonized pharmacopeia to confirm suitability.

Batch analysis

Batch analysis data for finished product batches used for nonclinical studies, analytical method validation, development studies, clinical studies, stability testing and PPQ are presented. All results met the acceptance criteria used at the time of release and confirm consistency of the manufacturing process.

Reference materials

See active substance section on Refence Materials, which is applicable also for the finished product.

2.4.3.4. Stability of the product

The presented stability protocols are considered acceptable. Stability studies are conducted in accordance with ICH Guidelines Q1A (R2) Stability Testing of New Drug Substance and Products, Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products, and Q5C Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Stability. The parameters tested are the same as for release, except for several quality attributes which are not expected to change over time. The approach is considered acceptable. Container closure system used in stability testing is considered representative of the finished product container closure system.

All primary and supportive stability batches have been manufactured at the finished product manufacturing site using the same commercial manufacturing process. Regarding the stability data provided, the degradation profile of the primary, supportive and PPQ batches are comparable. All presented data remained within the proposed acceptance criteria for long-term testing.

In conclusion, it is considered acceptable to approve the proposed finished product shelf-life of 36 months at 5°C, including storage at temperatures up to 30°C for up to 6 months. The finished product shelf-life was estimated based on statistical analysis using the ICH Q1E (Evaluation of Stability Data) approach, which is considered acceptable.

In order to support the transfer of lonapegsomatropin finished product in and out of the refrigerator (2°C to 8°C) to a maximum temperature of 30°C for 6 months during long-term storage, two temperature cycling studies were performed. Based on the provided data, justification of limits for several quality attributes and commitment provided by the applicant to re-evaluate the acceptance criteria once a sufficient number of

finished product batches will be manufactured. It can be concluded that the storage up to 30°C can be accepted. It is acknowledged that this provides a benefit for the patient in providing flexibility in storing lonapegsomatropin finished product.

The stability of lonapegsomatropin finished product after reconstitution is assessed by in-use stability studies conducted at study start and at selected testing time points up to the end of shelf-life. Although a minor increase in released hGH was observed 4 hours after reconstitution, all presented results comply with the proposed acceptance criteria. Available data therefore support an in-use storage period of up to 4 hours at up to 30°C.

Photostability studies were conducted in accordance with ICH Q1B.It is concluded that lonapegsomatropin finished product is sensitive to light and that the secondary packaging intended for market provides sufficient protection against light.

Based on available stability data, the shelf-life of lonapegsomatropin finished product of 36 months and storage conditions (*Store in a refrigerator 2°C - 8°C. Do not freeze. Store in the original package in order to protect from light*) or for up to 6 months at temperatures up to 30°C, as stated in the SmPC, are acceptable.

2.4.3.5. Adventitious agents

Viral safety

E. coli is used to manufacture lonapegsomatropin active substance. During the manufacturing process, no reagents derived from biological sources are used. As such the risk for viral contamination is negligible. The provided information does not give rise to specific comments or issues.

TSE issues

A white colorant is used for the closure of the active substance container; this colourant contains tallow of bovine or porcine origin. The material information sheet (MIS) from the manufacturer of the closure is provided. The MIS concludes that the tallow is unlikely to present any TSE risk. The provided information is considered sufficient.

2.4.3.6. GMO

N/A

2.4.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two Major Objections were raised, concerning (1) the definition of a starting material and (2) the completeness of the nitrosamine risk evaluation. The Major Objections, as well as all the other concerns, have been satisfactorily resolved.

In summary, from a quality point of view, a positive CHMP opinion of the quality part can be recommended to the CHMP.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertain to re-evaluation of the active substance and finished product acceptance criteria once a large number of batches are being manufactured. This point is put forward and agreed as recommendation for future quality development.

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. Data has been presented to give reassurance on viral/TSE safety.

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 point for investigation.

1. To re-evaluate the active substance and the finished product specifications after a sufficient number of batches are manufactured and available.

2.5. Non-clinical aspects

2.5.1. Introduction

A predecessor of lonapegsomatropin, ACP-001, with identical recombinant hGH and TransCon linker moieties, varying from lonapegsomatropin only in its mPEG composition (4 x 20 kDa chains for a total of 80 kDa), was used in early development. Based upon the overall similarity of the kinetics of the released hGH and subsequent insulin-like growth factor I (IGF-I) response and the associated efficacy and safety profiles investigated in nonclinical studies and in a clinical phase 1 study, data obtained for ACP-001 is judged applicable to lonapegsomatropin. Some studies, conducted as part of the ACP-001 program, were thus deemed supportive of lonapegsomatropin: IGF-I stimulation in repeat-dose study of ACP-001 in cynomolgus monkeys, potency testing of ACP-001 in hypophysectomized rats, human ether-a-go-go related gene (hERG) assay, skin sensitization test in mice and pre- and postnatal development toxicity study in rats.

Like hGH, somatropin, when released from lonapegsomatropin, exerts its biological action via binding and activation of the growth hormone receptor (GHR). The nonclinical safety programme was designed in accordance with relevant regulatory guidelines. Bioanalytical and immunogenicity assays were developed and validated according to current guidelines and relevant white papers. The nonclinical program involved a range of in vitro and in vivo toxicity studies in CBA/J mice, Sprague Dawley rats, New Zealand White rabbits, and cynomolgus monkeys, which are considered relevant species for safety evaluation of lonapegsomatropin. In all repeat-dose toxicity studies the animals were dosed weekly by SC injection at dose levels up to 20-fold the clinical therapeutic dose of 0.24 mg hGH/kg/week.

The lonapegsomatropin drug product strength is described in mg weight of hGH (as distinguished from mg weight of the entire prodrug). Exposure to lonapegsomatropin was confirmed throughout the once weekly dosing periods in all studies. The nonclinical development program for lonapegsomatropin has been designed

with special focus on supporting the paediatric population. Therefore, the chronic repeat-dose toxicity studies were conducted in juvenile cynomolgus monkeys.

The nonclinical program assessed both the parent prodrug, lonapegsomatropin, and the products of autocleavage (hGH, mPEG, the leaving group, and the remainder of the linker covalently bound to mPEG) as well as IGF-I, a biomarker of hGH receptor activation. In vitro assessment of the autocleavage products involved use of partly cleaved lonapegsomatropin as the test article. The nonclinical studies included assessment of the putative safety aspects of lonapegsomatropin, pharmacokinetics/pharmacodynamics (PK/PD) of lonapegsomatropin, hGH, the leaving group, mPEG (both in serum and cerebrospinal fluid [CSF]), mPEG-linker, and IGF-I as well as immunogenicity aspects of lonapegsomatropin (binding/neutralizing anti-hGH antibodies and binding anti-PEG antibodies).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Both *in vitro* and *in vivo* studies were conducted to evaluate the pharmacology and pharmacodynamics of lonapegsomatropin.

An analytical comparability study was undertaken to compare the integrity of the released hGH from lonapegsomatropin to unconjugated hGH by RP-HPLC-MS, tryptic peptide map MS, MALDI-TOF MS and free thiol quantification. The comparability study indicated a high similarity of the released hGH to the control hGH, demonstrating that hGH is unaltered and unmodified when released from lonapegsomatropin. Potency of the released hGH was 3.1 IU/mg, confirming that the hGH released from lonapegsomatropin is fully active.

The kinetic analyses of hGH and lonapegsomatropin were performed over a range of concentrations and tested in duplicate, by Surface Plasmon Resonance Technology. The concentration of free recombinant hGH liberated during analysis was assessed by RP-HPLC.

A mean association rate constant ka ~ 10^6 $M^{-1}s^{-1}$ and dissociation rate constant kd ~ 10^{-4} s^{-1} were determined for the hGH:hGHR interaction, over the concentration range assessed, and thereby comparable to literature values based on similar studies (Cunningham, 1993). Samples analysed by RP-HPLC following each analytical run indicated that no significant release of hGH occurred from lonapegsomatropin (≤ 0.14% of the total hGH) during the timespan (~ 2.75 h) of the sample analysis. Mean dissociation rate constants (kd) across the concentration range were slow (~ 10^{-4} s^{-1}) and were similar for hGH and lonapegsomatropin.

Thus, lonapegsomatropin was demonstrated to have markedly reduced binding to the GH receptor compared to hGH even under in vitro conditions optimized for binding and with equal access to the receptor for both lonapegsomatropin and hGH.

The biological potency of hGH is routinely determined using an *in vitro* cell-based proliferation bioassay using the rat lymphoma cell line Nb2-11. Since the residual activity of lonapegsomatropin cannot easily be determined, due to the release of significant amounts of hGH during the assay incubation time of 48 h, an assessment was conducted using a non-cleavable, permanently conjugated hGH designated PermCon hGH.

The evaluation of PermCon hGH in the cell-based proliferation bioassay indicated that PermCon hGH has a maximum residual potency of 0.087 IU/mg compared to 3.5 IU/mg for the hGH control sample (relative to the WHO NIBSC somatropin reference standard set to a potency of 3.0 IU/mg). The hGH control showed slightly increased values (3.5 IU/mg) compared to the reference standard of the bioassay. The residual activity of

PermCon hGH was calculated to be 2.5%, relative to the normalized hGH control sample even under in vitro conditions with unhindered accessibility to the receptor for both lonapegsomatropin and hGH. These results indicate that hGH is essentially inactivated following a permanent PEGylation mimicking the transient conjugation of mPEG to hGH in lonapegsomatropin. Therefore, lonapegsomatropin can be considered an essentially inactive hGH prodrug.

The *in vitro* studies conducted to evaluate the pharmacology and pharmacodynamics of lonapegsomatropin included the predecessor molecule ACP-001 as a comparator. Results from these *in vitro* studies demonstrated that ACP-001 and lonapegsomatropin are comparable in terms of mass and integrity of released hGH, *in vitro* dissociation (kd) from hGHR, and potency of released hGH. *In vitro* binding (ka) to hGHR was slightly lower for ACP-001 than for lonapegsomatropin (3.2% versus 6.8% of that for hGH), most likely due to the larger size of the mPEG chains in ACP-001.

In summary, ACP-001 and lonapegsomatropin were shown to be comparable, and therefore the nonclinical studies conducted with the predecessor molecule, ACP-001, (IGF-I stimulation in repeat-dose study of ACP-001 in cynomolgus monkeys, potency testing of ACP-001, hERG assay, skin sensitization test in mice, and pre- and postnatal development toxicity study in rats) are deemed relevant for the pharmacodynamic and safety evaluation of lonapegsomatropin.

Pharmacodynamics of hGH *in vivo* was evaluated via IGF-I, which is a recognized biomarker for hGH activity (Pawlikowska-Haddal, 2012), and via measurement of body weight, which is a biomarker of the growth promoting effect of hGH, as body weight gain correlates with longitudinal growth (Blutke et al, 2014).

Two dedicated pharmacology studies in hypophysectomized rats and in healthy monkeys were conducted to investigate the effects of hGH, when released from lonapegsomatropin, on IGF-I response, and subsequent pharmacological effect on growth measured as increased body weight. These studies included daily administration of somatropin as a comparator.

Studies with ACP-001 in hypophysectomised rats showed that on µg hGH dose/kg bodyweight basis ACP-001 was approximately twice as potent as hGH (measuring body weight gain), comparing 1q3d doses of ACP-001 with 1qd doses of hGH for 10 days. In cynomolgus monkeys, after weekly SC administrations of ACP-001 at 2.0 mg hGH/kg/week or daily SC administrations of somatropin at 0.3 mg hGH/kg/day (1 monkey/sex/group), the pre-treatment baseline corrected IGF-I AUCs for the female ACP-001 treated monkey was 47% and 268% higher during Week 1 and 4, respectively, compared to the female monkey treated with daily somatropin. For the male monkey, the AUCs for pre-treatment baseline corrected IGF-I were 109% and 208% higher during Week 1 and 4, compared to somatropin treated male monkey. Elevation of IGF-I was more or less consistent throughout the week after both the first and fourth weekly administration of ACP-001. However, since somatropin and ACP-001 were administered in two different experiments, no direct comparison can be made and because only one animal/sex/group was dosed, the strength of evidence is considered low.

Concerning longer-term treatment with lonapegsomatropin, data are available from the repeated dose toxicity studies in rats and cynomolgus monkeys, where body weight and IGF-I levels were measured. In cynomolgus monkeys treated for one month, no effects on body weight were observed, but a non-dose-related increase on baseline corrected (BLC) IGF-I was shown. When monkeys were treated for a longer period (26 weeks or 52 weeks), body weights were increased in both sexes, albeit in the 26-week study for males, the increase was non-dose-related. In the (sub)chronic studies in monkeys, BLC IGF-I increased dose-related, albeit in the 26 weeks study, the highest dose did not further increase BCL IGF-I. The IGF-I levels in monkeys administered lonapegsomatropin SC once per week remained consistently elevated throughout the week after administration.

In the repeated dose toxicity studies in rats, the effects on body weight and BCL-IGF-I were less consistent.

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamic effects were observed in the toxicology studies at supraphysiological levels, therefore, no dedicated studies were conducted.

In addition to an effect on growth, somatropin has secondary effects, e.g. on glucose transport, lipolysis or endocrine effects. These effects are considered to be mediated by hGH interaction with GH receptor in various tissues. hGH released from lonapegsomatropin is shown to be equivalent with somatropin (see primary pharmacology). Consequently, there is no need to study the secondary pharmacological effects of lonapegsomatropin. Where relevant, secondary effects have been included in the SmPC: insulin sensitivity, hypoadrenalism, thyroid function and oestrogen containing therapy.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies included the *in vitro* hERG assay (using ACP-001), and *in vivo* studies evaluating the potential effect of lonapegsomatropin on central nervous system and respiratory function in Sprague Dawley rats and cardiovascular function in cynomolgus monkeys. *In vivo* safety pharmacology evaluations were conducted at the estimated tmax of lonapegsomatropin as well as the products of autocleavage (hGH, mPEG, and the leaving group).

In vitro, the effects on the cardiovascular system were studied through the effects of partly hydrolysed ACP-001 on the hERG tail current. A pre-incubation step was conducted at physiological pH and temperature for 7 days to yield partly (approximately 61%) cleaved ACP-001. CHO-K1 cells expressing the hERG ion channel were exposed to two dilutions of Hydrolyzed ACP-001, 346- and 70-fold, which contained nominal concentrations of hGH (both in the conjugated and non-conjugated forms) of 15 and 72 µg/mL, PEG linker (both in the conjugated and non-conjugated forms) of 58 and 289 µg/mL and the leaving group of 48 ng/mL and 235 ng/mL, respectively. Hydrolyzed ACP-001 produced no statistically different effects on the hERG tail current compared to the Time Matched Control (at a 70-fold dilution, a mean loss of 2.9% from controls was calculated as a % of cisapride block).
The results are in accordance with the computational assessment (DEREK) of the leaving group, which did not identify structural alerts for hERG channel inhibition.

The *in vivo* cardiovascular evaluation of lonapegsomatropin was performed by including short-term electrocardiogram (ECG) recordings in the GLP 4-week repeat-dose toxicity studies in adult and 26 and 52-week repeat-dose toxicity studies in juvenile cynomolgus monkeys. No treatment related effects on the cardiovascular system were apparent in this study following SC administrations of lonapegsomatropin at dose levels up to and including 3.0 mg hGH/kg/week for 4 weeks. SC administration of lonapegsomatropin in monkeys did not impact qualitative or quantitative ECG parameters at doses up to and including 4.8 mg hGH/kg/week, the highest dose administered, for up to 52 weeks.

This respiratory evaluation was done in rats GLP study was conducted to evaluate the potential acute respiratory effects of lonapegsomatropin in male rats (n=8/group) and the assessment was based on mortality, clinical observations, and evaluations of respiratory function. Lonapegsomatropin following a single SC administration to male rats did not result in any effects on the evaluated respiratory parameters at dose levels up to and including 3.0 mg hGH/kg.

A study was conducted to evaluate the potential acute neurobehavioral effects of lonapegsomatropin in male rats (n=10/group). Assessments of neurobehavioral effects were based on a standard functional observational battery (FOB) evaluations. FOB evaluations were conducted on all animals Day 1 (pre-dose, 8, and 24 h post-dose) and Day 7, and assessments were performed by trained staff blinded to the assigned treatment groups. The parameters evaluated in the FOB were based on those outlined in Moser et al., 1988 and 1996 and a detailed clinical examination of each animal was performed following FOB examination. A single SC administration of lonapegsomatropin to male rats at dose levels up to and including 3.0 mg hGH/kg did not result in any effects on the neurobehavioral endpoints.

Similarly, in the repeated dose toxicity studies for up to 52 weeks at dose levels up to 4.8 mg hGH/kg/week, clinical signs or effects on renal functional parameters suggesting an adverse effect on the CNS function or the kidneys were not observed.

2.5.2.4. Pharmacodynamic drug interactions

Drug interactions for recombinant hGH are well-known from approved marketed hGH products with once daily administration. None of the other components following lonapegsomatropin autocleavage warrant assessment of drug interaction potentials as mPEG is considered biologically inert (Webster et al., 2007) and systemic concentrations of the leaving group was below LLOQ (25.0 pg/mL) at clinical steady state concentrations at the therapeutic dose level of 0.24 mg hGH/kg/week. Therefore, drug interaction studies have not been conducted, which was considered acceptable by the CHMP.

2.5.3. Pharmacokinetics

Assessments of toxicokinetic (TK) profile (lonapegsomatropin, hGH, the leaving group, mPEG(-linker)) and the response of the biomarker IGF-I (as PD marker) were included as part of the nonclinical safety assessments following subcutaneous (SC) administration of lonapegsomatropin to Sprague Dawley (SD) rats, female New Zealand White rabbits and Cynomolgus monkeys (*Macaca fascicularis*) for a total duration of up to 52 weeks. Studies also included the predecessor molecule, ACP-001. ACP-001 possesses identical recombinant hGH and TransCon Linker moieties (including the leaving group), varying from lonapegsomatropin only in its mPEG composition (4 x 20 kDa mPEG).

Methods of analysis

Assays were developed for the evaluation of PK, PD and immunogenicity in the nonclinical studies. For the GLP studies in rats, rabbits and monkeys, assays were validated according to guidelines and sample analysis conducted in compliance with GLP. Lonapegsomatropin, ADP-001, hGH, mPEG, and IGF-I were quantified using a sandwich enzyme-linked immunosorbent assays (ELISA). The provided validation reports, which included evaluating precision, accuracy (intra- and inter-assay), specificity, selectivity/matrix effects, and sample stability (long-term, freeze-thaw), demonstrate that the lonapegsomatropin and hGH assays were suitable to analyse monkey, rabbit, and rat serum. For the hGH assays, a pre-immunoprecipitation step was used to limit cross-reactivity with lonapegsomatropin, but incomplete removal of residual lonapegsomatropin still resulted in an overestimation of the hGH concentrations. For the rabbit, however, still, a 4 – 6-fold overestimation was found. In monkey and rat, the detection limit (LLOQ) was 5.0 and 2.0 ng/ml for lonapegsomatropin (hGH eq.) and hGH, respectively. The ELISA for mPEG detection (LLOQ 500 ng/ml) was developed and validated for rat, rabbit and monkey serum and for rat and monkey CSF. The assays were considered acceptable to evaluate systemic exposure based on incurred sample analysis for

lonapegsomatropin, hGH, mPEG, the leaving group and IGF-I. The leaving group and the mPEG-linker were quantified by liquid chromatography coupled with tandem mass spectrometry [LC-MS/MS]. The detection limit for the mPEG linker was 2.0 µg/ml. For the leaving group, the LLOQs for rat, rabbit and monkey plasma were 75, 75 and 50 pg/mL, respectively.

For detecting antibodies (ADAs) against both hGH and mPEG (monkey only), bridging ELISA immunoassays were developed for rat, rabbit and monkey serum. The anti-hGH ADA assays were selective, and the sensitivity was found to be 65.6, 63, and 250 ng/ml for the assay in rat, rabbit, and monkey serum, respectively. Drug tolerance was 20,000, 444, and 25,000 ng/mL lonapegsomatropin (hGH equivalents) in rat, rabbit, and monkey serum. For anti-mPEG ADA detection in monkey serum, drug tolerance was 15,000 ng/ml lonapegsomatropin (hGH eq.).

Serum samples confirmed positive for anti-hGH ADAs were assessed for the potency to neutralise the hGH-stimulated proliferation of a rat lymphoma cell (Nb2-11). Anti-hGH neutralizing antibody assays were developed for rat, rabbit and monkey serum. These assays were selective, sensitive and the drug tolerance was 111, 25 and 45.7 ng/mL lonapegsomatropin (hGH eq.) in rat, rabbit and monkey serum, respectively.

Absorption

In SD rats, the toxicokinetics (TK) of lonapegsomatropin and hGH was assessed in a 4- and 27-week repeat-dose toxicity study, in which lonapegsomatropin (0.75 up to 4.8 mg hGH/kg) was given subcutaneously (SC) every week (QW). A slow absorption (Tmax ~18h) was seen, and systemic exposure appeared sex-dependent as AUC0-168hr and Cmax values were about 3-fold greater in males than females. The terminal elimination half-life (T1/2) was ~15 – 27 h. With increasing dose, a more or less dose-proportional increase in exposure was found. Upon repeated dosing, up to 70% lower exposure was seen in the 4-wk repeated dose study. These data correlated with the observed high (~50%) incidence of anti-hGH binding antibodies (ADAs) / neutralizing antibodies found at Day 28. Somatropin (hGH) was also found in circulation, and its pharmacokinetic profile followed the lonapegsomatropin levels but at a 16 – 46-fold lower serum concentration level.

In the 27-week repeated dose study, anti-hGH binding ADAs were also widely detected in the treated animals (60 – 90% positive) upon repeated administration of lonapegsomatropin, and the majority of the binding ADAs were neutralizing. At several time points, only one or two individual concentrations above the assay LLOQ were found and, therefore, at week 13 and 26 of dosing, no AUC0-168hr values were available. For hGH, the systemic concentration also decreased over time, with a very limited number of animals being exposed for the entire week at the end of the 27-week treatment period.

Developmental and reproductive toxicity studies were performed in SD rats and New Zealand White rabbits. The pharmacokinetic profile of lonapegsomatropin in the rat reproductive studies was comparable to the 4-wk repeated dose study and was hampered by the hGH ADA formation (40 – 90% positive animals).
In rabbits, systemic exposure was not observed over the entire dosing period following weekly or every second-day dosing regimens as the presence of anti-hGH ADAs severely impacted serum concentrations of hGH and the subsequent IGF-I response.

Autocleavage of lonapegsomatropin, apart from hGH, also generates the mPEG-linker ('mPEG'), which can be assessed in serum samples. Systemic exposure to mPEG was shown throughout the 27-week repeated dosing study, and upon lonapegsomatropin dosing, a dose-proportional increase in mPEG exposure was seen leading, after 13 -26 weeks, to a 2- to 4-fold increase in exposure (AUC0-168). At week 26, the mPEG Cmax levels were found to be 89 – 193-fold higher than lonapegsomatropin Cmax. Systemic exposure of mPEG was still evident up to Week 43 in the recovery period for all dose levels. The terminal elimination half-life of

mPEG was in the range of 485 – 950 h. Cerebrospinal fluid (CSF) samples collected from main and recovery animals at necropsy were all below the LLOQ for the mPEG (500 ng/mL).

Studies using intravenous administration of lonapegsomatropin were not performed. Therefore, no information is available on absolute bioavailability, the volume of distribution and clearance in a preclinical species. A single-dose PK studies were performed in order to compare two manufacturing sites for both the hGH intermediate and for the drug substance. The PK of lonapegsomatropin following a single SC administration to monkeys of lonapegsomatropin generally appeared comparable.

In cynomolgus monkeys, in total five repeat-dose toxicity studies, two exploratory, non-GLP, and three under GLP, were conducted, of which two 4-wk studies in adult and three (the 26- and 52-wk) repeat-dose studies in juvenile (13 - 17 month old) monkeys. In general, TK data for lonapegsomatropin, hGH, and mPEG in serum were independent of sex and age. Upon SC administration of lonapegsomatropin (0.4 up to 4.8 mg/kg, QW), as in rats, a slow absorption was seen and maximum lonapegsomatropin serum exposure (Cmax) was reached after 24 – 36 hrs, after which it slowly declined with an elimination half-life of 40 - 60 hrs. Levels of serum hGH (above endogenous baseline) followed the lonapegsomatropin levels but at a 100-fold lower concentration level. An approximate dose-proportional increase in lonapegsomatropin and hGH exposure was observed following single and repeated dosing and both compounds were not considered to accumulate (< 2-fold) following repeated dosing. Increases in hGH levels were found to be associated with sustained elevated IGF-I levels.

Across all these monkey studies, anti-hGH binding ADAs were only detected in 3 out of 110 treated animals (~3%) with no apparent impact on exposure. Anti-PEG binding antibodies were not detected in the 26- and 52-week repeat-dose study.

Autocleavage of lonapegsomatropin releases hGH, the leaving group and the linker moiety attached to mPEG. Pharmacokinetic profiling was not performed for the leaving group. The leaving group was assessed in the 26- and 52-week monkey study, only at 24, 36, and 48 h post-dose, and found only in very low levels, below or up to 3-fold above the LLOQ (50 pg/ml) at the highest dose tested (4.8 mg/kg). Using LC-MS/MS, the mPEG-linker and the mPEG-backbone was quantified at week 26, and both concentration-time profiles were comparable at all dose levels, indicating the mPEG-linker molecule remains intact.

Concerning serum mPEG, which was assessed in all five monkey studies, a dose-proportional increase in exposure was found and a 2- to 4-fold increase upon repeated dosing. Steady-state (SS) serum concentrations of mPEG were obtained approximately by Week 13, and levels were about 10- to 16-fold higher than lonapegsomatropin. The accumulation may be due to a lower clearance as the serum terminal elimination half-life of mPEG was found to be above 370 hrs up to 1310 hrs. Although mPEG was present in the systemic circulation, there were no quantifiable levels of mPEG (LLOQ 500 ng/ml) in the CSF at necropsy from main study animals or recovery animals in the 26- and 52-week studies indicating at least a 634-fold margin (serum/CSF).

Distribution

Dedicated distribution studies of lonapegsomatropin have not been conducted. This was acceptable to the CHMP, since somatropin (hGH) released from lonapegsomatropin is considered to be distributed in the same manner as endogenous GH. Given the size of the mPEG molecule (40 kDa), transiently bound to hGH, the volume of distribution is expected to be limited to the vascular space and extravascular space of highly vascularized organs and lymphatic tissues as well as mononuclear phagocyte system containing organs such as liver, spleen, kidney, lung, heart, and choroid plexus.

The distribution pattern of PEG has been investigated extensively and is well described in the literature. The non-cleavable portion of the linker covalently attached to mPEG is expected to follow the distribution and excretion pattern for mPEG(-linker). The high molecular weight mPEG limits its diffusion across membranes, thereby retaining the complex in the circulation.

A semi-physiologically based PK model was established to estimate the time to reach steady-state, accumulation, and subsequent elimination of mPEG from the systemic circulation as well as from brain and peripheral tissue. In addition, the immunohistochemical presence of hGH (monkey only) and mPEG in the last injection site and selected areas of the brain is discussed in the toxicological section.

Metabolism

Autocleavage of lonapegsomatropin results in release of hGH, mPEG-linker and the leaving group.

Recombinant hGH, when released from lonapegsomatropin *in vivo*, is considered to be metabolized in the same manner as endogenous GH, where GH is catabolized in the liver and kidney to its constitutive amino acids.

In vitro release studies in phosphate-buffered saline (PBS), showed that lonapegsomatropin, via autocleavage, releases hGH in a temperature- and pH-dependent fashion reaching a plateau above 90% ultimately. At 37°C and pH 7.4, the in vitro hydrolysis release kinetics showed a half-life of 105 h for ACP-011 (lonapegsomatropin) and similar results were found with its predecessor ACP-001 (107 h). A faster release of hGH was observed at increased temperature or increased pH.

Excretion

Dedicated excretion studies on lonapegsomatropin have not been conducted. This was found acceptable by the CHMP, since somatropin released from lonapegsomatropin is considered to be excreted in the same manner as endogenous GH.

Clearance of (m)PEG molecules is largely through glomerular filtration and excretion in urine, predominantly as intact PEG, and to a much lesser degree as smaller-sized degraded PEG. Hepatobiliary removal via hepatocyte and/or Kupffer cell uptake in the liver represents a minor route of PEG excretion and mPEG was observed to clear from the systemic circulation during the recovery phase of the long-term toxicity studies in rat and monkeys.

In conclusion, within each species, similar TK data were obtained across the lonapegsomatropin studies. However, an interspecies comparison between rats, rabbits and monkeys is generally compromised given the high incidence of antibodies observed in rats and rabbits following repeated dosing, while there is a very low incidence of anti-hGH antibodies in monkeys.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were included in the non-clinical safety programme and this was considered acceptable by the CHMP, since such studies are not required for compounds requiring chronic administration.

2.5.4.2. Repeat dose toxicity

In the repeat-dose toxicity studies in rats, with dosages up to 4.8 mg hGH/kg/week SC, no adverse effects have been found. The rats were 6-8 weeks at study initiation and reached adulthood during the pivotal 26-week study. Noteworthy findings related to treatment with lonapegsomatropin were decreased body weight gain in male rats correlating with reduced food consumption and changes in cholesterol and triglyceride levels, which all resolved during the recovery period. These last two findings were expected pharmacological effects of exposure to hGH. Small vacuoles in choroid plexus epithelium at ≥1.2 mg/kg for 26 weeks were related to mPEG. Because there was no evidence of distortion of cytoplasmic or nuclear compartments, degeneration, or necrosis in cells containing mPEG IHC stained granules or vacuoles, the NOAEL was considered 4.8 mg hGH/kg/week.

In two 4-week repeat-dose toxicity studies in cynomolgus monkeys, no adverse or other important effects were shown up to the maximum dose of 3 mg hGH/kg/week SC. After an investigative non-GLP study of 3 mg hGH/kg/week SC, for 26 weeks in juvenile cynomolgus monkeys, a pivotal GLP 26-week study in this animal model was performed with doses up to 4.8 mg hGH/kg/week and a 26-week recovery period. The biomarker for hGH exposure IGF-I was increased above endogenous baseline levels for all treated animals and was dose depended. Most important findings at doses ≥1.2 mg/kg (lowest dose) were a minor increase in body weight, a minor decrease of cholesterol, and mild dilated mammary gland ducts, all expected exaggerated pharmacological responses to hGH, and completely resolved after the recovery period. Also, minimal vacuolation of choroid plexus epithelial cells, and granular mPEG IHC staining in several brain barrier elements were seen. The vacuolation was unlikely to represent a biologically significant finding. Due to the absence of distortion of cytoplasmic or nuclear compartments, degeneration or necrosis of the stained cells or surrounding cells/areas, none of these observations were considered adverse. Furthermore, the mPEG IHC staining and/or vacuolation was not associated with any adverse clinical signs, including CNS evaluation for tremors, convulsions, reactivity to handling, and unusual behaviour, conducted as part of the weekly clinical observations. The NOAEL was considered 4.8 mg hGH/kg/week.

In a 52-week toxicity study in juvenile monkeys, aged 13.5 to 17.5 months at the start of dosing, followed by a subsequent 52-week treatment-free period, doses up to 4.8 mg hGH/kg/week SC showed comparable effects as in the 26-week study. At ≥0.4 mg/kg body weight increased a little, and cholesterol, triglycerides, and glucose (only in females) decreased slightly. At ≥1.6 mg/kg (males 4.8 mg/kg) mild dilated mammary gland ducts were shown, and at ≥1.6 mg/kg, minimal vacuolation of choroid plexus epithelial cells and granular mPEG IHC staining in several brain barrier elements were shown. Again, the NOAEL was considered 4.8 mg hGH/kg/week. The amount of anti-drug antibodies was negligible, and the exposure margins related to the intended dose in GHD children of 0.24 mg hGH/kg/week were 38 for the AUC and 17 for the Cmax.

2.5.4.3. Genotoxicity

In the *in vitro* bacterial reverse mutation assay, partly cleaved lonapegsomatropin did not increase in revertant colony counts in the presence or the absence of Aroclor-induced rat liver S9 mix and was comparable to vehicle control values. In contrast, positive controls 2-NF, SA, 9AAD and MMS all resulted in a robust increase in the number of revertant colonies. *In vitro* assessment of chromosomal aberration of human peripheral blood lymphocytes showed no significant or dose-dependent increases in structural or numerical chromosomal aberrations across the entire dose range (50-500 µg/ml) after 4 and 20 hours without S9-mix and after 4 hours with S9 mix. No cytotoxicity was observed for any treatment group. In contrast, the positive control mitomycin resulted in a statistically significant increase in structurally aberrant

cells. Micronuclei formation was evaluated in the 1 month repeat dose toxicity study in rats. This is considered acceptable. Analysis of the bone marrow of the femoral bone did not show a significant increase in micronuclei at doses up to 3 mg/kg given once per week for 4 weeks. In contrast, the positive control cyclophosphamide increased the number of micronuclei significantly. In conclusion, the genotoxicity of lonapegsomatropin has been studied concerning gene mutations in bacteria and mammalian cells and chromosomal aberrations *in vitro* and *in vivo*. The genotoxic potential for lonapegsomatropin is low.

2.5.4.4. Carcinogenicity

A weight of evidence approach based on non-clinical and clinical literature indicated that hGH and IGF-I did not have any relevant cancer risk. Recently published data from several long-term clinical studies showed no evidence of increased malignancy or cancer incidence in patients treated with recombinant hGH in childhood. These clinical data are supported by published nonclinical data from 2-year carcinogenicity studies in rats and mice with daily administration of high levels of recombinant rodent GH, demonstrating a complete absence of GH-related carcinogenic effects. Toxicology studies with lonapegsomatropin and the products of autocleavage (the leaving group, linker and mPEG) as well as supporting literature searches and computational assessments and genotoxicity evaluations were not suggestive of carcinogenic potential. Based on this assessment, no formal carcinogenicity studies in rodents have been performed. This is acknowledged and agreed. Lonapegsomatropin has no carcinogenic potential.

2.5.4.5. Reproductive and developmental toxicity

In the fertility and early embryonic development study, rats were administered 0, 0.35, 0.7 and 1.4 mg hGH/kg lonapegsomatropin by SC every 48 h. This dosing regimen was implemented as an attempt to increase the exposure coverage to lonapegsomatropin and the products of autocleavage, as complete coverage over the dosing period could not be claimed for the weekly administration. The majority of animals were exposed to lonapegsomatropin, hGH, and mPEG at 1.4 mg hGH/kg, but anti-hGH binding antibodies were detected in nearly all animals. Some non-adverse changes in body weight gain were observed. There was no evidence of effects on reproductive performance/fertility, including ovarian, uterine or male reproductive parameters, and there were no embryo-lethal effects, at any dose level, and the NOAEL was considered to be 1.4 mg hGH/kg/48 h.

In an embryo-foetal developmental toxicity study, rats were administered lonapegsomatropin by SC injection on Days 6 and 13 of gestation. Administration of 0.75, 1.5, or 3.0 mg hGH/kg/dose resulted in binding anti-hGH antibodies in 12/20, 16/20, and 10/20 animals, respectively, but none of the animals tested positive for neutralizing antibodies. There was no test article related effects on pregnancy performance or foetal weights or morphology, including skeletal ossification.

In rabbits, pregnant animals were administered 0, 0.35, 0.70, and 1.4 mg hGH/kg/48 h lonapegsomatropin from GD 7 to 19. Binding anti-hGH antibodies were detected in most samples at GD 17 and 29, impacting the serum concentrations of lonapegsomatropin and hGH. Body weight loss (especially after GD13), reduced food intake (especially after GD13), and increased serum FFA levels (4 to 9 times) were noted, possibly related to an exaggerated pharmacological effect. There was evidence of embryo-foetal mortality (increased number of resorptions and foetal death) at 1.4 mg hGH/kg/48 h and a number of different foetal abnormalities (dysmorphogenesis, including hydrocephaly, heart and major vessel malformations, and/or mispositioned kidney) at all dose levels.

In a pre- and post-natal development study, ACP-001 was administered SC to female rats at doses of 0.75, 1.5, 3.0 mg hGH- equivalent/kg/week for 6 weeks on Days 6, 13, and 20 of gestation, and Days 6, 13, and 20 of lactation. There were no adverse treatment-related effects on pre and postnatal development, but anti-hGH binding antibodies were present in the majority of the F0 generation animals over the course of the study; a proportion of these exhibited neutralizing capacity. Only at the first days after each dosing, sufficiently high peak levels are reached, but this peak and valley pattern appears different from the human situation. No specific mPEG IHC staining was noted in the F1 pups. Also, there was an absence of quantifiable concentrations of ACP-001, and hGH in serum from F1 pups on Day 22 of lactation, 2 days following the last dose to F0 animals, indicating that ACP-001 and products of autocleavage do not pass the placenta or are excreted in milk.

2.5.4.6. Toxicokinetic data

The program assessed the safety of lonapegsomatropin as well as the products of autocleavage (hGH, mPEG, and the leaving group) through SC administration at dose levels up to 20-fold the clinical therapeutic dose of 0.24 mg hGH/kg/week. Within each species, similar TK data were obtained across the lonapegsomatropin studies after a slow absorption. However, an interspecies comparison between rats, rabbits and monkeys is generally compromised given the high incidence of antibodies observed in rats and rabbits following repeated dosing, while there is a very low incidence of anti-hGH antibodies in monkeys.

In the rat, a dose related increase in exposure was observed for hGH and lonapegsomatropin. Upon repeated dosing, however, given the ADA response, exposure decreased, and dose proportionality could not be assessed. In the monkey, systemic exposure to lonapegsomatropin, hGH, and mPEG was independent of sex, was comparable in juvenile and adult monkeys, and increased in an approximate dose proportional manner. In the rat, sex differences were observed resulting in higher exposures in males than females, whereas, in the monkey no sex differences were apparent. In general, the pharmacokinetic profile of hGH followed the lonapegsomatropin levels but at a 100- and 16- to 46-fold lower serum concentration level in monkey and rat, respectively.

Steady state of mPEG in the systemic circulation was reached at approximately Week 13 in both rats and monkeys. In the monkey, mPEG accumulated by approximately 2- to 4-fold at steady state leading to 10-fold higher levels than lonapegsomatropin. A long half-life was observed in both species: 485 to 950 h in rats and 370 to 1,310 h in monkeys, following the end of the 26/27- and 52-week dosing period in both rats and monkeys.

2.5.4.7. Local Tolerance

Local tolerance following SC administration of lonapegsomatropin was assessed as part of the repeat-dose toxicity studies conducted in rats and monkeys, covering both the 'acute' and longer-term periods. In these studies, comprehensive observations of the injection sites were based on dermal scoring and histological examination (H&E staining). In the rats, only very slight to slight oedema and/or erythema were occasionally noted in treated animals and controls. In the 52-week monkey study, the microscopic finding of increased adipocytes in injection sites was limited to lonapegsomatropin treated animals. Vacuolated macrophages and mononuclear cell infiltration were observed in injection sites more prominent at 4.8 mg hGH/kg/week and was considered related to a local effect of lonapegsomatropin. All injection site findings demonstrated full reversibility.

In a local lymph node assay (LLNA) with mice with partly cleaved ACP-001 at concentrations of the leaving group up to 23 µg/mL, this did not induce skin sensitization. This concentration of the leaving group is at a high overage compared to the clinical steady-state concentrations. Since ACP-001 and lonapegsomatropin contain the same TransCon linker and consequently release the leaving group during autocleavage of the linker, the results from the LLNA study conducted with ACP-001 were considered relevant, which is agreed by the CHMP.

No significant absorbance was observed in the range of wavelengths from 230 to 700 nm, in alignment with the lack of chromophores in the leaving group. Thus, no concern for phototoxicity for the leaving group was demonstrated. The phototoxicity assay was not considered relevant for lonapegsomatropin, hGH, mPEG, or the remainder of the TransCon linker.

2.5.4.8. Other toxicity studies

No immunotoxicity or dependence studies have been conducted for Lonapegsomatropin, which is accepted by the CHMP.

Based on comprehensive evaluations of literature searches, review of expert opinions, and QSAR evidence, it was concluded that the structural elements of the leaving group, TransCon linker, and mPEG did not show evidence of carcinogenicity or genetic toxicity in humans.

The results of the nonclinical safety studies on impurities sufficiently justify the specification limits set for release and throughout the entire shelf-life for lonapegsomatropin drug substance and drug product.

The excipients were also tested, as in all nonclinical safety studies the animals received dose formulations with the same excipients at similar or higher concentrations as in the clinical presentations. Tromethamine, trehalose dihydrate (Nelson 2015), and succinic acid are commonly used excipients in parental formulations for human use and are regarded as safe.

2.5.5. Ecotoxicity/environmental risk assessment

The active substance somatropin is a nonglycosylated 22 kDa protein consisting of 191 amino acids, that is identical to the human growth hormone (hGH). Considering that the substance is a protein, the ERA can consist of a justification for not submitting ERA studies. As per the EMA Q&A document on ERA (EMA/CHMP/SWP/44609/2010 Rev.1), this is also applicable to protein substances that might be potential endocrine-disrupting substances such as hGH. Therefore, the CHMP agrees that the ERA can consist of a justification for not submitting ERA studies. Consequently, a phase I and PBT assessment are not required for the active substance somatropin.

Based on the highest dose reported in the SPC of 22 mg somatropin weekly, which corresponds to 41.6 mg of the linker and mPEG succinimide molecule, and a refined Fpen of 0.004 based on prevalence for growth hormone deficiency in the EU of 4 in 10,000 (EU/3/19/2213), a refined PECsw of 0.0012 µg/L is calculated for the linker and mPEG succinimide molecule. As this is below the action limit of 0.01 µg/L, a phase II is not warranted for the linker and mPEG succinimide molecule.

2.5.6. Discussion on non-clinical aspects

Pharmacology

No dedicated *in vivo* pharmacology studies were performed with lonapegsomatropin. *In vivo* studies were performed with ACP-001, the 4x20 kDa predecessor of lonapegsomatropin. ACP-001 was used as a comparator in the *in vitro* studies and was shown to release comparable hGH in terms of mass and integrity of released hGH, *in vitro* dissociation (kd) from hGHR, and potency of released hGH. Furthermore, PD equivalence with respect to the serum concentration-time profiles of IGF-I was demonstrated in the clinical bioequivalence study CT-101 with ACP-001 and lonapegsomatropin. These *in vitro* and clinical findings support the view that pharmacodynamic data obtained with ACP-001 can be supportive for the evaluation of the PD of lonapegsomatropin. PD studies in rats (1q3d) and cynomolgus monkeys (1qw) indicate that ACP-001 is approximately twice as potent as somatropin (1qd) on µg hGH/kg body weight basis. Nevertheless, the strength of this evidence is limited due to the low number of animals and in monkeys, somatropin and ACP-001 were administered in two different experiments so that no direct comparison can be made.

More convincing PD data were obtained in the repeated dose toxicity studies, especially those in cynomolgus monkeys, where the IGF-I levels in monkeys administered lonapegsomatropin SC once per week remained consistently elevated throughout the week after administration. These increases were generally dose related. In the repeated dose toxicity studies in rats, the PD effects were less consistent. Interference of anti-hGH anti-drug antibodies or changes in food intake may have affected the results.

No secondary pharmacology studies were performed. In addition to an effect on growth, somatropin has secondary effects, e.g. on glucose transport, lipolysis or endocrine effects. These effects are considered to be mediated by hGH interaction with the GH receptor in various tissues. hGH released from lonapegsomatropin is shown to be equivalent to somatropin (as indicated above). Consequently, there is no need to study the secondary pharmacological effects of lonapegsomatropin. Where relevant, secondary effects have been included in the SmPC: insulin sensitivity, hypoadrenalism, and thyroid function.

Drug interactions for recombinant hGH are well-known from approved marketed hGH products with once-daily administration. Potential interaction with oestrogen containing therapy is included in the SmPC. None of the other components following lonapegsomatropin autocleavage warrant assessment of drug interaction potentials as mPEG is considered biologically inert and systemic concentrations of the leaving group was below LLOQ (25.0 pg/mL) at clinical steady-state concentrations at the therapeutic dose level of 0.24 mg hGH/kg/week. Therefore, it can be agreed that drug interaction studies have not been conducted.

Pharmacokinetics

The bioanalytical methods used to quantify lonapegsomatropin, hGH, mPEG, IGF-I and the leaving group in the GLP studies have been adequately validated. In rat, however, the toxicokinetic (TK) hGH concentration data are impacted by anti-hGH antibodies and assay interference. Therefore, the safety margins concerning human exposure in GHD children as determined in the monkey are the most relevant.

No formal ADME studies have been performed with lonapegsomatropin to characterize the pharmacokinetic profile of lonapegsomatropin and its release products: hGH, mPEG and the leaving group. Toxicokinetic data were used, as generated in the context of the repeat-dose toxicity studies performed in adult rats and monkeys and juvenile monkeys with once-weekly sc administration as in clinical. The toxicokinetic profile of the leaving group was assessed in rats, and only a sparse sampling was performed at 3 time points in the juvenile studies in cynomolgus monkeys. The choice of a sparse sampling in juvenile monkeys was acknowledged and the theoretical Cmax values were estimated using available PK data and the fact that

lonapegsomatropin is releasing the leaving group in a 1:1 ratio. According to these estimations, the exposure ratio to human was at least 3, demonstrating that the animals were appropriately exposed to the leaving group to assess the safety profile.

Within each species, similar TK data were obtained across the lonapegsomatropin studies after a slow absorption. However, an interspecies comparison between rats, rabbits and monkeys is generally compromised given the high incidence of antibodies observed in rats and rabbits following repeated dosing, while there is a very low incidence of anti-hGH antibodies in monkeys.

In the rat, a dose-related increase in exposure was observed for hGH and lonapegsomatropin. Upon repeated dosing, however, given the ADA response, exposure decreased, and dose proportionality could not be assessed. In the monkey, systemic exposure to lonapegsomatropin, hGH, and mPEG was independent of sex, was comparable in juvenile and adult monkeys, and increased in an approximately dose-proportional manner. In the rat, sex differences were observed, resulting in higher exposures in males than females, whereas, in the monkey, no sex differences were apparent. In general, the pharmacokinetic profile of hGH followed the lonapegsomatropin levels but at a 100- and 16- to 46-fold lower serum concentration level in monkey and rat, respectively.

Steady-state of mPEG in the systemic circulation was reached at approximately Week 13 in both rats and monkeys. In the monkey, mPEG accumulated by approximately 2- to 4-fold at steady-state leading to 10-fold higher levels than lonapegsomatropin. A long half-life was observed in both species: 485 to 950 h in rats and 370 to 1,310 h in monkeys, following the end of the 26/27- and 52-week dosing period in both rats and monkeys.

Toxicology

Repeat dose:

No adverse effects were found in rats; however, anti-hGH antibodies were evident. The effective amount of exposure is uncertain by the effect of neutralizing antibodies and the exposure margins in the rat (0.7 to 1.4) are much too small. Therefore, the rat studies are considered insufficient reliable to produce firm statements on toxicity.

mPEG:

An extensive evaluation of mPEG was performed. This is appreciated because there is a concern regarding PEGylated products for the PEG moiety, or that of the very closely related mPEG, with a high molecular weight (MW ≥30 kDa) when given to young children. Relatively low doses of PEG can cause vacuoles in the brain barrier elements of laboratory animals, especially in the choroid plexus (CP), and there is no marker for CP functionality. Because of the still developing brains in very young children and the uncertainty considering the consequences of the observed vacuolisation, currently, PEGylated products for long-term use are not approved for children <12 years old, as a precaution.

A recent paper of Fletcher et al., 2019 tried to establish a threshold for PEG burden beyond which there are alterations in tissue architecture that could potentially lead to dysfunction. A high SC dose of 160 mg PEG/kg/week of a 40 kDa PEGylated molecule to cynomolgus monkeys for 3 months was still clinically well tolerated but led to adverse histopathological findings, while a dose of ≤120 mg PEG/kg/week did not lead to any adverse findings. The high PEG dose applied in this publication is about 360 times higher than the mPEG dose administered with lonapegsomatropin to GHD children (0.45 mg mPEG/kg/week). However, the exposure time is much shorter than that of lonapegsomatropin, and the monkeys were considerably older,

namely 3 to 7 years old instead of 13.5 to 17.5 months at the start of dosing. Also, no kinetic data were measured or shown.

At PEG doses ≤120 mg/kg/week, the choroid plexus tissue architecture appeared normal and, other than the presence of vacuoles, was comparable to vehicle-treated controls (Fig. 8A, B). At 160 mg/kg/week, individual, small clusters, or sheets of vacuolated macrophages expanded the choroid plexus interstitium and surrounded blood vessels (Fig. 8C). As a result of the severity of vacuolation in several monkeys, the presence of a continuous sheet of perivascular vacuolated macrophages, and the expansion of the interstitium by sheets of macrophages, choroid plexus macrophage vacuolation at a PEG dose of 160 mg/kg/week was considered to be adverse due to the potential for functional consequences, despite the lack of overt signs of neurologic effects in this study (Fletcher et al., 2019).

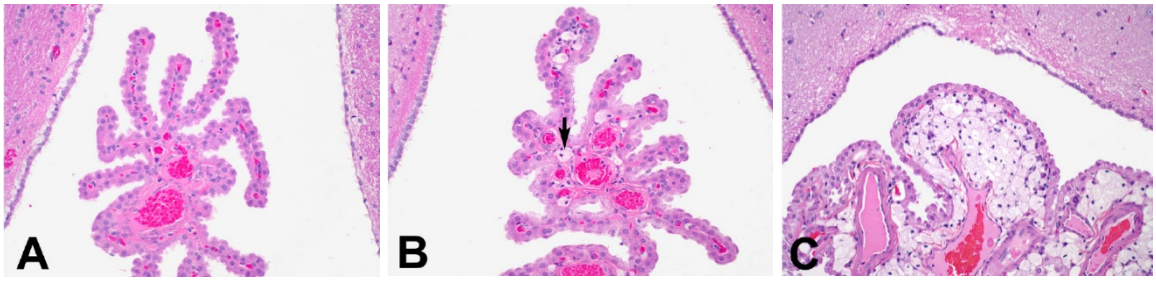


Figure 8: A: Choroid plexus from a control monkey. B: Choroid plexus from a monkey with a PEG dose of 120 mg/kg/week for 3 months. Note vacuolated cells (macrophages) in the stroma (arrow). C: Choroid plexus from a monkey with a PEG dose of 160 mg/kg/week for 3 months. Note marked expansion of the choroid plexus stroma by vacuolated cells. All images are 20X objective and H&E stain (Fletcher et al, 2019).

An extensive nonclinical evaluation of potential mPEG toxicity was conducted in adolescent/adult rats and juvenile monkeys following weekly SC dosing of lonapegsomatropin for up to 27 and 52 weeks, respectively. In these studies, mPEG levels were investigated in both the systemic circulation and in CSF. Standard histopathology included routine H&E staining of the central (cerebrum, midbrain, cerebellum [including CP], medulla/pons, and spinal cord) and peripheral (sciatic nerve) nervous system. Comprehensive hGH and mPEG IHC staining, using a highly sensitive staining methodology, was performed on multiple brain regions with high GHR expression and high vascularization, including the 2 circumventricular organs (CVOs) CP and median eminence, considered representative for other CVOs in the brain. Detailed clinical observation focusing on the CNS were also included. However, because of the forming of anti-drug antibodies, the effects in rats are considered of minor importance.

In the monkey, after administration of lonapegsomatropin at 0.40 mg hGH/kg/week (0.75 mg mPEG/kg/week) for 52 weeks, vacuolation was not observed by light microscopy (H&E staining) in CP or any other brain area. Therefore, this dose was considered the NOEL. At 1.6 and 4.8 mg hGH/kg (3.0 and 9.0 mg mPEG/kg/week, respectively) the observed vacuolation of CP epithelial cells and macrophages was not associated with evidence of distortion of cytoplasmic or nuclear compartments, degeneration, necrosis, or inflammation, was considered unlikely to impact cell or organ function, and hence was considered non-adverse. Besides, no adverse clinical signs, including CNS evaluation for tremors, convulsions, reactivity to handling, and unusual behaviour, conducted as part of the weekly clinical observations, were seen. Therefore, 4.8 mg hGH/kg/week was considered the NOAEL, which is 18 times lower than the considered adverse PEG dose in the study of Fletcher et al., 2019.

However, at 0.4 mg hGH/kg for 52 weeks, mPEG IHC staining did reveal granular staining in CP epithelial cells (all animals, minimal to mild in intensity; very rare to occasional in frequency), in <1% of macrophages

(in 1 animal, minimal to mild in intensity), and in <1% of specialized glial cells (in 2 animals, minimal in intensity). IHC stained vacuoles were only observed in a few CP epithelial cells (all animals) and specialized glial cells (in 1 animal). Full reversibility of mPEG IHC staining of macrophages, specialized glial cells, and CP epithelial cells (in the third ventricle only) was observed after the treatment-free period at the low dose level and partially at the high dose level. Because of the highly sensitive IHC methodology, it is concluded that it is unlikely that it represents a biologically significant finding.

In the 27-week rat study and the 52-week monkey study, mPEG IHC staining was predominantly detected in tissues associated with brain barrier function with high vascularity and only observed in cell types with a physiological direct exposure to plasma macromolecules either in circulation or in the interstitial vicinity of CVOs, and that lonapegsomatropin and mPEG did not pass or compromise the blood-brain barrier or blood-CSF barrier structure. There are no indications in the literature that the brain barriers in children, including infants, should be more permeable to mPEG than those of adults.

It is noted that the monkeys in the 52-week study were exposed for close to 10 months at steady-state (based on Cmax) and even longer above the mPEG systemic exposure vacuolation threshold of 100 µg PEG/mL (defined by Jacobsen 2017 and BPAC 2017).

During the 52-week treatment-free period in monkeys, systemic exposure to mPEG declined and was below the LLOQ of 500 ng/mL at 7, 39, or 52 (in 2/4 animals) weeks into the treatment-free period for the 0.40, 1.6, and 4.8 mg hGH/kg/week dose groups, respectively. The reversibility of mPEG IHC staining in the different cell types is likely a combined process of cell turnover, potential reuptake, migration of cells (macrophages), phagosome degradation of mPEG, and/or exocytosis, and mPEG is expected to be predominantly excreted unchanged in the urine by renal filtration.

Steady-state (SS) levels of mPEG in the systemic circulation in monkeys were reached following approximately 13 weeks of repeated dosing. In a 52-week phase 3 study in GHD children (CT-301), investigating the safety and efficacy of lonapegsomatropin in prepubertal children, systemic mPEG levels were approaching SS around 3 months.

In a 2-compartment allometrically scaled PK-model the mPEG concentration in serum and choroid plexus in monkey and GHD children for up to 4 years of treatment followed by a 2-year treatment-free period was predicted. The time to reach SS in the CP in GHD children is estimated to be 16 months, which reflects the very slow distribution from the circulation to CP. The predicted median SS level of mPEG in CP of GHD children administered lonapegsomatropin at 0.24 mg hGH/kg/week was ~2-fold below the SS levels in CP of monkeys at the NOEL of H&E stained vacuoles (0.40 mg hGH/kg/week), and furthermore, ~30-fold below the SS level in CP of monkeys at the NOAEL (4.8 mg hGH/kg/week) after 52 weeks repeated dosing. In GHD children, 90% of mPEG is cleared from the systemic circulation within approximately 3 months from the end of treatment, based on a predicted systemic half-life of 26 days, and 90% of mPEG is cleared from CP within 16 months, based on the predicted half-life of approximately 5 months. However, some uncertainties remain regarding the used PK-model.

The Safety Working Party (SWP) defined a threshold for observation of vacuolation in CP epithelial cells (H&E stained) at 0.4 µmol PEG/kg/month equivalent to 3.7 mg PEG (40 kDa)/kg/week (CHMP 2012). In comparison, the dose of mPEG in the 52-week toxicity study in juvenile cynomolgus monkeys at the NOEL of H&E stained vacuoles (0.40 mg hGH/kg/week) is 0.75 mg mPEG/kg/week and hence almost 5-fold below this threshold. The mPEG dose at the clinical therapeutic dose level of 0.24 mg hGH/kg/week is 0.45 mg mPEG/kg/week, and hence more than 8-fold below the CHMP indicated threshold.

The systemic SS mPEG level in monkeys (Cmax) for the low dose group (0.40 mg hGH/kg/week) at the NOEL of vacuoles (H&E staining) was ~25 µg/ml. In the GHD paediatric population (CT-301), the observed systemic SS mPEG level was ~13 µg/ml at the therapeutic lonapegsomatropin dose of 0.24 mg hGH/kg/week, giving an exposure margin close to 1.9-fold. However, there is not a NOEL for vacuolation detected by IHC staining; therefore, vacuolation in children's CP is possible; though it would be expected to be a very slight effect. The problem is that vacuolation tends to grow with a longer duration, and the monkey study was only one year (or about two years when the recovery period is also taken into account). According to ICH S11, the central nervous system develops during the whole children's lifespan but is strongest until the age of 2 - 3 years, which would be more or less covered by the monkey study. Besides, according to Fletcher et al. (2019), comparison with the 120 mg/kg/week PEG dose group in a previous 2-week toxicity study in monkeys (unpublished data in Fletcher 2019) demonstrated that increasing dose duration was only associated with an increase in the number of affected tissues with no qualitative changes in the level of vacuolation observed. Their interpretation is that the rate of PEG uptake in tissues appeared to be only slightly higher than the rate of excretion from the body at doses ≤ 120 mg/kg/week, which resulted in fairly minimal, albeit more widespread, vacuolation over time. This seems to be also the case in the studies with lonapegsomatropin. This makes it reasonable that a very low dose of 0.45 mg PEG/kg/week (ca. 360 times lower than the adverse dose (Fletcher, 2019), and 8 times lower than the acclaimed safe dose of 3.7 mg PEG/kg/week (CHMP, 2012) has a very low chance of getting adverse.

In conclusion, from a non-clinical point of view the risk for adverse effects caused by vacuolation in the brains of young children at the intended dose of lonapegsomatropin is very small.

Reproduction toxicology:

There was no evidence of effects on fertility and embryo-fetal development at any dose level in rats. However, the exposures to lonapegsomatropin, hGH and mPEG at this dose were lower or around the intended human exposures; therefore, no firm conclusions can be made. For the embryo-fetal development study in rabbits the levels of lonapegsomatropin, hGH and mPEG during GD7 and GD13 were about 5 times higher than in the clinical intended exposure and dose-related, although with a large spreading. Also, the number of abnormalities induced in this interval were dose-related, although possibly not by type; there were a lot of types. Lower food consumption was stated as maternal toxicity, but those who were losing weight were fed extra with a special diet, so there was no large weight loss. Besides, reduced food intake and induced body weight loss occurred in the period from GDs 13 to 17, while the sensitive period for malformation is in the second week. Also, FFA spiked on GD13 only at a high dose. It was demonstrated by Laron et al. (1966) that in rabbits, hGH does not reach the foetus during the third week of gestation (i.e., approximately GDs 14 to 21), and Fhölenhag et al. (1994) similarly demonstrated that the foetuses of female rats exposed to GH during late gestation (GD 20/21) were unexposed to GH. Also, exaggerated pharmacology by hGH would be expected to induce teratogenicity by hyperglycaemia, but there was no indication for this. Therefore, the findings are inconclusive, as reflected in sections 4.6 and 5.3 of the SmPC.

Phototoxicity:

The phototoxicity assay was not considered relevant for lonapegsomatropin, hGH, mPEG, the remainder of the TransCon linker or the leaving group. The leaving group is not considered relevant as it is not expected that the leaving group accumulates in the skin or eye and is found only in very low levels in the systemic circulation.

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, lonapegsomatropin is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Overall, the primary pharmacodynamic studies provided adequate evidence that lonapegsomatropin is a long-acting, transiently pegylated somatropin growth hormone designed to release somatropin with the same mode of action and distribution as daily somatropin, but with a once-weekly injection. In long-term studies in cynomolgus monkeys, a consistent elevation of plasma IGF-I has been demonstrated. The safety studies did not reveal untoward functional effects in vital organ systems.

From a non-clinical point of view, there are no outstanding other concerns that need to be addressed. Therefore, lonapegsomatropin is considered approvable from a non-clinical point of view.

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.

- **Tabular overview of clinical studies**

Study ID	Objectives / Description / Administration Modality	Status
Phase 1		
CT-101	PK/PD bridging Comparing lonapegsomatropin with ACP-001 on PK (somatropin C_{max} and AUC) and PD (IGF-I E_{max} and AUEC) parameters following a single dose. Syringe/needle. 45 subjects	Completed
CT-102	Bioequivalence Comparing administration of lonapegsomatropin via syringe/needle (reconstituted drug from single-use glass vial) with the administration via GH Auto-Injector. PK (somatropin C_{max} and AUC) and PD (IGF-I E_{max} and AUEC) parameters following a single dose were analysed. Syringe/needle and GH Auto-Injector. 28 subjects	Completed
Phase 2		
CT-004	Safety, efficacy, PD and PK and dose-finding in the target population Multicenter, randomized, open-label, active-controlled, parallel-group, 26-week study comparing weekly ACP-001 at 3 dose levels with daily somatropin in children with GHD. Syringe/needle. 40 subjects ACP-001, 13 subjects somatropin	Completed
Phase 3		
CT-301	Pivotal study; efficacy, safety, PK, and PD in the target population Multicenter, randomized, open-label, active-controlled (somatropin), parallel-group, 52-week study, in prepubertal children with GHD. Syringe/needle. 105 subjects received lonapegsomatropin.	Completed

Study ID	Objectives / Description / Administration Modality	Status
CT-302	Safety, efficacy, and PD in the target population Multicenter, open-label, single-arm, 26-week study in treatment-experienced children with GHD. Syringe/needle. 146 subjects.	Completed
CT-301EXT	Safety, efficacy, and PD in the target population Multicenter, long-term, open-label, single-arm study in children with GHD who have completed a prior lonapegsomatropin hGH clinical study. Syringe/needle and GH Auto-Injector. 296 subjects	Ongoing

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

At physiologic pH and temperature, lonapegsomatropin releases fully active, unmodified hGH via autocleavage of the linker in a controlled manner that follows first-order kinetics.

Two clinical pharmacology studies were conducted to investigate PK and PD of lonapegsomatropin (CT-101 and CT-102). Both were randomized, open-label, single dose studies in healthy volunteers. In addition, PK and PD assessments were made in Phase 2 (CT-004) and Phase 3 studies (CT-301 and CT-302) in paediatric subjects. In Phase 3 studies this was in part based on intensive sampling with non-compartmental analysis as well as sparse sampling and population analyses.

Single dose, cross-over Study CT-101 compared (for bridging purposes) PK and PD, measured as hGH and IGF-I, between lonapegsomatropin and ACP-001 (predecessor molecule of lonapegsomatropin). ACP-001 was used in the dose finding Phase 2 study, CT-004, which was conducted before Study CT-101. Furthermore, Study CT-101 investigated PK and PD of lonapegsomatropin at three different dose levels. A formal endpoint for bioequivalence was not included in the study, however, the study was designed following the principles for bioequivalence studies as provided in applicable EMA guidelines.

Single dose, cross-over bioequivalence Study CT-102 compared PK and PD, measured as hGH and IGF-I, of lonapegsomatropin administered via syringe/needle (reconstituted drug from single-use glass vial) or via GH Auto-Injector. The study was conducted following the principles for bioequivalence studies as provided in applicable EMA "Guideline on the investigation of bioequivalence".

Bioanalysis

The bioanalytical methods applied to PK and PD analyses were validated according to applicable guidelines. Incurred sample reproducibility (ISR) was included in both studies and passed acceptance for all analytes assessed.

With respect to the anti-lonapegsomatropin and anti-hGH immunogenicity assays, these have been validated to a sufficient extent. Drug tolerance was acceptable for the binding assays. For the neutralising anti-hGH assay, lonapegsomatropin and hGH concentrations exceeded the tolerance level of the assay. However, this issue was resolved by taking samples at the trough level, allowing reliable assessment of the neutralising anti-hGH antibodies.

Qualification of PK and PK/PD models

The popPK model MODHGH002 was developed to estimate the serum PK for lonapegsomatropin and the

popPK/PD model for hGH/IGF-I. Lonapegsomatropin was described by a one-compartmental PK model with parallel first- and zero-order absorption from the subcutaneous administration site, with body weight and dose being a covariate for the volume of distribution, and body weight and gender being a covariate for maximum elimination rate. For hGH, PK was best described with a one-compartmental PK model with first-order absorption and linear clearance, with body weight was a covariate for clearance and volume of distribution, gender and dose were also found to be covariates on clearance. For IGF-I, the final PK/PD model was an IGF-I turnover model with IGF-I-production stimulation by hGH, body weight as a covariate on E_{max} and k_{out} and a correlation between k_{out} and clearance.

Another popPK model, MODHGH001, was developed in order to estimate the mPEG choroid plexus PK in cynomolgus monkey and human, extrapolated from mPEG choroid plexus data in rats. The outcome of this popPK study is discussed in the preclinical part of this AR in relation to the vacuolisation-related safety evaluation.

Absorption

Following SC administration, lonapegsomatropin distributes slowly (median t_{max} 36 h) from the SC administration site to the systemic circulation. Due to the autocleavage mechanism to release hGH, hGH can be liberated from lonapegsomatropin both at the administration site and in the systemic circulation. In paediatric GHD patients, the mean steady-state peak serum C_{max} of lonapegsomatropin was 1230 ng /mL with a median T_{max} of 25 hours.

Systemic hGH was liberated from lonapegsomatropin with median T_{max} for hGH observed at 16 h (range 8–48 h) following dosing at 0.24 mg hGH/kg to healthy subjects in CT-101. At this dose, the mean observed hGH C_{max} was 13.4 ng/mL, and hGH AUC_{0-168} was 617 h*ng/mL. In paediatric GHD patients, the mean steady-state peak serum C_{max} for released somatropin was 15.2 ng/mL with a median T_{max} of 12 hours. The shape of the hGH concentration-time curve was similar to the lonapegsomatropin curve from the popPK study. This indicates that the linker release rate determines the shape of the hGH PK curve obtained by lonapegsomatropin, and the clearance of the free hGH determines the concentration difference between lonapegsomatropin and free hGH. The measured median T_{max} of mPEG at 240 h is later than for hGH and lonapegsomatropin. This likely reflects the slow absorption of mPEG from the subcutaneous tissue.

The leaving group serum levels could hardly be detected with the assay having a LLOQ of 25/50 pg/ml. Although the exact levels of this leaving group are unknown, considering the low levels, this issue is not further pursued.

Results of bioequivalence Study CT-101 indicate that hGH levels are comparable for lonapegsomatropin and predecessor molecule ACP-001 at the 0.24 mg hGH/kg dose level, with the 90% CIs for the ratios for hGH AUC_{0-168}, AUC_{0-336}, and C_{max} within the standard bioequivalence limits of 80-125%. Further, PD equivalence concerning the serum concentration-time profiles of IGF-I was demonstrated. Based on this outcome, PK data obtained with the predecessor molecule ACP-001 (e.g. in Study CT-004) are considered valuable for evaluating lonapegsomatropin PK a dose-finding.

Results from Study CT-102 indicate that SC administration of lonapegsomatropin either via a syringe/needle or via the GH Auto-Injector results in comparable serum hGH and IGF-I exposure, since relevant 90% CI of C_{max}, AUC_{0-168}, AUC_{0-t}, and AUC_{0-inf} were all within the standard bioequivalence range of 80-125%. No appreciable difference in hGH or IGF-I inter-subject variation was observed between the two injection modalities. Based on this outcome, the clinical data obtained with lonapegsomatropin administered via a needle/syringe can be used to support the registration of lonapegsomatropin with the GH Auto-Injector.

Distribution

Based on popPK modelling, the volume of distribution of lonapegsomatropin is 7.2 L (based on a 70 kg body weight). This Vd is close to the plasma volume, suggesting lonapegsomatropin is largely retained in the systemic circulation, probably due to its high molecular weight (63.2 kDa) limiting diffusion into tissues. The apparent volume of distribution *V/F* of lonapegsomatropin in children with GHD, an age of 8.5 years and a typical body weight of 19 kg for this age, was found to be 1.3 L.

The assumed Vd of hGH is 70 mL/kg (i.e., 4.9 L based on a 70 kg body weight), based on the somatropin prescribing information. In the popPK model MODHGH002, the estimated Vd for hGH was much larger, i.e., 374 L. The difference between the Vd for somatropin and hGH from lonapegsomatropin may be caused by the reduced bioavailability and the prolonged release rate of hGH when delivered in the form of lonapegsomatropin.

Elimination

The apparent half-life of lonapegsomatropin following single-dose administration to healthy subjects is approximately 52 h, whereas, in paediatric GHD patients, the mean half-life at steady-state was 30.7 h. The apparent half-life of hGH (when released from lonapegsomatropin) of approximately 24 h is much longer than for daily administered somatropin (2-3 h). The longer half-life is consistent with sustained release of hGH from lonapegsomatropin.

The metabolic fate of mPEG has been investigated extensively in the literature, and the metabolism and excretion of mPEG are well understood. High molecular weight mPEGs such as from lonapegsomatropin are expected to be predominantly excreted unchanged in the urine by renal filtration. The apparent half-life of mPEG is approximately 500 h.

Dose proportionality and time dependencies

Dose-proportionality studies indicate a slightly higher than proportional increase in hGH levels with increasing dose, in a comparable fashion after a single dose and multiple-doses. Lonapegsomatropin is intended to be given as a 0.24 mg/kg weekly dose. Due to this fixed-dose posology, the observed more than dose-proportional increase in lonapegsomatropin and hGH exposure, comparable after single and multiple-dose, is not considered an issue and will not be further pursued.

Following multiple weekly administrations of lonapegsomatropin, no relevant accumulation was observed for hGH and Lonapegsomatropin. This finding is in line with the $t_{1/2}$ of 25 and 50h for hGH and lonapegsomatropin, respectively. A marked 4.7-fold accumulation was observed for mPEG, which is expected based on the long $t_{1/2}$ of 485h for this substance.

Special populations

Renal impairment

Lonapegsomatropin is considered to be cleared by the release of hGH and the PEG moieties. The hGH released from lonapegsomatropin is considered to be excreted in the same manner as endogenous GH. Data from the literature indicate that GH is cleared by 2 mechanisms, i.e., clearance by glomerular filtration and internalization and degradation of GH following interaction with growth hormone receptors present in a large number of tissues including the liver.

GHR binding and subsequent internalization and degradation are only considered relevant for the released hGH, as hGH within lonapegsomatropin is effectively shielded from receptor binding by the mPEG carrier (see preclinical AR).

Clearance of the released mPEG molecules is known to proceed largely through glomerular filtration and excretion in urine, predominantly as intact mPEG.

In light of the available knowledge on the clearance of hGH, the lack of specific studies on renal impairment is considered acceptable.

Hepatic impairment

In light of the available knowledge on the clearance of hGH and mPEG, the lack of specific studies towards hepatic impairment is considered acceptable.

Gender

Based on data from Studies CT-101 and CT-301 in PopPK Study MODHGH002, males have on average 33% higher hGH exposure than females. This difference is not considered to be clinically relevant.

Race

The effect of race on exposure to hGH from lonapegsomatropin provided in the Clinical Pharmacology summary is only based on data from Studies CT-101 and CT-301 in PopPK Study MODHGH002. Due to the limited number of non-White subjects in these 2 studies, no conclusion on the effect of race can be drawn at this stage.

Body weight

Lonapegsomatropin and hGH clearance increases with increasing body weight.

Elderly

No lonapegsomatropin and hGH PK data are available in the elderly, which is acceptable given the indication which is limited to paediatric GHD patients.

Children

In PopPK Study MODHGH002, no impact of age on hGH PK was evident once differences in body weight were accounted for. Therefore, age was not considered to have any additional impact on hGH exposure down to 3.2 years of age, being the youngest patient included in Study CT-301.

Pharmacokinetic interaction studies

Pharmacokinetic drug-drug interaction studies have not been conducted with lonapegsomatropin. As neither lonapegsomatropin, hGH nor mPEG are CYP substrates, the likelihood of drug-drug interactions is considered low.

2.6.2.2. Pharmacodynamics

Pharmacology, primary pharmacodynamics and safety pharmacology endpoints have been obtained from *in vitro* and *in vivo* studies conducted with lonapegsomatropin.

In vitro studies have established that lonapegsomatropin can be considered as essentially inactive, since human growth hormone is effectively inactivated when bound to the carrier. Human growth hormone released from lonapegsomatropin is unmodified and shows a biopotency comparable to somatropin.

Dedicated pharmacology studies on lonapegsomatropin were conducted in rats and monkeys and evaluated relative to daily somatropin. The continuous exposure to human growth hormone, following lonapegsomatropin administration, in contrast to intermittent exposure following daily somatropin, resulted in a more pronounced increase in systemic IGF-I concentration in monkeys as well as superior increases in body weight gain in hypophysectomized rats, compared to once-daily administration of somatropin at equivalent weekly doses. IGF-I is a recognized biomarker for human growth hormone activity.

In contrast to human growth hormone released from lonapegsomatropin, other methods for creating long-acting human growth hormone, based on modification by protein enlargement, exhibit an increased molecular size (range from 47.5 to >100 kDa). Hence their half-life is prolonged due to decreased renal and receptor-mediated clearance. These compounds may, however, as a result of increased molecular size, have restricted access to growth hormone receptors in some target tissues (e.g. growth plates and adipocytes) due to compromised tissue distribution while still effectively stimulating hepatic IGF-I production. This is due to facilitated access to hepatic growth hormone receptor via the glycocalyx-free open-fenestrated sinusoidal endothelium found in the liver. This can result in altered tissue ratios of human growth hormone and IGF-I, altering safety and efficacy compared to unmodified human growth hormone.

Mechanism of action

Growth hormone exerts its effects via growth hormone receptors, which are ubiquitously expressed in the body. GHR mRNA expression has been detected in multiple human tissues, including liver, fat tissue, skeletal muscles and bone tissues, such as the growth plates. The GHR is a member of the class I cytokine receptor family and consists of an extracellular cytokine binding domain, a single-pass transmembrane domain and a cytoplasmic domain with binding sites for non-receptor tyrosine kinases. GHR signal transduction is mainly handled by Janus kinase 2 (JAK2) and mediated by signal transducer and activator of transcription (STAT) 1, 3, and 5, which promote cellular growth and proliferation.

In addition to activation of membrane-bound growth hormone receptor, active growth hormone/ receptor complexes have been demonstrated to be internalized to the cell nucleus or mitochondria of rat hepatocytes and Chinese hamster ovary cells. Although the exact function of these internalized receptors remains to be elucidated, they seem to be involved in the regulation of cell proliferation and metabolism.

Growth hormone is an anabolic hormone. It induces anabolic effects on the metabolism of proteins, lipids, and carbohydrates. Apart from this, growth hormone – among others - modulates cardiovascular function, and cognition. These effects are mediated both directly by growth hormone and indirectly by IGF-I. Growth hormone induces the production of IGF-I in the liver and peripheral tissues such as long bone growth plates and skeletal muscles. The liver is the primary source of circulating IGF-I, which regulates endogenous growth hormone production via a negative feedback loop, while locally produced IGF-I acts in an autocrine and paracrine fashion.

Primary and Secondary pharmacology

Primary pharmacology

Growth hormone is a key regulator of postnatal longitudinal growth, affecting the epiphyseal plate of long bones directly and indirectly via IGF-I. In the resting zone (also called the reserve zone), mesenchymal stem cells are recruited and serve as a cellular reserve and matrix secretory cells. Stimulated by growth hormone, these cells differentiate and give rise to clonal lineages of chondrocytes. The further propagation of these chondrocytes in the proliferative zone is stimulated by growth hormone, both directly and indirectly, via IGF-I. Stimulated by IGF-I, the chondrocytes then differentiate and expand to form hypertrophic chondrocytes. Finally, the hypertrophic chondrocytes undergo either apoptosis or differentiation to an osteoblast-like phenotype and eventually give way to growing vasculature and further osteoblasts in the ossification zone. The enhanced activity of osteoblasts is mediated by direct effects of GH as well as indirectly via IGF-I.

The relative importance of local versus systemic IGF-I production in mediating bone growth remains a matter of some scientific debate, but the body of evidence points towards local IGF-I concentration being the determining factor. Govoni (2007) studied the effects of specific IGF-I knockout in chondrocytes of mice. In this model, IGF-I concentration in cartilage was reduced by 40%, while circulating levels of IGF-I were unaltered. During the prepubertal growth from 4 to 12 weeks of age, body elongation was concurrently reduced by 27% compared to wild-type littermates. Likewise, the effects of reduced circulating IGF-I levels on longitudinal growth have been studied in detail. Yakar et al. (1999) found that 75% reduction of circulating IGF-I levels by specific knockdown of hepatic IGF-I did not significantly affect longitudinal growth. Taken together, these studies indicate that while circulating levels of IGF-I are needed for maintaining a basal level of anabolic effects and for regulating growth hormone secretion, local concentrations of IGF-I may be of proportionally greater importance for longitudinal growth.

Secondary pharmacology

The growth hormone/IGF-I axis has profound effects on the metabolism of lipids, proteins, and carbohydrates. Growth hormone directly increases lipolysis in adipose tissue and inhibits the uptake of free fatty acids (FFAs) into adipocytes. FFAs are converted into triglycerides in the liver and released into the bloodstream as lipoproteins. Furthermore, growth hormone reduces overall protein oxidation and increases protein synthesis in skeletal muscles, leading to increased muscle mass.

Growth hormone effects on carbohydrate metabolism are highly dependent on the systemic concentrations of growth hormone. Insulin resistance is thus observed both in adults suffering from excess production of growth hormone (acromegaly) and in those with growth hormone deficiency. Low doses (≤0.1 mg/day fixed-dose) of human growth hormone in patients with growth hormone deficiency can improve insulin sensitivity by increasing IGF-I secretion without increasing lipolysis or hepatic gluconeogenesis and glycogenolysis. Conversely, at supraphysiological doses (>0.6 mg hGH/day fixed-dose) hepatic glycogenesis is stimulated directly by growth hormone and decreased insulin sensitivity.

In addition to its effects on growth and metabolism, growth hormone also exerts effects on the central nervous system, and human growth hormone replacement therapy has been shown to influence cognitive function, appetite, and sleep positively. Growth hormone enters the central nervous system from the systemic circulation and can thus be measured in cerebrospinal fluid (CSF) after systemic administration. The manner of how growth hormone enters the CSF and brain has yet to be elucidated. The presence of growth hormone receptors in the choroid plexus has led numerous authors to suggest that growth hormone may pass into the central nervous system via a receptor-mediated mechanism. However, these receptors' exact location and function remain to be fully explored, and to date, no direct evidence for receptor-mediated uptake of growth hormone into the central nervous system has been found. This is in contrast to the demonstrated receptor-mediated uptake of other hormones such as IGF-I and hepatocyte growth factor. Furthermore, growth hormone passed from the systemic circulation into the brain mesenchyme of mice

through a non-saturable process. This indicates that the majority of growth hormone entering the central nervous system from the circulation does so by passive diffusion through the blood-brain barrier.

Relationship between plasma concentration and effect

IGF-I Response to treatment in paediatric GHD patients was initially assessed in study CT-004 that employed ACP-001. IGF-I was assessed at doses of 0.14 (N=12), 0.21 (N=14) and 0.30 mg hGH/kg/week (N=14) in pre-pubertal pediatric GHD subjects versus the active comparator somatropin administered once daily at 0.03 mg hGH/kg/day (equivalent to 0.21 mg hGH/kg/week, n=13). Figure 9 illustrates the profiles of IGF-I and shows that ACP-001 produced elevated levels of IGF-I throughout the study.

Figure 9. IGF-I serum concentration arithmetic means (+SD) over time following once-weekly administration of ACP-001 (Study CT-004)

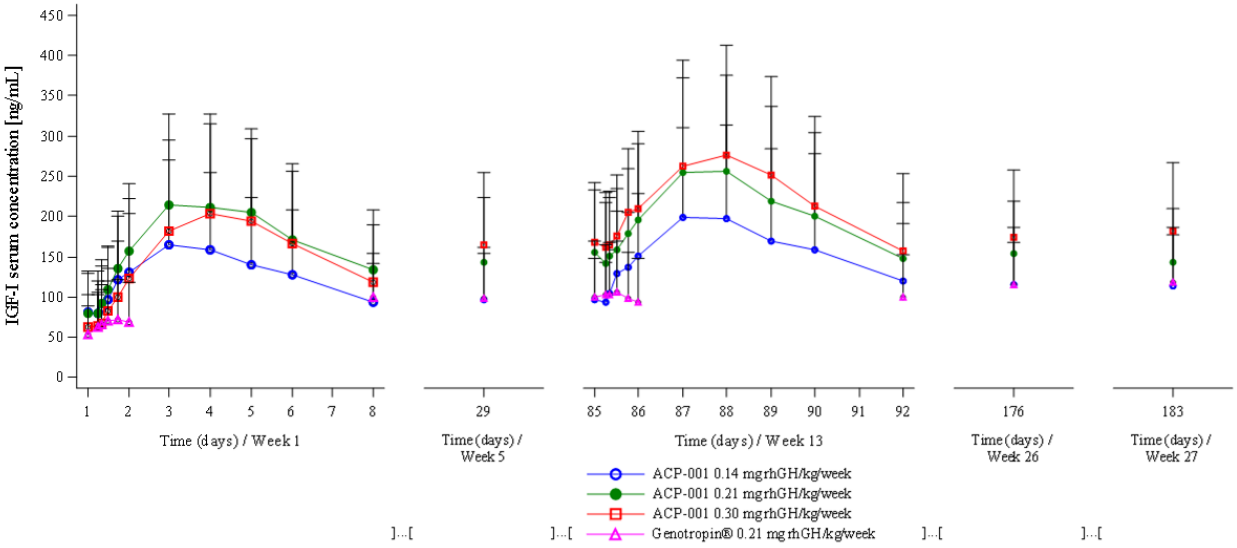


Figure 10 illustrates the relationship between the ACP-001 dose used in CT-004 and the average IGF-I SDS response. Both figures show that higher doses of ACP-001 were associated with greater IGF-I increases.

Figure 10. Average IGF-I SDS versus lonapegsomatropin dose at week 13 following once weekly administration of ACP-001 (Study CT-004)

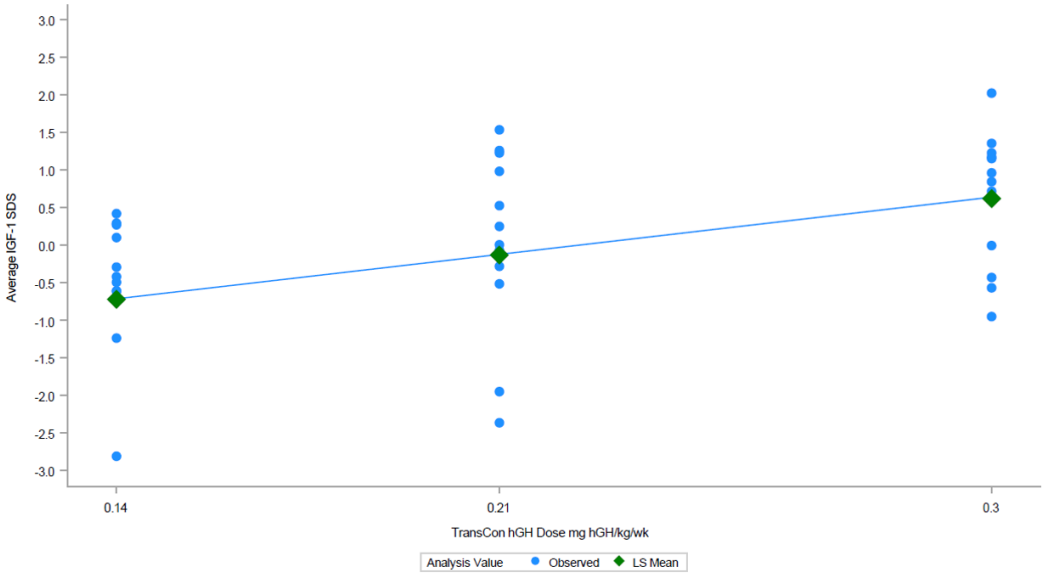


Figure 10 also shows the linear regression line of average IGF-I SDS at week 13 over lonapegsomatropin dose overlaid by observed average IGF-I SDS data and LS means of average IGF-I SDS at week 13. The LS means of average IGF-I SDS coincide well on the regression line, demonstrating a dose proportionality for lonapegsomatropin. The estimated regression coefficient of lonapegsomatropin dose is 8.45, which means on average a 0.1 mg/kg/week dose increase/decrease in lonapegsomatropin will result in an increase/decrease of 0.845 SDS in average IGF-I level. The results of change from baseline in IGF-I SDS are similar

The observed prolonged hGH exposure in systemic circulation resulted in an IGF-I response supporting once-weekly dose administration.

The observed C_{max} range of hGH released from lonapegsomatropin was generally overlapping with somatropin hGH concentration data obtained at the assumed T_{max} of daily hGH.

Lonapegsomatropin and hGH did not accumulate in the systemic circulation following once-weekly dose administration for 52 weeks. Systemic mPEG steady-state was reached at or before week 26.

Within the popPK/PD analysis MODHGH002 it was identified that weight and gender were covariates on the hGH/IGF-I response. The apparent effect of gender was primarily associated with the adult population and not with the pediatric subjects.

As IGF-I levels are known to be sex- and age-dependent, the IGF-I SDS was used to investigate whether there was clinical relevance for these covariates. Predictions of IGF-I SDS were made for males and females across a range of body weights. Predicted IGF-I SDS response differences between males and females and between lower (13kg) and higher (50 kg) body weight subjects were small and unlikely to be clinically relevant or require dose adjustment. In addition, monitoring of IGF-I would allow for increasing or decreasing the lonapegsomatropin dose in response to IGF-I levels.

The Population PKPD model has been expanded to include data from CT-301EXT and CT-302, thereby encompassing paediatric subjects with BW >50 kg and their corresponding relevant ages. The new simulation in children with BW > 50 kg shows that, even less relevant than in the previous simulation, the spread of

IGF1-SDS responses still increased 1 unit (between 1.5 and 2 for BW of 60 kg and around 2 for BW of 70 kg). Concerns were raised related to the tendency that for children >50 kg, the proposed dosing regimen would generate IGF-I SDS levels above the upper target limit of +2 SDS. Upon this, the SmPC was adjusted to clarify the appropriate starting dose based on the patient's weight.

For a dose reduction of 0.02 mg growth hormone/kg, a reduction in IGF-I of 0.21 SDS occurred. This analysis included treatment-naïve and treatment- experienced children with GHD with a wide range of ages and pubertal stages. When evaluated by Tanner Stage, the consistency was maintained: for a dose reduction of 0.02 mg growth hormone/kg, a reduction in IGF-I of 0.25 SDS and 0.19 SDS was observed for Tanner Stages 1-2 and 3-5, respectively.

Somatropin starting doses with lonapegsomatropin

The recommended starting dose in growth hormone treatment naïve GHD patients is 0.24 mg somatropin/kg body weight, given once weekly. This dosage was chosen based on the results of study CT-004.

For paediatric GHD patients switching from daily somatropin medicinal products at a total weekly dosage of 0.24 mg/kg/week or higher, the recommended somatropin starting dosage with lonapegsomatropin is 0.24 mg somatropin/kg/week. In those who received somatropin doses at a total weekly dosage, somatropin dosage with lonapegsomatropin is lowered to the equivalent of the weekly dose of daily somatropin.

The aforementioned starting dosages are recommended irrespective of age, gender, and Tanner stage.

Lonapegsomatropin dosing may need to be adjusted during treatment. After lonapegsomatropin dose adjustment, the average IGF-I SDS level can be appropriately determined 4-5 days after the second lonapegsomatropin dose i.e. during stable dosing.

Monitoring of IGF-I SDS levels

Somatropin dosages with lonapegsomatropin are titrated based on IGF-I SDS levels. An individualized approach is mandatory in this respect due to interindividual differences in the sensitivity to somatropin.

The IGF-I SDS levels 4-5 days after stable dosing provide an indication of the average IGF-I SDS levels during the interval of one week in between subsequent lonapegsomatropin doses. The peak IGF-I SDS levels are about 1 SDS higher than the average IGF-I SDS level. The trough IGF-I SDS levels are about 1 SDS lower than the average IGF-I SDS level. For this reason, determination of the average IGF-I SDS level 4-5 days after stable dosing also indicates the variability in IGF-I SDS levels during the interval of one week in between subsequent lonapegsomatropin doses. Because of this, there is no need to determine peak and trough IGF-I SDS levels for lonapegsomatropin.

For lonapegsomatropin treatment in children with GHD, evaluation of efficacy and safety is recommended at approximately 6 to 12-month intervals based on auxological parameters, biochemistry (IGF-I, hormone, glucose, and lipid levels), and pubertal status. In paediatric GHD patients who undergo pubertal transition and in advanced pubertal stages, more frequent monitoring of IGF-I may be considered based on analyses that showed a higher likelihood of IGF-I >2 SDS among Tanner Stages III-V.

Somatropin dose adjustments based on IGF-I SDS levels

IGF-I SDS levels are used as guidance for somatropin dosing with lonapegsomatropin. This dosing is targeted to achieve IGF-I SDS levels within the range between -2 and +2 (preferably close to 0 SDS). The somatropin

dosing with lonapegsomatropin is adjusted in case of IGF-I SDS levels outside the normal range. Since the growth response is higher in case of IGF-I SDS levels within the range between 0 and +2 as compared to the range -2 up to 0,[4] it may be decided on an individual base to target IGF-I SDS levels within the upper normal range.

Based on analyses of the somatropin dose with lonapegsomatropin and IGF-I SDS levels, changing to the next higher or lower somatropin dose strength with lonapegsomatropin increases or decreases IGF-I levels on average by 0.3 SDS. Based on this, recommendations with respect to somatropin dosing with lonapegsomatropin based on IGF-I SDS levels have been developed and included in the SmPC.

The dosage adjustments are recommended for paediatric GHD patients irrespective of any prior growth hormone treatment, age, gender, and Tanner stage.

IGF-I SDS levels in clinical studies

Study CT-301

IGF-I SDS levels were within the IGF-I SDS range of -2 up to +2 for ≥50% of the time in 104/105 (99.0%) of lonapegsomatropin-treated study patients and 53/56 (94.6%) of somatropin-treated study patients in pivotal study CT-301.

IGF-I SDS levels >+2 were observed in 7.6% of lonapegsomatropin-treated study patients and 3.6% of somatropin-treated study patients (Table 13).

Table 13 Proportion of study patients with average IGF-I SDS >+2.0 and >+3.0 at any point during study CT-301 by treatment group (ITT Population)

Category	Lonapegsomatropin (N=105) n (%)	Somatropin (N=56) n (%)
>+2.0	8 (7.6)	2 (3.6)
> +2.0 for at least two consecutive visits	3 (2.9)	1 (1.8)
>+3.0	0	0
>+3.0 for at least two consecutive visits	0	0

Source: Table 14.2.3.17
Note: Average IGF-I SDS values for lonapegsomatropin were derived from the population PD model as described in Section 9.7.1.6.3. Average IGF-I SDS values for somatropin shown above are based on observed data.

In the lonapegsomatropin treatment arm, the proportions of study patients with IGF-I SDS levels >+2 tended to increase with time (week 13: 0%, week 26: 1.9%, week 39: 2.9%, week 52: 7.7%). Such a trend was not observed for the proportions of somatropin-treated study patients with IGF-I SDS levels >+2 (week 13: 3.6%, week 26: 1.8%, week 39: 1.8%, week 52: 1.9%).

Study CT-302

[4] Cohen P, Rogol AD, Howard CP, et al. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. J Clin Endocrinol Metab. 2007;92(7):2480-2486.

At each time point, the majority of study patients had IGF-I SDS levels in between -2 and +2 at baseline (78.1%), week 13 (61.8%), and week 26 (60.6%).

In the majority of study patients (56.8%) serum IGF-I SDS levels >+2 were observed at any point during the study, including baseline. In 25.3% of study patients, IGF-I SDS levels >+3 were observed. The proportions of study patients with IGF-I SDS levels >+2 (baseline: 21.9%, week 13: 38.2%, week 26: 38.7%) and >+3 (baseline: 3.4%, week 13: 11.8%, week 26: 15.5%) increased during follow-up.

IGF-I SDS levels above +2 were observed in all GHD study patients under 3 years of age.

Study CT-301 EXT

In CT-301, average IGF-I SDS > +2 was observed in 7.7% of the lonapegsomatropin group versus 1.9% of the daily somatropin group at week 52 (at any time during study CT-301: 7.6% versus 3.6%). As stated above, no average IGF-I SDS >+3 were observed during CT-301 in either treatment group.

At week 104, the proportions of patients who had IGF-I SDS levels >+2 were 19.0% and 22.6% for study patients who had been treated with respectively lonapegsomatropin and somatropin in study CT-301 (data lock-off June 2020). For paediatric GHD patients enrolled into study CT-302, the proportions of study patients with IGF-I SDS >+2 and >+3 at each visit was approximately 30% and 15%, respectively, through week 91 (data lock-off June 2020).

Among study patients who were included in study CT-301 followed by study CT-301 EXT, the proportions of study patients with IGF-I SDS levels above the normal range increased over time, especially after 52 weeks of treatment. However, among study patients who were included in study CT-302 followed by study CT-301EXT the proportions of study patients in whom IGF-I SDS levels above the normal range were observed remained stable in study CT-301EXT as compared to study CT-302.

The patient characteristics of study patients who did or did not experience IGF-I SDS levels above +2 in conducted Phase 3 studies on lonapegsomatropin were studied. Differences in Tanner stage were observed in these subgroups. Age (in years; odds ratio 1.20; p< 0.0001), weight (in kg; odds ratio 1.07; p< 0.0001), and more advanced Tanner stage (i.e. stage III, IV, and V)(odds ratios respectively 7.41, 11.55, and 12.55; all p< 0.0001) were significantly associated with IGF-I SDS levels >+2 in a logistic regression analysis.

2.6.3. Discussion on clinical pharmacology

Bioanalysis

Further clarification was requested on the bioanalytical method for hGH, lonapegsomatropin and mPEG. For the hGH ELISA used in Studies CT-101, CT301 and CT302, in a late amendment of the validation report CA16502-01, 0.29 % cross-reactivity with lonapegsomatropin was identified. The specificity of the ELISA for hGH in the presence of lonapegsomatropin should however be further clarified. As lonapegsomatropin levels are typically approximately 100-fold higher than hGH, the 0.29 % cross-reactivity translates to an approximate 18 % lower Cmax and 26% lower AUC0-t for hGH than actually measured in the assay.

The bioanalytical method for hGH, lonapegsomatropin and mPEG and the results of the ELISA specificity were discussed for hGH in presence of lonapegsomatropin. The cross-reactivity was sufficiently clarified and

characterized. hGH serum concentration data was corrected for cross-reactivity only in study CT-301 and hGH data provided both as measured and with the correction. This was due to the fact that the reference standard used in analysis of the samples from that study contained 0.4% free hGH. In other trials only the measured values were reported.

With respect to the anti-mPEG immunogenicity assay, mPEG tolerance was 2500 ng/ml, whereas actual mPEG concentration at time of sampling were >7000 ng/ml. Additional data on drug-tolerance of the anti-mPEG immunogenicity assay was provided, using a human positive control instead of a rabbit anti-mPEG monoclonal antibody positive control used during validation. Drug tolerance against the human mPEG was estimated to be 15000 ng/ml, which is higher than the 2500 ng/ml tolerance obtained using the rabbit positive control. It is agreed that the data obtained using the human positive control are deemed more clinically meaningful. Further relief of potential concerns on undetected anti-mPEG antibodies comes from the fact that the lonapegsomatropin, hGH and IGF-I concentration-time curves do not indicate (potentially unnoticed) antibodies affecting PK or PD.

The PK of the leaving group is considered sufficiently characterised in children with GHD, and it has been demonstrated that the leaving group is rapidly removed from the system.

Qualification of PK and PK/PD models

During SC administration of the product, relatively high levels of mPEG are expected in the patients' serum. An important potential safety issue that has been raised for other pegylated product is the chance of vacuolisation in the choroid plexus. In order to estimate the mPEG levels in the choroid plexus of paediatric patients with GHD, a popPK model was developed, aiming to extrapolate the choroid plexus data in rats to those in the choroid plexus PK in cynomolgus monkey and human, thereby allowing a link between the preclinical safety data and the expected choroid plexus exposure in human. For this purpose, in part 1 of the popPK study, mPEG serum PK in rat and human were described with a one-compartmental model with first-order absorption from the administration depot. In cynomolgus monkey, a dose-dependency was added.

In part 2 of this popPK study, in order to predict the mPEG concentrations in the choroid plexus of cynomolgus monkey and human, the PEG40(N9-GP) rat choroid plexus half-life of 49 days determined by whole-body autoradiography was scaled to cynomolgus monkey and human. This was considered possible since the mPEG serum PK data that were obtained in rat, cynomolgus monkey and human obeyed the expected scaling factors to a reasonable extent. For this exercise, it was assumed that 1) the half-life in the different species scale allometrically with body weight with a scaling coefficient of $\beta T1/2,BWT = 0.25$, 2) the volume of distribution of mPEG in the choroid plexus was equal to the physiological volume of the choroid plexus of the respective species, and 3) the biodistribution coefficient K, that is the ratio between plasma and choroid plexus mPEG concentration at steady-state, is the same as for PEG40(N9-GP) and the same between the species. The Applicant provided an extensive discussion on the assumptions made in PopPK model.

It is acknowledged that a serious effort was made to predict the mPEG exposure in human choroid plexus. Assuming that the underlying assumptions on the biodistribution coefficient, the scalability of the PEG40(N9-GP) and the vacuolisation process in different species are true, the model indicated that steady state mPEG levels are reached in the human choroid plexus which are much lower than those predicted to result in vacuolisation in preclinical studies.

However, the assumptions are considered highly theoretical and cannot be verified without generating additional data of mPEG in choroid plexus in different species. Further optimisation of the model without such additional data is not expected to yield a more trustworthy predicted mPEG exposure in the choroid plexus.

Without verification of the assumptions, the predicted human mPEG concentrations in choroid plexus by the current model should be interpreted with great caution.

Still, it is important to highlight that the assumption that transport of mPEG to the choroid plexus is driven by non-specific mechanisms is now considered plausible. Therefore, the assumption that the biodistribution coefficient in principle can be extrapolated from one to another species is now considered more likely to be true and accepted. This is assumed to apply in the provided popPK model intended for bridging of the preclinical safety data to the human situation.

It is concluded that the model-predicted human mPEG concentrations, reaching steady state in the choroid plexus, should be interpreted with great caution. However, one reason for possible differences in mPEG distribution between serum and choroid plexus between different species, i.e. active transport of mPEG, when linked to lonapegsomatropin, by species specific transporters, via e.g. the growth hormone receptor, is now considered to be unlikely, since the somatropin part of lonapegsomatropin is shielded from this growth hormone receptor by mPEG. Therefore, from a theoretical point of view, it can be considered that the mechanism for transport of mPEG to the choroid plexus in different species proceeds via comparable non-specific mechanisms.

Since further optimisation of the model without additional mPEG choroid plexus data is not expected to yield more trustworthy predictions, this issue is not further pursued.

Absorption

Lonapegsomatropin is to be injected SC to the abdomen, buttock or thigh. In Study CT-301, the vast majority of patients rotated the injection sites as indicated in the proposed SmPC. Overall exposure to lonapegsomatropin, hGH, and IGF-I were broadly similar between administration sites, with no systematic differences observed. Based on this outcome, it is not expected that efficacy or safety would be sensitive to the administration site.

Distribution

In paediatric GHD patients, the absolute bioavailability following subcutaneous dose administration of lonapegsomatropin has not been investigated, which is indicated in the SmPC section 5.2. Further, the lonapegsomatropin NCA-based volume of distribution in children is reported in the same section.

Special populations

A theoretical discussion was provided on the potential effect of renal impairment, assuming mPEG was completely renally cleared. In a worst-case scenario, in case of severe renal impairment, a 4-fold increase in mPEG exposure to approximately 60 µg/ml may result. Additional data were provided, providing nuance to this previously sketched worst-case scenario, indicating that effects of renal impairment on mPEG concentration are expectedly lower, amounting up to a 2-fold increase. Provided data are considered sufficiently reassuring to omit a suggestion for alternate non-PEG containing products in case of renal impairment.

Based on popPK analysis and visual inspection of the data, race and ethnicity (White, Black/African American, Asian, Hispanic) do not appear to be a significant covariate on hGH exposure. Information on the number of male/female subjects and the number of subjects per origin included in the clinical studies is adequately provided in section 5.2 of the SmPC.

Lonapegsomatropin and hGH clearance increases with increasing body weight. The dose advice for children >50 kg was carefully assessed. It was agreed that dose titration should be based on average IGF-I SDS

levels and it is recommended to ensure that levels remain within the normal range between -2 and +2 SDS, preferably close to 0. Changing to the next higher or lower lonapegsomatropin dose strength increases or decreases IGF-I on average by 0.3 SDS and this relationship held true for both treatment-naïve and treatment-experienced patients; hence, one set of dose adjustment recommendations is provided for all patients.

In the popPK Study MODHGH002, age was not considered to have any additional impact on hGH exposure down to 3.2 years of age, being the youngest patient included in Study CT-301. hGH and mPEG PK data in patients <3.2 years of age appear limited. Treatment of patients at this young age is considered unlikely. Since the indication was restricted to paediatric GHD patients aged 3 years and above, this issue was not further pursued.

Interactions

With regard to potential DDI's for lonapegsomatropin as a perpetrator, an extensive literature-based discussion on the potential for GH-related DDIs was provided. It is agreed that the information shows some inconsistency but that most reported changes in activity appear to concern CYP3A4 and CYP1A2 mediated interactions. Considering the limited data and the inconsistencies in the data, it is agreed that the clinical significance of the potential interactions is considered to be unknown and is adequately expressed in the SmPC.

PK/PD analysis based on IGF-I SDS levels

The actual lonapegsomatropin-IGF-I exposure-response analysis was not provided; however, the relationship between lonapegsomatropin dose and IGF-I response was discussed. In Study CT-004 at an ACP-001 dose of 0.14, 0.21 or 0.30 mg hGH/kg/week in paediatric GHD subjects, IGF-I SDS at steady-state increases dose proportionality to ACP-001.

In the PK/PD subset of Study CT-301, applying a 0.24 mg/kg/week lonapegsomatropin dose, IGF-I levels reached steady-state at or before Week 13. There was an approximate +1 increase in IGF-I SDS observed from baseline to Week 13 pre-dose. PopPK/PD predicted IGF-I SDS response differences between males and females and between lower (13 kg) and higher (50 kg) bodyweight subjects were small and unlikely to be clinically relevant.

According to the model MODHGH003 IGF-I reaches a steady-state after 13 weeks of treatment with an IGF-I concentration around 0 SDS for the lonapegsomatropin and about -0.5 for daily growth hormone. For both treatments, IGF-I remained within de -2 and +2 SDS for the majority of the patients. Eight (8) patients treated with lonapegsomatropin reported IGF-I above 2 SDS for more than 50% of the time.

A similar pattern was observed in the conducted clinical studies CT-301, CT-302, and CT-301 EXT.

Based on the unknown exposition of growth hormone and IGF-I, there are concerns about the possible carcinogenetic effect of such an exposition. Further, there might be an increase in the development of diabetes mellitus type 2.

Considering these potential safety risks, lonapegsomatropin dosing should be adapted to avoid supratherapeutic IGF-I SDS levels in (subgroups of) paediatric GHD patients as much as possible. The proportions of lonapegsomatropin-treated GHD study patients in whom IGF-I SDS levels above +2 were observed at any point upon lonapegsomatropin treatment were 7.6% in study CT-301, 48.6% in study CT-301EXT, and 56.8% in study CT-302. The higher proportions in studies CT-302 and CT-301EXT as compared to study CT-301 are probably partially related to the less strict monitoring of IGF-I SDS levels in studies CT-

302 and CT-301EXT as compared to study CT-301. Hence, regular monitoring of IGF-I SDS levels is mandatory.

The fact that the proportion of study patients with IGF-I levels above +2 was highest among study patients in study CT-302 indicates that other factors apart from deliberate IGF-I SDS monitoring may explain the relatively high proportion of paediatric GHD patients with IGF-I SDS levels above +2. Respective factors include demographic factors. In line with this, advanced Tanner stages (3, 4, and 5) were associated with IGF-I SDS levels above +2 in logistic regression analyses.

Practical guidance for somatropin starting doses, IGF-I SDS monitoring, and somatropin dose adjustments with lonapegsomatropin were upon request provided and reflected in the SmPC. The applicant indicated later that evaluation of efficacy and safety should be considered at approximately 6 to 12-month intervals and may be assessed by evaluating auxological parameters, biochemistry (IGF-I, hormones, glucose, and lipid levels), and pubertal status.

The follow-up of conducted clinical studies is too short for the evaluation of long-term safety risks of lonapegsomatropin treatment. The applicant committed to conducting a PASS to evaluate the long-term clinical safety, including the risk of malignancies and/or diabetes mellitus type 2.

2.6.4. Conclusions on clinical pharmacology

Human growth hormone released from lonapegsomatropin maintains the same mode of action, including receptor-binding affinity, as human growth hormone administered on a daily basis.

Overall, the CHMP agreed that the PK of lonapegsomatropin has been investigated to a satisfactory extent.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Introduction

Study CT-004 is a Phase 2, randomized, open-label active-controlled study in which the clinical effects of three different dose levels of weekly ACP-001, a predecessor of lonapegsomatropin, were compared with those of daily somatropin treatment over a study period of 26 weeks.

Selection of study population

55 Male and female pre-pubertal growth hormone treatment naïve children with GHD in Tanner stage I (boys: 3-12 years, girls: 3-11 years) were included.

The diagnosis of GHD was based on the criteria laid down in the consensus guidelines for the diagnosis and treatment of GH deficiency in childhood and adolescence, issued by the Growth Hormone Research Society (GH Research Society, 2000).

Impaired height was defined as the height of at least 2 standard deviations below the mean height for chronological age and sex according to CDC standards (2000). Impaired height velocity was defined as a mean height velocity which was at least 1 standard deviation below the mean height velocity for chronological age and sex according to the standards of Prader et al., (1989), whereas the time between 2 height measurements is not less than 6 months.

Baseline IGF-I levels of GHD patients were at least 1 standard deviation below the mean IGF-I level standardized for age and sex (IGF-I Standard Deviation Score [SDS] ≤ -1.0) according to the central laboratory reference values.

The Body Mass Index (BMI) of GHD patients had to be within ±2 standard deviations of the mean BMI for chronological age and sex according to the 2000 CDC standards (Kuczmarski et al., 2002).

Randomization

55 Included study patients were centrally randomized to one of four cohorts: one of three weekly ACP-001 dose groups (0.14, 0.21, and 0.30 mg/kg/week) or a daily somatropin control dose group (0.03 mg/kg/day, i.e. 0.21 mg/kg/week) in a 1:1:1:1 ratio.

Prior to randomization, subjects were stratified using the minimization rule according to their age (> 3 to ≤ 6 years and > 6 years), peak GH levels in stimulation tests (≤ 5 ng/mL and >5 ng/mL) and gender. The minimization dynamic randomization method was used.

Study treatment

Both the investigational product (ACP-001) and the somatropin reference product (Genotropin) were administered subcutaneously by the study staff or by the parent or legal guardian.

ACP-001 was administered in the morning hours, and somatropin was administered in the evening hours (at bedtime). The dose calculation was initially calculated based on the subject's body weight prior to dosing at visit 1 and was subsequently adjusted according to the subject's body weight at visit 3, prior to dosing and PK/PD sampling.

Endpoints

The following efficacy endpoints and criteria were taken for evaluation:

- Annualized height velocity (cm/year)
- Delta height SDS
- Change in serum IGF-I levels (ng/ml) and IGF-I SDS
- IGF-I SDS and number and percentage of subjects achieving normalization of serum IGF-I levels

Treatment compliance

Treatment compliance was evaluated at each study visit during the treatment period, based on the patient diary and completion and review of the dosing log and drug accountability records.

Safety endpoints

Safety endpoints included among other endpoints, the incidence of adverse events, local tolerability, immunogenicity, and IGF-I levels. The safety endpoints are described in more detail in the safety section of this assessment report.

Statistical and analytical plan

As this was an exploratory study, with safety as the primary endpoint, no hypothesis tests were performed to assess the efficacy of the investigational product. Efficacy analysis was performed (and tabulated) on both the FAS and the PP analysis set.

ANCOVA tables were generated for different endpoints, including annualized height velocity and the change in the height standard deviation scores, estimating least-square means (and 95% confidence intervals [CIs]) of the endpoint based on Week 13 and 27 data for each cohort, accounting for the cohort effect, gender, baseline value of the variable, age (in years) and peak GH level category.

Other descriptive statistics (n, mean, SD, median, min, max) were calculated for the cohorts by visit and time point for the other efficacy endpoints (summarized, by gender and by age group).

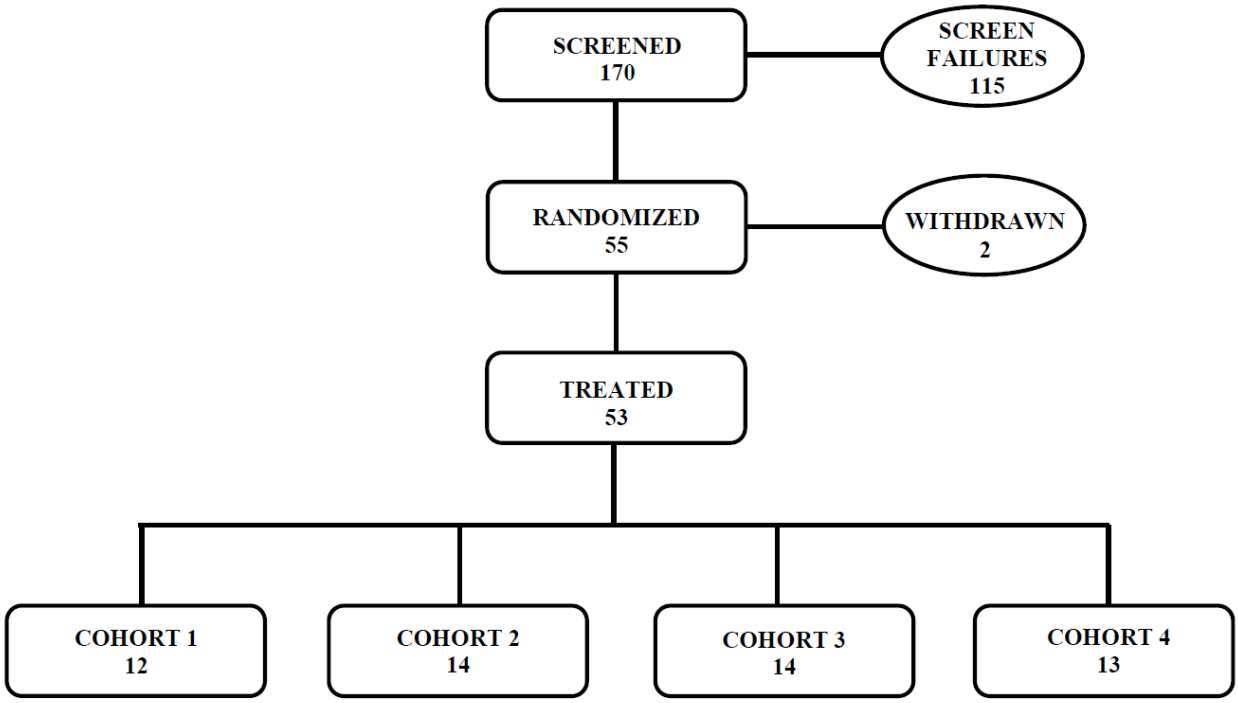
Disposition of study patients

In total, 170 patients with growth hormone deficiency were screened for inclusion at 38 centres (Figure 11). 55 Study patients were randomized.

One hundred and fifteen (115) patients were considered as screen failures. The most common reasons for discontinuation of the screening phase (~68%) were failure to comply with at least inclusion criteria numbers 2 (IGF-I SDS > -1 SD) or 6 (GH stimulation test peak(s) > 10 ng/mL).

Two study patients discontinued the study after screening, but prior to the administration of study treatment. The reason for discontinuation for both study patients was withdrawal of consent by the subject or parent(s)/legal guardian(s). These 2 study patients were not included in SAS, FAS or PP analysis set.

Figure 11 Subject disposition



Baseline data

A total of 55 study patients were randomized at 20 centres in 10 countries located in Europe and North Africa.

The demographics and baseline data of included patients are presented in Table 14. Mean age in cohorts 1 up 4 was 8.0, 8.2, 7.3, and 7.5 years respectively. The majority of study patients (i.e. > 64%) was older than 6 years of age. Most included study patients were men (≥ 64%). Mean IGF-I SDS levels were below -2.00 in all cohorts. Average height velocity was 3.36, 3.13, 3.52, and 3.86 cm/year in respectively cohort 1, 2, 3, and 4. In about half of the study population, the mean peak growth hormone concentration was > 5 ng/ml.

In the SAS, FAS and PP populations, a total of 7 study patients (13.2%) had thyroid axis deficiency of pituitary origin (i.e. 2, 0, 4 and 1 subject in Cohorts 1, 2, 3 and 4, respectively). None of the other types of pituitary axis deficiencies screened for (i.e. ADH insufficiency, adrenal axis deficiency and gonadal axis deficiency of pituitary origin) were documented among the study patients.

Table 14 CT-004 demographic and baseline characteristics (Full Analysis Set)

Characteristic	ACP-001 dose			Cohort 4 somatropin 0.21 mg hGH/kg/week (N = 13)[a]	Total (N = 53)
	Cohort 1 0.14 mg hGH/kg/week (N = 12)	Cohort 2 0.21 mg hGH/kg/week (N = 14)	Cohort 3 0.30 mg hGH/kg/week (N = 14)		
Age (years), mean (SD)	8.0 (2.9)	8.2 (2.1)	7.3 (2.8)	7.5 (2.5)	7.8 (2.5)
Age (years), range	3.2-11.4	5.0-10.8	3.7-11.9	3.2-11.0	3.2-11.9
≤6 years, n (%)	4 (33.3)	3 (21.4)	5 (35.7)	4 (30.8)	16 (30.2)
>6 years, n (%)	8 (66.7)	11 (78.6)	9 (64.3)	9 (69.2)	37 (69.8)
Male sex, n (%)	9 (75.0)	10 (71.4)	9 (64.3)	10 (76.9)	38 (71.7)
White race, n (%)	12 (100)	14 (100)	14 (100)	13 (100)	53 (100)
IGF-I SDS, mean (SD)	−2.03 (0.74)	−2.02 (0.77)	−2.19 (0.72)	−2.50 (0.89)	NR
AHV (cm/year), mean (SD)	3.36 (1.38)	3.13 (0.97)	3.52 (1.08)	3.86 (1.23)	NR
Height SDS, mean (SD)	−3.05 (1.13)	−2.75 (0.38)	−3.17 (1.04)	−3.27 (1.08)	NR
Peak GH concentration (ng/mL), mean (SD) [range]	5.1 (3.2) [0.2, 9.7]	5.2 (2.6) [1.2, 8.5]	4.4 (2.8) [0.4, 8.8]	5.2 (3.1) 0.8, 9.5]	5.0 (2.8) 0.2, 9.7]
≤5 ng/mL, n (%)	5 (41.7)	7 (50.0)	7 (50.0)	5 (38.5)	24 (45.3)
>5 ng/mL, n (%)	7 (58.3)	7 (50.0)	7 (50.0)	8 (61.5)	29 (54.7)
Weight-based dose change at visit 3, n (%)	10 (83.3)	13 (92.9)	12 (85.7)	4 (30.8)	39 (73.4)
Dose (mg) planned for use, mean (range)	76.5 (45.9 – 104.8)	110.2 (73.0 – 155.7)	153.0 (95.2 – 248.3)	107.2 (54.6 – 172.2)	N/A
Dose (mg) used, mean (range)	76.4 (45.9 – 104.4)	110.2 (73.8 – 155.7)	153.2 (95.2 – 248.3)	107.4 (54.6 – 171.2)	N/A
Compliance (%), mean	99.97	100.11	100.11	100.29	N/A

[a]somatropin daily dose of 0.03 mg hGH/kg/day is equivalent to 0.21 mg hGH/kg/week.

Source: CT-004 CSR Dem_T4, Table 14.1.4; Dem_T11, Table 14.1.10; Eff_T17, Table 14.2.1.21; Eff_T42, Table 14.2.2.37; and Eff_L2, Table 16.2.6.2

Abbreviations: ACP-001 = lonapegsomatropin; hGH = human growth hormone; NR = not reported; SD = standard deviation

Growth evaluation

Across ACP-001 dose groups, a dose-dependent response at week 27 was observed for the annualized height velocity (12.0 to 13.58 cm/year) and change from baseline in height SDS (0.69 to 0.84). Importantly, the annualized height velocity was numerically higher for ACP-001 0.21 mg human growth hormone/kg/week compared with somatropin 0.21 mg human growth hormone /kg/week, 13.46 cm/year vs 11.67 cm/year,

respectively. The difference in LS mean concerning this parameter for these treatments was, however, not statistically significant.

At week 27, the result for change from baseline in height SDS similarly demonstrated numerically higher values for equivalent weekly doses of ACP-001 compared to somatropin (0.79 vs 0.61, respectively). The difference in LS mean concerning this parameter for these treatments was, however, not statistically significant.

Table 15 CT-004 annualized height velocity (cm/year) by visit (ANCOVA model, Full Analysis Set)

Visit Statistic	**ACP-001 0.14 mg hGH /kg/week (N=12)**	**ACP-001 0.21 mg hGH/kg/week (N=14)**	**ACP-001 0.30 mg hGH/kg/week (N=14)**	**Somatropin 0.21 mg hGH/kg/week (N=13)**
Baseline				
Mean (SD)	3.36 (1.38)	3.13 (0.97)	3.52 (1.08)	3.86 (1.23)
Week 13				
Mean (SD)	14.96 (7.0)	14.20 (5.6)	14.24 (5.3)	12.93 (6.4)
Range	5.97 – 31.85	6.08 – 31.11	7.50 – 25.38	6.62 – 29.55
LS Mean (SE) [95% CI]	15.24 (1.86) [11.49, 19.00]	14.70 (1.70) [11.28, 18.13]	14.12 (1.70) [10.70, 17.53]	12.95 (1.85) [9.23, 16.68]
Difference in LS Mean (SE)[a] [95% CI]	2.29 (2.50) [−2.74, 7.32]	1.75 (2.45) [−3.19, 6.69]	1.16 (2.41) [−3.69, 6.01]	—
P-value	0.3637	0.4784	0.6314	—
Week 27				
Mean (SD)	11.93 (4.1)	12.89 (3.5)	13.85 (4.0)	11.64 (3.6)
Range	6.42 – 18.97	8.62 – 20.98	6.82 – 22.00	6.22 – 19.25
LS Mean (SE) [95% CI]	12.00 (1.05) [9.88, 14.11]	13.46 (0.96) [11.53, 15.39]	13.58 (0.96) [11.66, 15.50]	11.67 (1.04) [9.57, 13.77]
Difference in LS Mean (SE)[a] [95% CI]	0.33 (1.41) [−2.50, 3.16]	1.79 (1.38) [−0.99, 4.57]	1.91 (1.36) [−0.82, 4.64]	—
P-value	0.8163	0.2014	0.1658	—

[a]Difference in LS Mean was calculated as ACP-001 − somatropin.
Source: CT-004 CSR Table 14.2.1.1.1
Abbreviations: AHV = annualized height velocity; ANCOVA = analysis of covariance; CI = confidence interval; hGH = human growth hormone; LS = least square; SD= standard deviation; SDS = standard deviation score; SE = standard error
Note: An ANCOVA model with by-visit AHV as the dependent variable, cohort and gender as factors, age, baseline peak growth hormone level (log transformed), and baseline height SDS as covariates was fitted.

Table 16 CT-004 Change from baseline in height SDS (ANCOVA Model, Full Analysis Set)

Visit Statistic	**ACP-001 0.14 mg hGH/kg/week (N=12)**	**ACP-001 0.21 mg hGH/kg/week (N=14)**	**ACP-001 0.30 mg hGH/kg/week (N=14)**	**Somatropin 0.21 mg hGH/kg/week (N=13)**
Height SDS at baseline				
Mean (SD)	-3.05 (1.1)	-2.75 (0.4)	-3.17 (1.0)	-3.27 (1.1)
Range	-6.12; -1.85	-3.45; -2.25	-5.59; -1.86	-5.39; -2.24
Change in height SDS compared to baseline				
Week 13				
LS Mean (SE) [95% CI]	0.47 (0.08) [0.32, 0.62]	0.43 (0.07) [0.29, 0.56]	0.41 (0.07) [0.27, 0.55]	0.35 (0.07) [0.20, 0.50]
Difference in LS Mean (SE)[a] [95% CI]	0.13 (0.10) [−0.08, 0.33]	0.08 (0.10) [−0.12, 0.28]	0.06 (0.10) [−0.13, 0.26]	—
P-value	0.2134	0.4208	0.5139	—
Week 27				
Mean (SD)	0.68 (0.5)	0.70 (0.3)	0.88 (0.5)	0.62 (0.4)
Range	0.14; 1.78	0.35; 1.22	0.12; 2.04	0.14; 1.39
LS Mean (SE) [95% CI]	0.69 (0.10) [0.50, 0.88]	0.79 (0.09) [0.62, 0.97]	0.84 (0.09) [0.66, 1.01]	0.61 (0.10) [0.42, 0.80]

Visit Statistic	**ACP-001 0.14 mg hGH/kg/week (N=12)**	**ACP-001 0.21 mg hGH/kg/week (N=14)**	**ACP-001 0.30 mg hGH/kg/week (N=14)**	**Somatropin 0.21 mg hGH/kg/week (N=13)**
Height SDS at baseline				
Mean (SD)	-3.05 (1.1)	-2.75 (0.4)	-3.17 (1.0)	-3.27 (1.1)
Range	-6.12; -1.85	-3.45; -2.25	-5.59; -1.86	-5.39; -2.24
Difference in LS Mean (SE) [a] [95% CI]	0.08 (0.13) [−0.18, 0.34]	0.18 (0.13) [−0.07, 0.43]	0.23 (0.12) [−0.02, 0.48]	—
P-value	0.5278	0.1538	0.0698	—

[a] Difference in LS Mean was calculated as ACP-001 − somatropin.
Source: CT-004 CSR Table 14.2.1.27.2
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; hGH = human growth hormone; LS = least square; SDS = standard deviation score; SE = standard error
Note: An ANCOVA model with by-visit delta height SDS as dependent variable, cohort and gender as factors, age, baseline peak growth hormone level (log transformed), and baseline height SDS as covariates was used.

IGF-I SDS levels

Descriptive statistics for absolute baseline-corrected IGF-I SDS by treatment arm, based on absolute baseline-corrected IGF-I trough levels, are presented in Table 17. Overall, IGF-I SDS levels tended to increase during follow-up.

Table 17 IGF-I SDS levels

	Characteristic	**ACP-001 dose**			**Cohort 4 somatropin 0.21 mg hGH/kg/week (N = 13)[a]**
		Cohort 1 0.14 mg hGH/kg/week (N = 12)	**Cohort 2 0.21 mg hGH/kg/week (N = 14)**	**Cohort 3 0.30 mg hGH/kg/week (N = 14)**	
IGF-SDS levels	Baseline Week 13 Week 27	-2.03 -1.61 -1.56	-2.02 -0.70 -0.94	-2.19 0.02 0.02	-2.50 -1.54 -1.16
IGF-I SDS levels in the range -2 up to +2	Baseline Week 27	58.3% 81.8%	50.0% 85.7%	46.2% 100%	23.1% 76.9%
IGF-I SDS levels in the range 0 up to +2	Baseline Week 27	0% 0%	0% 21.4%	0% 38.5%	0% 15.4%

2.6.5.2. Main study

Study CT-301 (heiGHt study)

Study CT-301 was a randomized, open-label Phase 3 clinical study evaluating once-weekly lonapegsomatropin as compared to somatropin product Genotropin administered daily over a period of 52 weeks.

Paediatric patients with growth hormone deficiency in the age range 3-12 years were included. The study consisted of a screening period of up to 6 weeks (plus a recommended period of up to 2 weeks between randomization and visit 1).

Study patients who successfully completed the study were eligible to participate in extension study CT-301EXT (see below).

Methods

- **Study Participants**

Treatment-naïve, pre-pubertal paediatric GHD patients were included. The diagnosis of GHD was confirmed by 2 different growth hormone stimulation tests, defined as a peak GH level of ≤10 ng/mL, determined with a validated assay (GH Research Society, 2000).

Additional criteria for enrolment were height SDS ≤−2.0, IGF-I SDS ≤−1.0, and delayed bone age (≥6 months relative to chronological age). Subjects born small for gestational age, with idiopathic short stature, or with other causes of short stature were excluded.

- **Treatments**

An identical total dose of 0.24 mg human growth hormone/kg/week was used for once-weekly lonapegsomatropin and daily somatropin product Genotropin. Both study treatments were administered via a vial and syringe/needle.

Table 18 shows the dose volumes of lonapegsomatropin to be used for each weight range, both when only the 12.1 mg growth hormone/vial (11.0 mg/ml when reconstituted) was available early in the Phase 3 study, and the dose volumes that were used when both the 12.1 and 24.2 mg growth hormone/vials (11.0 and 22.0 mg/ml when reconstituted, respectively) were available. All of these dose volumes provided an average dose of 0.24 ± 0.02 mg growth hormone/kg/week within each weight range.

Table 18 Drug concentration after reconstitution with 1 ml water for injection, dosing brackets, and volumes to be administered

Only 12.1 mg hGH/ vial available			12.1 mg hGH/vial and 24.2 mg hGH/ vial available		
Drug Concentration in Vial	Subject Weight Range (kg)	Volume Dosed (mL)	Drug Concentration in Vial	Subject Weight Range (kg)	Volume Dosed (mL)
11.0 mg hGH/mL	11.5-13.9	0.27	11.0 mg hGH/mL	11.5-13.9	0.27
11.0 mg hGH/mL	14.0-16.4	0.33	11.0 mg hGH/mL	14.0-16.4	0.33
11.0 mg hGH/mL	16.5-19.9	0.39	11.0 mg hGH/mL	16.5-19.9	0.39
11.0 mg hGH/mL	20.0-23.9	0.47	11.0 mg hGH/mL	20.0-23.9	0.47
11.0 mg hGH/mL	24.0-28.9	0.57	22.0 mg hGH/mL	24.0-28.9	0.29
11.0 mg hGH/mL	29.0-34.9	0.69	22.0 mg hGH/mL	29.0-34.9	0.35
11.0 mg hGH/mL	35.0-41.9	0.83	22.0 mg hGH/mL	35.0-41.9	0.41
11.0 mg hGH/mL	42.0-50.9	0.50 x 2	22.0 mg hGH/mL	42.0-50.9	0.50
11.0 mg hGH/mL	51.0-60.5	0.60 + 0.61	22.0 mg hGH/mL	51.0-60.5	0.60

Somatropin product Genotropin was supplied as a lyophilized powder, dispensed in a 2-chamber cartridge. Genotropin was administered as a daily SC injection in a standard dose of 0.24 mg hGH/kg/week. The total weekly dose was equally split into 7 daily doses of 0.034 mg hGH/kg/day.

Dose adjustment

Treatment could be discontinued or dose-modified at any time during the trial. The following symptoms and laboratory abnormalities were considered to be the main guide for decision making concerning treatment discontinuation or dose modification:

• IGF-I levels: For daily somatropin dosed in the evening, the morning IGF-I value on any visit day (including visit 6) represents the $E_{average}$, whereas for lonapegsomatropin, the values measured 48-72 h post-dose at

visits 3 up to 5 represent at or close to E_{max} for IGF-I, whereas the IGF-I value at visit 6 (7-days post-dose) represents the E_{trough}.

IGF-I >+2.0 SDS at any visit was to be confirmed by a second measurement as soon as possible if deemed to be clinically significant by the investigator. Follow-up blood samples were to be collected 5-7 days post-dose in the lonapegsomatropin treatment arm, or at any day in the somatropin treatment arm.

If the IGF-I SDS was still elevated above +2.0 and of clinical concern, the dose could be decreased to the next lower dose bracket for lonapegsomatropin or a 20% decrease in dose (initially to 0.19 mg/kg/week) for subjects on somatropin. Any re-establishment of the original dose (0.24 mg/kg/week) due to a subsequent sub-optimal IGF-I response needed to be discussed with the medical monitor.

• Glucose parameters

• HbA1c >6.2%

• Fasting glucose level >5.5 mmol/l (100 mg/dl)

• 2-h post-dose glucose level during oral glucose tolerance test (OGTT) ≥7.8 mmol/l

For a subject who had evidence of borderline glucose intolerance or diabetes prior to starting growth hormone treatment (e.g., fasting plasma glucose (FPG) ≥98 mg/dL and/or HbA1c ≥5.9%), it might have been appropriate to treat for hyperglycaemia as needed, without initial trial drug treatment adjustment.

However, if a subject with no evidence of glucose intolerance reached the above glucose parameter levels, the FPG and HbA1c were to be repeated within 2 to 4 weeks. If the repeat values were the same or worse, the lonapegsomatropin dose could be decreased to the next lower dose bracket (~20%) and the dose could be reduced by ~20% for a subject on somatropin (e.g., to 0.19 mg/kg/week or 0.027 mg/kg/day) or appropriate anti-glycaemic therapy(ies) could be started. If appropriate follow-up monitoring showed progressively worsening glucose intolerance, additional dose adjustments could be appropriate. If in any case treatment was to be discontinued, all subsequent visits and assessments were to continue as planned.

If a subject developed any of the above listed criteria or developed a severe growth hormone-related adverse event at any time during the course of the study (e.g., peripheral oedema, severe headache, intracranial hypertension, or other adverse drug reaction and/or abnormal laboratory values), the investigator or medical monitor/sponsor (and independent safety committee if needed) could propose a dose modification.

- **Objectives**

Primary objective

The primary objective was to evaluate and compare the annualized height velocity (AHV) for once-weekly lonapegsomatropin compared to the commercially available daily human growth hormone formulation at 52 weeks.

Secondary objectives

Secondary efficacy objectives were to evaluate and compare the annualized height velocity and change in height standard deviation score (SDS) of once-weekly lonapegsomatropin to daily human growth hormone over 52 weeks.

An additional secondary objective was to evaluate IGF-I, insulin-like growth factor binding protein 3 (IGFBP-3), IGF-I SDS, and IGFBP-3 SDS, and the normalization of IGF-I SDS over 52 weeks of weekly lonapegsomatropin or daily somatropin therapy.

- **Outcomes/endpoints**

Primary efficacy endpoint

• Annualized height velocity at 52 weeks for weekly lonapegsomatropin and daily somatropin treatment groups

Secondary efficacy endpoints

• Annualized height velocity for the weekly lonapegsomatropin and the daily somatropin treatment groups over 52 weeks

• Change in height SDS over 52 weeks for the weekly lonapegsomatropin and the daily hGH treatment groups

• Serum IGF-I and IGFBP-3 levels and IGF-I SDS and IGFBP-3 SDS; and the normalization of IGF-I SDS over 52 weeks for the weekly lonapegsomatropin and the daily somatropin treatment groups

- **Sample size**

Approximately 150 prepubertal, hGH-treatment naïve children (males and females) with growth hormone deficiency were included. Subjects were allocated to 1 of 2 treatment groups in a 2:1 ratio. Two thirds of the 150 subjects (approximately 100 subjects) received lonapegsomatropin treatment to obtain an expected 90 per protocol subjects in this cohort. One third of the 150 study patients (approximately 50 subjects) received somatropin treatment to obtain an expected 45 per protocol study patients in this cohort.

In EMA scientific advice EMA/CHMP/SAWP/588843/2016 the CHMP indicated that a non-inferiority margin of 1.8 cm/year had been accepted previously for a long-term growth hormone. The CHMP concluded that a non-inferiority margin of 2.0 cm/year might be acceptable provided that the applicant would include an extensive justification for the chosen non-inferiority margin and its clinical relevance. A similar conclusion was drawn in EMA scientific advice EMA/CHMP/SAWP/711581/2017. A substantiation about the appropriateness of the non-inferiority margin is however no longer relevant, since the annualized height velocity at week 52 of lonapegsomatropin was superior to that of somatropin (see below).

- **Randomisation and Blinding (masking)**

Randomisation

The study patients included were centrally allocated to 1 of 2 cohorts: either lonapegsomatropin or somatropin, in a 2:1 ratio. Dynamic allocation was used, with a complete randomization probability of 15%.

Study patients were stratified using the minimization rule according to their age (≤6 and >6 years), peak growth hormone levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender. All strata were assigned equal weights.

Blinding

Due to different administration frequencies for the treatment arms (lonapegsomatropin administered once-weekly versus somatropin administered daily), the study was conducted in an open-label manner with procedures in place to keep selected sponsor staff (including the clinical and biometrics teams) blinded to treatment assignment during the study, and before finalization of the statistical analysis plan (SAP, Amendment 5, dated 19Feb2019). Study auxologists were kept blinded to treatment allocation as far as possible at sites.

- **Statistical methods**

Analysis of primary endpoint
The primary endpoint, annualized height velocity at week 52, was compared between lonapegsomatropin and daily somatropin by a non-inferiority comparison with a non-inferiority margin of 2.0 cm/year, followed by a test of superiority if non-inferiority was established.

An ANCOVA model was used to analyse annualized height velocity at week 52, after multiple imputation of missing data. The annualized height velocity at week 52 was included in the model as a response variable. The model included baseline age, peak growth hormone levels (log-transformed) at stimulation test, baseline height SDS – average SDS of parental height as covariates and treatment and gender as factors.

In case the result for the primary endpoint was missing, height values were imputed using a multiple imputation model that contained the following variables: gender, baseline age, peak growth hormone levels (log-transformed) at stimulation test, baseline height SDS – average SDS of parental height, and height values at post-baseline visits. The multiple imputation was stratified by treatment. The estimates from the 100 fitted models for each of the 100 imputed datasets were combined to provide an overall estimate of the between treatment group difference with a corresponding confidence interval and a p-value.

For the primary efficacy analysis, a 2-sided 95% confidence interval was calculated for the difference in least-square means between the 2 treatment groups [lonapegsomatropin minus somatropin] at week 52. If the lower confidence bound was >-2.0 cm, non-inferiority was demonstrated in terms of effectiveness. If the lower confidence bound was >0, superiority was established.

Average IGF-I values were derived for lonapegsomatropin based on population pharmacodynamic (PD) modelling.

Treatment-by-covariate interactions were examined as appropriate as part of the analysis model examination. Height velocities at other post-baseline visits were analysed similarly using the same ANCOVA model as described above for the primary efficacy analysis. The same ANCOVA model described above was also used to analyse observed cases as a sensitivity analysis of the primary analysis.

Populations analysed

Given that the primary objective of the study was based on testing for non-inferiority, the primary efficacy analyses was performed on both (intention-to-treat) ITT and (per-protocol) PP populations. The primary analysis population was the ITT population. The ITT population was analysed on the basis of the intention to treat a subject, i.e. the planned treatment regimen. The PP subset was analysed on the basis of the actual treatment given. Because the PP population excludes subjects who have missing data at week 52, the multiple imputation method described above was not used for the PP analysis.

Intention-To-Treat Population (ITT): The Intent-to-Treat population included all randomized subjects who have received at least one dose of active treatment.

Per Protocol Population (PP): The basis of PP population is the ITT population who have relevant data evaluable for the primary efficacy endpoint of annualized height velocity at 52 weeks. Specifically, study patients were excluded from the PP population if they: had a diagnosis known to impact growth (exclusion criteria 4, 5, 6, 10, 12, 13); took the wrong treatment (e.g. randomized to TransCon hGH cohort but took Genotropin; in error); missed or overdosed on at least 5 doses of TransCon hGH, or 35 doses of Genotropin; used prohibited concomitant medications at study entry (exclusion criteria 15, 16); failed to have a height measurement at the week 52 visit.

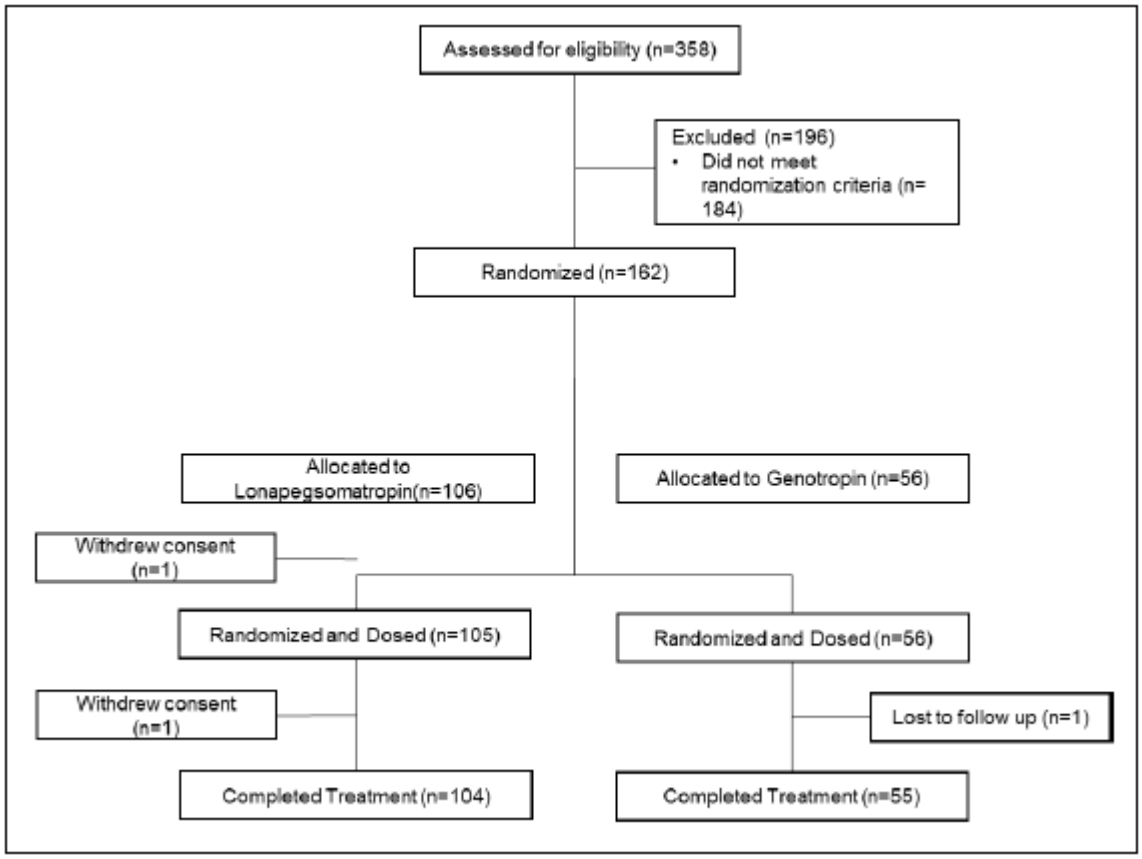
Results

- **Participant flow**

358 Persons were screened for eligibility for study participation. 196 Persons were excluded prior to randomization. The majority of these persons (184/196 (93.9%)) did not meet the randomization criteria.

A total of 162 subjects were randomized 2:1 to lonapegsomatropin (N = 106) or somatropin (N = 56) (Figure 12). Among randomized study patients, 161 (99.4%) were dosed with study treatment. 159 of 161 study patients (98.8%) completed the study. Two study patients withdrew from the study: one study patient from the lonapegsomatropin arm withdrew consent, and another study patient from the somatropin arm was lost to follow-up. The particular reasons for withdrawal of consent were not reported.

Figure 12 Participant flow study CT-301



Eighteen major protocol deviations were reported.

- **Recruitment**

The first subject was screened on 15 November 2016. The last subject completed study CT-301 on 17 January 2019.

- **Conduct of the study**

There were no changes in the planned analyses. The following *ad-hoc* analyses have been conducted:

- By visit analysis of change from baseline in height SDS by ANCOVA models to account for by visit difference in covariate effect.
- ANCOVA analysis of change from baseline in QTcF at Week 26 and QTcF summary by baseline QTcF subgroups to adjust for baseline difference in QTcF analysis.
- Subgroup analysis by US vs non-US to assess treatment effect by region.
- Logistic regression to analyse the ratio of subjects with annualized height velocity <8 cm/year at week 52 to evaluate subjects with a reduced treatment response in growth.
- Summarize the change from baseline in average IGF-I SDS for subjects with annualized height velocity <8 cm/year and ≥8 cm/year to evaluate potential causes for a reduced treatment response in growth.
- To assess treatment-emergent adverse events that are essentially the same but coded under different preferred terms, summary of treatment-emergent adverse events by combined term (aggregate preferred term groupings into combined terms based on clinical judgement) and preferred term was performed.
- Anti-lonapegsomatropin antibodies were tested post database lock and summaries were provided.

- **Baseline data**

Overall, the demographics and baseline data between the treatment groups were balanced (Table 19).

Study patients between 3.2 and 13.1 years of age were enrolled in the study. The mean age in each treatment group was similar (8.5 years in the lonapegsomatropin group vs 8.5 years in the somatropin group), with a similar proportion of study patients <6 years in each treatment group (23.8% vs 25.0%, respectively). More male than female study patients were enrolled (82.0% versus 18.0%).

At baseline, study patients had diminished growth with a mean height velocity of 3.93 cm/year and a mean height SDS of -2.93. The mean average-parental height SDS was −0.52 (0.78). At baseline, bone age was delayed by an average of 2.42 years relative to chronological age. The majority of study patients (65.2%) had isolated, idiopathic aetiology of growth hormone deficiency. Equal proportions of study patients had isolated, organic aetiology of growth hormone deficiency (17.4%) and multiple pituitary hormone deficiencies (17.4%).

Medical history and prior medication

Overall, the medical history and type and frequency of prior treatments were balanced across treatment groups.

Concomitant treatments

Overall, the type and frequency of concomitant treatments, including hormone replacement therapies for thyroid and adrenal deficiencies were balanced across treatment groups.

Table 19 CT-301 Key demographic and baseline characteristics (ITT population)

Characteristic	Lonapegsomatropin (N = 105)	Somatropin (N = 56)	Total (N = 161)
Age (years)			
Mean (SD) [range]	8.5 (2.7) [3.3, 13.1]	8.5 (2.8) [3.2, 12.9]	8.5 (2.7) [3.2, 13.1]
<6 years, n (%)	25 (23.8)	14 (25.0)	39 (24.2)
⩾6 years, n (%)	80 (76.2)	42 (75.0)	122 (75.8)
Male, n (%)	86 (81.9)	46 (82.1)	132 (82.0)
White race, n (%)	100 (95.2)	52 (92.9)	152 (94.4)
Region, n (%)			
North America	27 (25.7)	15 (26.8)	42 (26.1)
Europe	66 (62.9)	31 (55.4)	97 (60.2)
Middle-East and North Africa	6 (5.7)	8 (14.3)	14 (8.7)
Oceania	6 (5.7)	2 (3.6)	8 (5.0)
Height (cm), mean (SD)	112.9 (14.1)	112.2 (15.3)	112.7 (14.5)
Height SDS, mean (SD)	−2.89 (0.85)	−3.00 (0.90)	−2.93 (0.87)
Data available for HV at baseline (Visit 1), n	94	54	148
Baseline HV (cm/year), mean (SD)	3.93 (2.04)	3.93 (1.66)	3.93 (1.91)
Data available for parental height, n	103	56	159
Average-parental height SDS, mean (SD)[a]	−0.56 (0.77)	−0.44 (0.79)	−0.52 (0.78)
Delta average-parental height SDS, mean (SD)[b]	−2.32 (1.14)	−2.55 (1.27)	−2.40 (1.19)
BMI (kg/m^2)	16.1 (1.8)	16.5 (2.2)	16.2 (1.9)
BMI SDS, mean (SD)	−0.3 (1.0)	−0.1 (1.1)	−0.3 (1.0)
Bone age (years), mean (SD)	5.8 (2.6)	6.0 (2.7)	5.9 (2.6)
Delay in bone age (years), mean (SD)	2.5 (1.3)	2.3 (1.1)	2.4 (1.2)
Etiology/extent/associations of GHD, n (%)			
Isolated idiopathic	68 (64.8)	37 (66.1)	105 (65.2)
Isolated organic	19 (18.1)	9 (16.1)	28 (17.4)
Multiple pituitary hormone deficiencies	18 (17.1)	10 (17.9)	28 (17.4)
IGF-I SDS, mean (SD)	−2.08 (0.88)	−1.96 (0.98)	−2.04 (0.92)
Peak stimulated GH concentration			
Mean (SD), ng/mL	5.89 (2.78)	5.48 (2.97)	5.75 (2.85)
≤5 ng/mL, n (%)	37 (35.2)	21 (37.5)	58 (36.0)
>5 to ≤10 ng/mL, n (%)	68 (64.8)	35 (62.5)	103 (64.0)

[a] Average-parental height SDS = (height SDS_{mother} + height SDS_{father})/2

[b] Delta average-parental height SDS = (height $SDS_{subject}$ − average-parental height SDS)

Source: CT-301 CSR Table 14.1.3.1.1

Abbreviations: BMI = body mass index; GH = growth hormone; GHD = growth hormone deficiency; HV = height velocity; ITT = intention-to-treat; SD = standard deviation; SDS = standard deviation score; US = United States

Note: Age was the age at Visit 1.

Compliance

The compliance was between >95% and ≤100% for nearly all subjects (lonapegsomatropin: 104 subjects [99.0%], somatropin: 53 subjects [94.6%]).

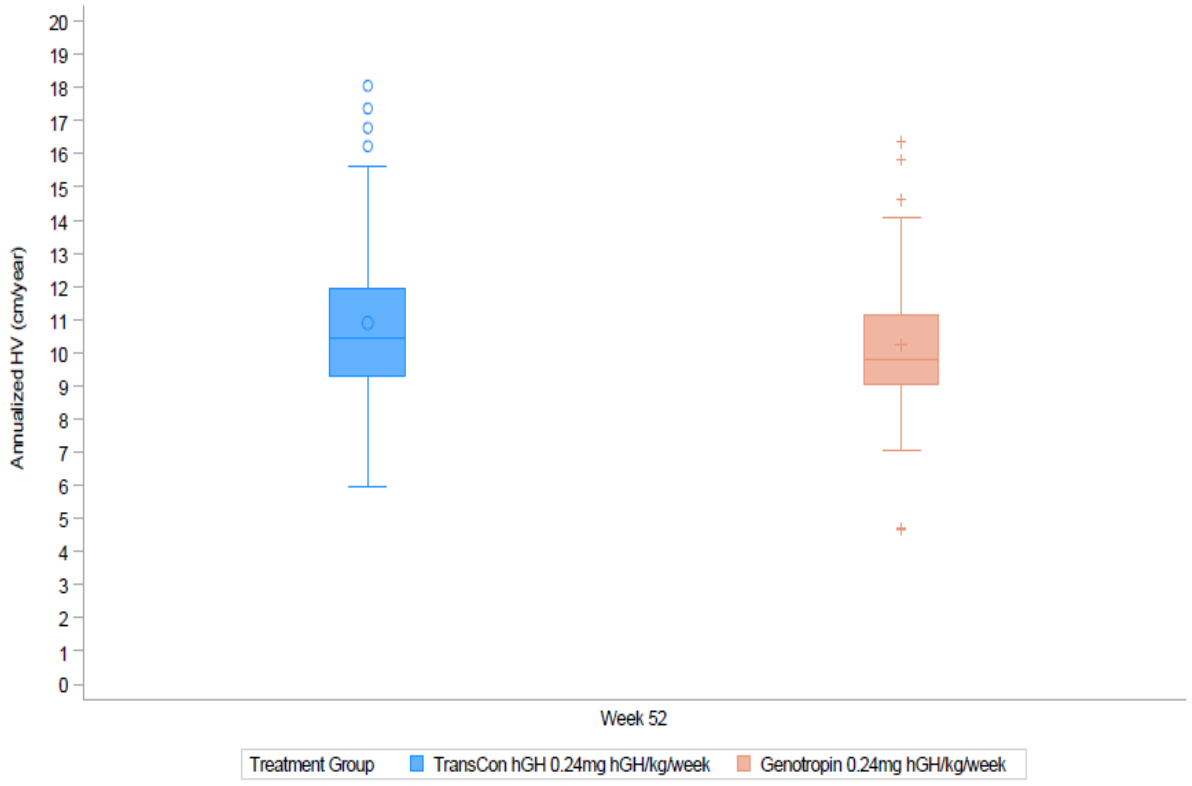
- **Numbers analysed**

Overall, 161 subjects were randomized and received at least one dose of study treatment and were included in the safety and ITT populations. 159 of 161 randomized subjects (98.1%) had relevant data evaluable for the primary efficacy endpoint at 52 weeks and were included in the PP population.

- **Outcomes and estimation**

Primary efficacy endpoint: annualized height velocity at week 52
For observed cases, for lonapegsomatropin, the mean (SD) annualized height velocity at week 52 was 10.90 (2.29) cm/year, and for somatropin, the mean (SD) annualized height velocity was 10.22 (2.37) cm/year (Figure 13). Consistent results were seen in the analyses of the per-protocol set.

Figure 13 Distribution of annualized height velocity at week 52 for weekly lonapegsomatropin and daily somatropin treatment (observed cases ITT population)



Source: Figure 14.4.2

The LS mean (SE) of annualized height velocity at week 52 was 11.17 (0.23) cm/year for lonapegsomatropin compared with 10.31 (0.30) cm/year for somatropin, with a difference in LS means (SE) of 0.86 (0.33) cm/year (95% CI: 0.22 to 1.50) (Table 20). The treatment difference was statistically significant in favour of lonapegsomatropin (P = 0.0088).

Since the lower confidence bound was above the non-inferiority margin of -2.0 cm/year, non-inferiority was demonstrated.

Table 20 Primary efficacy endpoint – annualized height velocity (cm/year) at week 52 based on primary ANCOVA model with multiple imputation (ITT Population)

Summary Statistic	Lonapegsomatropin (N=105)	Somatropin (N=56)	Estimate of Difference (lonapegsomatropin - somatropin)	P Value
LS Mean (SE) [95% CI]	11.17 (0.23) [10.71, 11.62]	10.31 (0.30) [9.73, 10.89]	0.86 (0.33) [0.22, 1.50]	0.0088

Note: Missing data were imputed with multiple imputation method with 100 simulated datasets. For each imputed data set, an ANCOVA model with by visit annualized height velocity as the dependent variable, treatment and gender as factors, baseline age, baseline peak growth hormone levels (log transformed) at stimulation test, and baseline height SDS - average parental height SDS as covariates were fitted. The LS means, CIs, and p-values presented in the table are the overall estimates combined from all the 100 models.

The statistical superiority outcome in week 52 annualized height velocity in study CT-301 for lonapegsomatropin vs somatropin is supported by a larger annualized height velocity for lonapegsomatropin at all visits during the study, with differences from week 26 onwards. Similar results were obtained in sensitivity analyses with different analysis models and missing data handling methods.

Although the superiority of lonapegsomatropin was demonstrated statistically, it was not demonstrated clinically. Indeed, the upper bound of the 95% confidence interval (0.22, 1.50) is inferior to the +2 cm limit of non-inferiority.

The reported annualized height velocities in Table correspond to a mean (SD) height velocity SDS of 5.87 (2.76) for once-weekly lonapegsomatropin and 5.27 (3.01) for somatropin.

CT-301 analysis model examination: ANCOVA model considering treatment and age interaction

Treatment-by-covariate interactions were evaluated for the primary analysis model as part of the analysis model examination. The treatment-by-age interaction was statistically significant (Table 21). Therefore, the interaction term was added to the primary analysis model.

Table 21 Annualized height velocity at week 52: ANCOVA model with multiple imputation, considering treatment and age interaction (ITT population)

Visit Baseline age	Estimate of Difference (lonapegsomatropin – somatropin)		*P* value
	LS mean (SE)	95% CI	
Overall treatment effect (at mean age = 8.5 years)	0.87 (0.32)	0.23, 1.50	0.0073
4 years	2.24 (0.63)	1.01, 3.47	0.0004
5 years	1.94 (0.53)	0.90, 2.97	0.0003
6 years	1.63 (0.44)	0.77, 2.49	0.0002
7 years	1.32 (0.37)	0.60, 2.05	0.0003
8 years	1.02 (0.33)	0.37, 1.66	0.0019
9 years	0.71 (0.33)	0.07, 1.35	0.0301
10 years	0.41 (0.37)	-0.32, 1.13	0.2721
11 years	0.10 (0.44)	-0.76, 0.96	0.8223

Source: Table 14.99.2.1.10

Note: Missing data were imputed with multiple imputation method with 100 simulated datasets. For each imputed data set, an ANCOVA model with by visit AHV as the dependent variable, treatment and gender as factors, baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS – average SDS of parental height as covariates, and interaction term between treatment and baseline age were fitted. The LS means, confidence intervals, and p-values presented in the table are the overall estimates combined from all the 100 models.

Key secondary analyses in study CT-301

Annualized height velocity by study visit

Annualized height velocity by visit using an ANCOVA model is presented in Table 22. Statistical significance was met at week 26 and maintained through the end of the study at week 52.

Table 22 CT-301 Annualized height velocity (cm/year) by visit (ANCOVA model with multiple imputation, ITT population)

Visit	Lonapegsomatropin LS mean (SE) [95% CI] N = 105	Somatropin LS mean (SE) [95% CI] N = 56	Estimate of Difference (lonapegsomatropin – somatropin) LS mean (SE) [95% CI]	P-value
Week 5	13.54 (1.07) [11.41, 15.66]	12.83 (1.37) [10.11, 15.54]	0.71 (1.51) [-2.28, 3.70]	0.6402
Week 13	13.28 (0.49) [12.31, 14.25]	12.22 (0.63) [10.98, 13.47]	1.06 (0.69) [-0.31, 2.42]	0.1286
Week 26	12.65 (0.32) [12.01, 13.28]	11.21 (0.42) [10.40, 12.02]	1.44 (0.46) [0.54, 2.33]	0.0017
Week 39	11.89 (0.26) [11.39, 12.39]	10.90 (0.33) [10.26, 11.54]	0.99 (0.36) [0.28, 1.69]	0.0061
Week 52	11.17 (0.23) [10.71, 11.62]	10.31 (0.30) [9.73, 10.89]	0.86 (0.33) [0.22, 1.50]	0.0088

Source: CT-301 CSR Table 14.2.1.7.1
Abbreviations: AHV = annualized height velocity; ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention-to-treat; LS = least square; SDS = standard deviation score; SE = standard error
Note: Missing data were imputed with multiple imputation method. For each imputed data set, an ANCOVA model with by visit AHV as the dependent variable, treatment and gender as factors, baseline age, baseline peak growth hormone levels (log transformed) at stimulation test, and baseline height SDS – average parental height SDS as covariates were fitted. The LS means, CIs, and p-values presented in the table are the overall estimates combined from all 100 models.

Height SDS

Change from baseline in height SDS by visit using an ANCOVA model is presented in Table 23. The treatment difference favouring once-weekly lonapegsomatropin over daily somatropin continued to increase from week 5 to week 52. The outcomes were comparable to those of annualized height velocity in the study.

Table 23 CT-301 Change from baseline in height SDS by visit (ANCOVA model, ITT Population)

Visit	Lonapegsomatropin LS mean (SE) [95% CI] N = 105	Somatropin LS mean (SE) [95% CI] N = 56	Estimate of difference (lonapegsomatropin – somatropin) LS mean (SE) [95% CI]	P-value
Week 5	0.13 (0.02) [0.10, 0.16]	0.12 (0.02) [0.08, 0.16]	0.01 (0.02) [-0.04, 0.05]	0.7795
Week 13	0.38 (0.02) [0.34, 0.42]	0.33 (0.03) [0.28, 0.38]	0.05 (0.03) [-0.01, 0.10]	0.1078
Week 26	0.68 (0.03) [0.63, 0.74]	0.58 (0.04) [0.51, 0.65]	0.11 (0.04) [0.03, 0.18]	0.0085
Week 39	0.92 (0.03) [0.85, 0.98]	0.80 (0.04) [0.72, 0.88]	0.12 (0.05) [0.03, 0.21]	0.0130
Week 52	1.10 (0.04) [1.02, 1.18]	0.96 (0.05) [0.85, 1.06]	0.14 (0.06) [0.03, 0.26]	0.0149

Source: CT-301 CSR Table 14.99.14.2.2.3.3
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intention-to-treat; LS = least square; SDS = standard deviation score; SE = standard error
Note: This was an *ad hoc* analysis. The ANCOVA model included baseline age, peak growth hormone levels (log transformed) at stimulation test and baseline height SDS as covariates, as well as treatment and gender as factors.

CT-301 average IGF-I SDS

ANCOVA results of average IGF-I SDS by visit are presented in Table 24. As IGF-I levels follow a predictable profile over the course of a week with a peak at approximately post-dose day 2 and return to pre-dose steady-state levels at post-dose day 7, average model-derived IGF-I SDS values are presented for lonapegsomatropin.

In both treatment arms, IGF-I SDS values increased relative to baseline following treatment initiation and increased over time at subsequent visits. Compared to the somatropin arm, the once-weekly lonapegsomatropin arm reached the clinically desirable range of IGF-I SDS 0-2 sooner and stayed within this range, with a higher average observed IGF-I SDS throughout the study, thus paralleling the observed superior growth outcomes.

Average IGF-I SDS levels rarely exceeded 2.0 at any time (7.6% in the once-weekly lonapegsomatropin arm vs. 3.6% in the somatropin arm), and never exceeded 3.0 in either arm.

Table 24 CT-301 average IGF-I SDS by visit (ANCOVA model, ITT population)

Visit	Lonapegsomatropin LS mean (SE) [95% CI] N =105	Somatropin LS mean (SE) [95% CI] N = 56	Estimate of difference (lonapegsomatropin – somatropin) LS mean (SE) [95% CI][a]
Week 13	0.31 (0.09) [0.14, 0.49]	-0.60 (0.11) [-0.82, -0.37]	0.91 (0.12) [0.66, 1.16]
Week 26	0.46 (0.08) [0.30, 0.62]	-0.51 (0.10) [-0.72, -0.31]	0.97 (0.12) [0.75, 1.20]
Week 39	0.59 (0.09) [0.41, 0.77]	-0.30 (0.11) [-0.52, -0.07]	0.89 (0.13) [0.64, 1.14]
Week 52	0.72 (0.09) [0.54, 0.89]	-0.02 (0.12) [-0.25, 0.21]	0.74 (0.13) [0.49, 1.00]

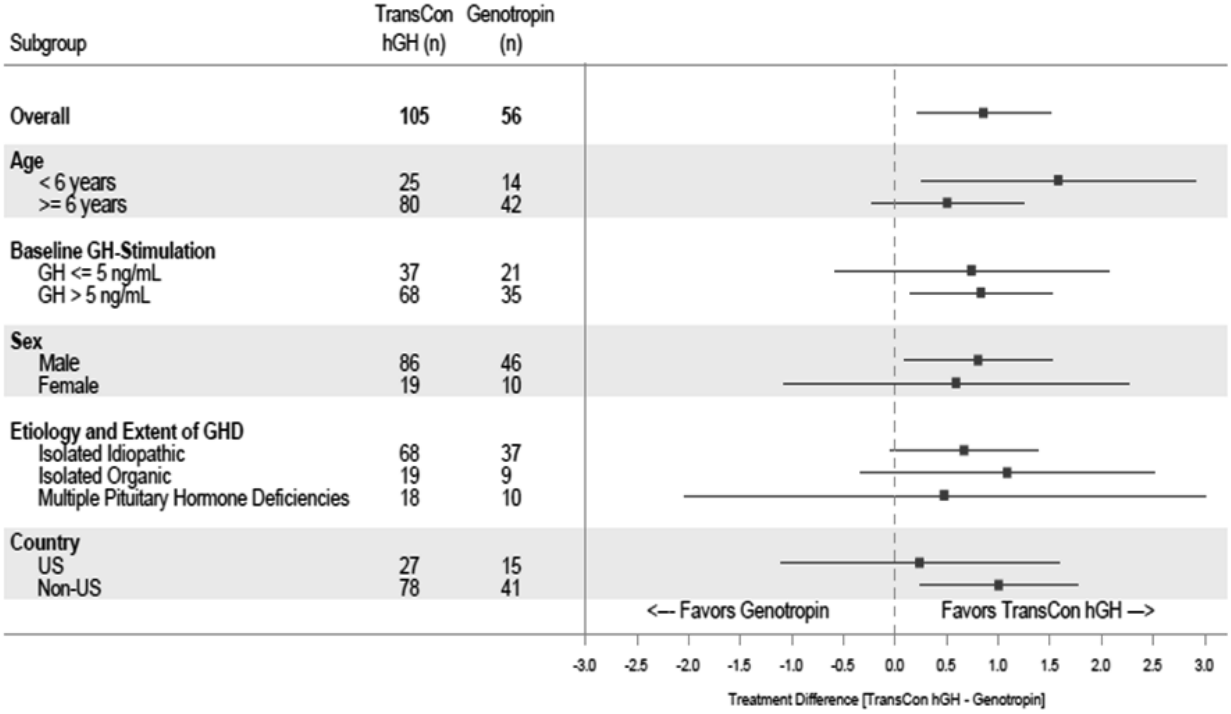
[a] Comparisons of the LS mean (SE) for lonapegsomatropin vs. somatropin had p- values <0.0001 at each visit.
Source: CT-301 CSR Table 14.2.3.16
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; IGF-I = insulin-like growth factor 1; ITT = intention-to-treat; LS = least square; SDS = standard deviation score;
SE = standard error
Note: The ANCOVA model included baseline age, peak growth hormone levels (log transformed) at stimulation test, baseline IGF-I SDS as covariates, treatment and gender as factors. Modelled values begin at Week 13 corresponding with achievement of IGF-I steady-state. Average IGF-I SDS values for lonapegsomatropin were derived from the population pharmacodynamic model as described in CT-301 CSR Appendix 16.1.7. Average IGF-I SDS values for somatropin are based on observed data.

- **Ancillary analyses**

Results from subgroup analyses for annualized height velocity at week 52 are illustrated in Figure 14. In each subgroup analysis, the clinical effects of once-weekly lonapegsomatropin tended to be larger relative to daily somatropin.

A subgroup analysis of the clinical effects with respect to the primary endpoint within countries in the European Union was not available.

Figure 14 CT-301 forest plot of subgroups: annualized height velocity (cm/year) at week 52 (ANCOVA model with multiple imputation, ITT Population)



Source: CT-301 CSR Figure 14.4.57.1
Abbreviations: ANCOVA = analysis of covariance; AHV = annualized height velocity; CI = confidence interval; GH = growth hormone; GHD = growth hormone deficiency; ITT = intention-to-treat; LS = least square; TransCon hGH = lonapegsomatropin; SDS = standard deviation score; US = United States
Note: LS means with 95% CI are shown. Missing data were imputed with a multiple imputation method. For each imputed data set, an ANCOVA model with by visit annualized height velocity as the dependent variable, treatment and gender as factors, baseline age, baseline peak growth hormone levels (log transformed) at stimulation test, and baseline height SDS – average SDS of parental height SDS as covariates are fitted. The LS means and CIs are the overall estimates combined from all 100 models.

Supportive studies CT-302 and CT-301EXT

Supportive studies CT-302 and CT-301EXT are discussed below after the summary of main efficacy results and the description of efficacy pool I and II.

- **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 25 Summary of Efficacy for trial CT-301

Title: **"HeiGHt trial": a multicenter, phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability and efficacy of lonapegsomatropin administered once a week versus standard daily human growth hormone (hGH) replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency**			
Study identifier	2016-001145-11/126053		
Design	Multicenter, phase 3, randomized, open-label, active-controlled, parallel-group trial (lonapegsomatropin versus somatropin) over 52 weeks		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks not applicable Extension data of 26 weeks were provided in the original marketing application (extension study is ongoing)
Hypothesis	Superiority and non-inferiority of lonapegsomatropin versus somatropin		
Treatments groups	Lonapegsomatropin group		**0.24 mg hGH/kg/week (weekly administration)**, 52 weeks, n = 106 randomized but 105 randomized and dosed
	Somatropin group		**0.24 mg hGH/kg/week (daily administration)**, 52 weeks, n = 56 randomized
Endpoints and definitions	Primary endpoint	AHV at W52	Annualized height velocity (cm/year) at week 52
	Key Secondary endpoints	AHV over 52 weeks	AHV over 52 weeks
		Height SDS over 52 weeks	Change in height standard deviation score over 52 weeks
		Average IGF-I SDS over 52 weeks	Average IGF-I SDS over 52 weeks
Database lock	02 May 2019		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	- Intention to treat (ITT) - Per protocol (PP; for evaluation of non-inferiority) **52 weeks**		
Descriptive statistics and estimate variability	Treatment group	**lonapegsomatropin**	**somatropin**
	Number of subjects in intention to treat (ITT) analysis	105	56
	AHV (cm/year) LS mean (ANCOVA model with multiple imputation, ITT) At Week (W) 52	11.17 (0.23)	10.31 (0.30)
	95% CI	[10.71; 11.62]	[9.73; 10.89]
Effect estimate per comparison	**Primary endpoint** AHV (cm/year) LS mean (SE) (ANCOVA model, ITT) At W52	Comparison groups	**lonapegsomatropin group versus somatropin**
		Estimated difference (lonapegsomatropin-somatropin)	0.86 (0.33)
		95% CI	[0.22, 1.50]
		P-value ANCOVA with multiple imputation	0.0088
	Treatment group	lonapegsomatropin	somatropin
	Number of subjects in per-protocol (PP) analysis	104	55
	AHV (cm/year) LS mean	11.16 (0.23)	10.31(0.30)
	95% CI	[10.70, 11.62]	[9.72, 10.90]
	Primary endpoint AHV (cm/year) LS mean (SE) (ANCOVA model as	Comparison groups	**lonapegsomatropin group versus somatropin**
		Estimated difference (Lonapegsomatropin-Genotropin)	0.85 (0.33)
		95% CI	[0.20, 1.50]

	for the primary analysis, PP) At W52	P-value ANCOVA with multiple imputation (PP)	0.0112
	Key Secondary endpoints AHV (cm/year) by visit (ITT) LS mean (SE)	Comparison groups	**lonapegsomatropin group versus somatropin**
		Estimated difference (lonapegsomatropin-somatropin) LS mean (SE)	W5 : 0.71 (1.51) W13: 1.06 (0.69) W26 : 1.44 (0.46) W39: 0.99 (0.36) W52: 0.86 (0.33)
		95% CI	W5: [-2.28; 3.70] W13: [-0.31; 2.42] W26: [0.54; 2.33] W39: [0.28; 1.69] W52: [0.22; 1.50]
		P-value ANCOVA with multiple imputation (ITT)	W5: 0.6402 W13: 0.1286 W26: 0.0017 W39: 0.0061 W52: 0.0088
	Change from baseline in Height SDS by visit (ITT) LS mean (SE)	Comparison groups	**lonapegsomatropin group versus somatropin**
		Estimated difference (lonapegsomatropin-somatropin)	W5 : 0.01 (0.02) W13: 0.05 (0.03) W26: 0.11 (0.04) W39: 0.12 (0.05) W52: 0.14 (0.06)
		95% CI	W5: [-0.04; 0.05] W13: [-0.01; 0.10] W26: [0.03; 0.18] W39: [0.03; 0.21] W52: [0.03; 0.26]
		P-value ANCOVA model (ITT)	W5: 0.7795 W13: 0.1078 W26: 0.0085 W39: 0.0130 W52: 0.0149
	Average IGF-I SDS by visit (ITT) LS mean (SE)	Comparison groups	**lonapegsomatropin group versus somatropin**
		Estimated difference (lonapegsomatropin-somatropin)	W13: 0.91 (0.12) W26: 0.97 (0.12) W39: 0.89 (0.13) W52: 0.74 (0.13)
		95% CI	W13: [0.66; 1.16] W26: [0.75; 1.20] W39: [0.64; 1.14] W52: [0.49; 1.00]
		P-value ANCOVA model	W13, W26, W39, W52 : P < 0.0001

Analysis description

1) Subgroup analysis of primary efficacy endpoint – AHV (cm/year) at week 52 based on primary ANCOVA model with multiple imputation (ITT Population)

Subgroup	n for Subgroup	Subgroup Strata	Lonapegsomatropin LS Mean (SE) (N=105)	Somatropin LS Mean (SE) (N=56)
Age	39	<6 years	12.41 (0.49)	10.82 (0.63)
	122	≥6 years	10.72 (0.26)	10.21 (0.33)
Peak Stimulated GH	58	≤5 ng/mL	11.98 (0.45)	11.23 (0.59)
	103	>5 ng/mL	10.56 (0.26)	9.72 (0.32)
Gender	132	Male	10.74 (0.21)	9.93 (0.29)
	29	Female	11.79 (0.46)	11.20 (0.64)
Etiology of GHD	105	Isolated idiopathic GHD	10.40 (0.29)	9.73 (0.34)
	28	Isolated organic GHD	11.57 (0.44)	10.48 (0.53)
	28	Multiple pituitary hormone deficiency	12.68 (0.69)	12.20 (1.03)
Country	42	US	9.50 (0.56)	9.26 (0.54)
	119	Non-US	11.65 (0.26)	10.64 (0.35)

Source: Tables 14.2.1.10.1 and 14.1.3.1.1
Note: Missing data were imputed with multiple imputation method with 100 simulated datasets. For each imputed data set, an ANCOVA model with by visit AHV as the dependent variable, treatment and gender as factors, baseline age, baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS - average SDS of parental height SDS as covariates were fitted. The LS means presented in the table are the overall estimates combined from all the 100 models.

2) Post-hoc analysis
CT-301 analysis for AHV Categories (≥8 or <8 cm/year) at week 52 – observed Cases (ITT Population)

AHV Category	Lonapegsomatropin (N=105)[a] n (%)	Somatropin (N=56)[a] n (%)	Odds Ratio of lonapegsomatropin vs Somatropin [95% CI]	*P* Value
≥8 cm/year, n (%)	100 (96.2)	49 (89.1)	2.79 [0.70, 11.15]	0.1457
<8 cm/year, n (%)	4 (3.8)	6 (10.9)		

Source: Table 14.2.1.9

[a] One subject in each treatment group did not have AHV at Week 52; 104 and 55 were used as the denominator for percentage calculation in the lonapegsomatropin and somatropin treatment groups, respectively.
Note: Logistic regression model includes treatment and is adjusted for gender, baseline age and baseline peak GH levels (log transformed) at stimulation test, and baseline height SDS - average SDS of parental height.

CT-301 mean change from baseline in average IGF-I SDS for AHV <8 cm/ year and ≥8 cm/year across 52 weeks (per protocol population)

Visit	Lonapegsomatropin			Somatropin		
	AHV <8 cm/year (N=4)	AHV ≥8 cm/year (N=100)	Ratio (AHV <8 cm/year/ ≥8 cm/year)	AHV <8 cm/year (N=6)	AHV ≥8 cm/year (N=49)	Ratio (AHV <8 cm/year/ ≥8 cm/year)
Week 13	2.85	2.24	1.27	0.76	1.42	0.54
Week 26	2.78	2.42	1.15	0.71	1.55	0.46
Week 39	3.02	2.56	1.18	1.01	1.79	0.56
Week 52	3.29	2.68	1.23	1.15	2.03	0.57

Source: CT-301 CSR Table 14.2.3.3.2 and Listing 16.99.2.6.4
Abbreviations: AHV = annualized height velocity, IGF-1 insulin-like growth factor 1; SDS=standard deviation score
Note: AHV categories represented in this table (<8 cm/year and >8 cm/year) are based on Week 52 data. Average IGF-1 SDS values for lonapegsomatropin were derived from the population pharmacodynamics PD model as described in CT-301 CSR Appendix 16.1.7. Average IGF-1 SDS values for somatropin shown above were based on observed data.

2.6.5.3. Clinical studies in special populations

In submitted clinical studies, the clinical effects of lonapegsomatropin have been evaluated in paediatric patients with growth hormone deficiency. In this population, no particular analyses were conducted in study patients with concomitant renal or hepatic impairment.

Comparator somatropin medicinal product Genotropin is indicated in paediatric GHD patients aged 4 years and above. Clinical effects of lonapegsomatropin have been evaluated in paediatric patients aged 6 months and above. In total, 4 study patients under 3 years of age were included in submitted Phase 3 studies on lonapegsomatropin for paediatric GHD. All respective patients were included in single-arm study CT-302 (Table 26).

Table 26 Overview of study patients included in controlled and non-controlled Lonapegsomatropin Phase 3 studies by age categories at study baseline

	Age ≥0.5 and <3 years at start of trial (study patient numbers /total number)	**Age ≥3 – 18 years at start of trial (study patient number /total number)**	**Age 18+ years (study patient number /total number)**
Controlled studies	CT-301: 0/161	CT-301: 161/161	Not applicable
Non-controlled studies	CT-302: 4/146	CT-302: 142/146	Not applicable

Sources: CT-301 Table 14.1.3.1.1, CT-302 Table 14.1.2.1, CT-301EXT 120-day Table 14.1.2.1

Long-term efficacy data will be obtained in paediatric GHD study patients treated with lonapegsomatropin as part of the secondary objectives of the requested PASS.

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

An integrated analysis was conducted across studies CT-301, CT-302, and CT-301EXT. Study CT-302 is an open-label study in which the clinical effects of lonapegsomatropin were evaluated in paediatric GHD patients aged 6 months and above. Study CT-301EXT is a long-term extension of parent open-label studies CT-301 and CT-302 wherein the study patients differ in duration of study drug exposure, treatment experiences, and other demographical characteristics. Supportive studies CT-302 and CT-301EXT are discussed below.

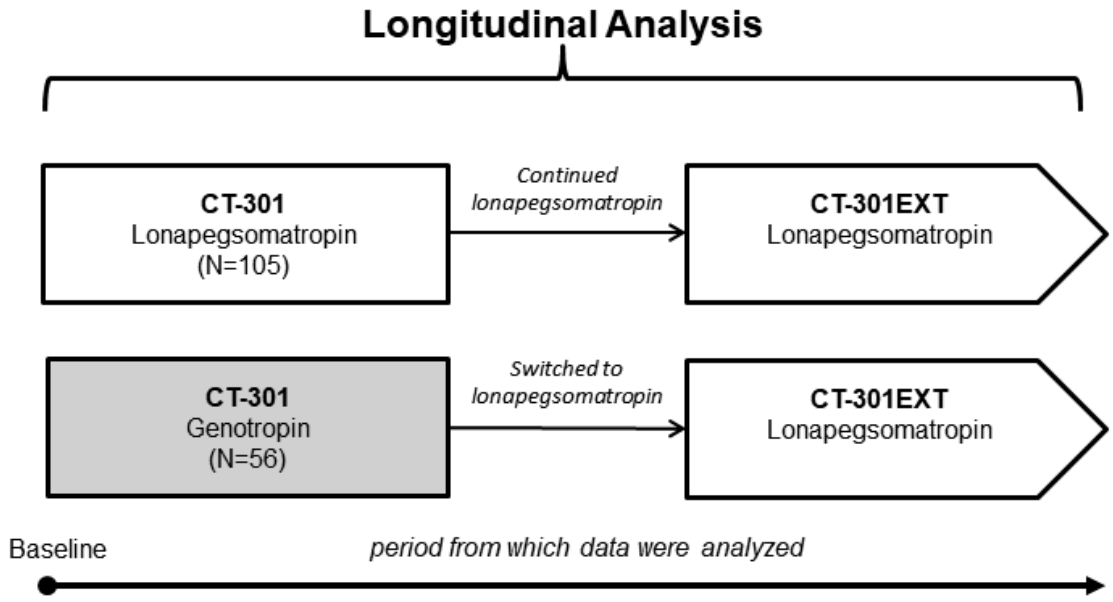
Separate integration analyses for efficacy were conducted for growth hormone treatment-naïve and growth hormone treatment-experienced study patients.

Efficacy across studies was evaluated in two pools:

- **Efficacy pool I**: a longitudinal review of a treatment-naïve study population that received lonapegsomatropin or somatropin in study CT-301 and lonapegsomatropin in study CT-301EXT. Study patients in this pool were randomized and received at least one dose of study treatment in study CT-301 (Figure 15).
- **Efficacy pool II**: a pooled review of efficacy data in study CT-301EXT in study patients who had received treatment with somatropin product Genotropin in study CT-301, and study patients in study CT-302 who had received prior somatropin treatment (Figure 16).

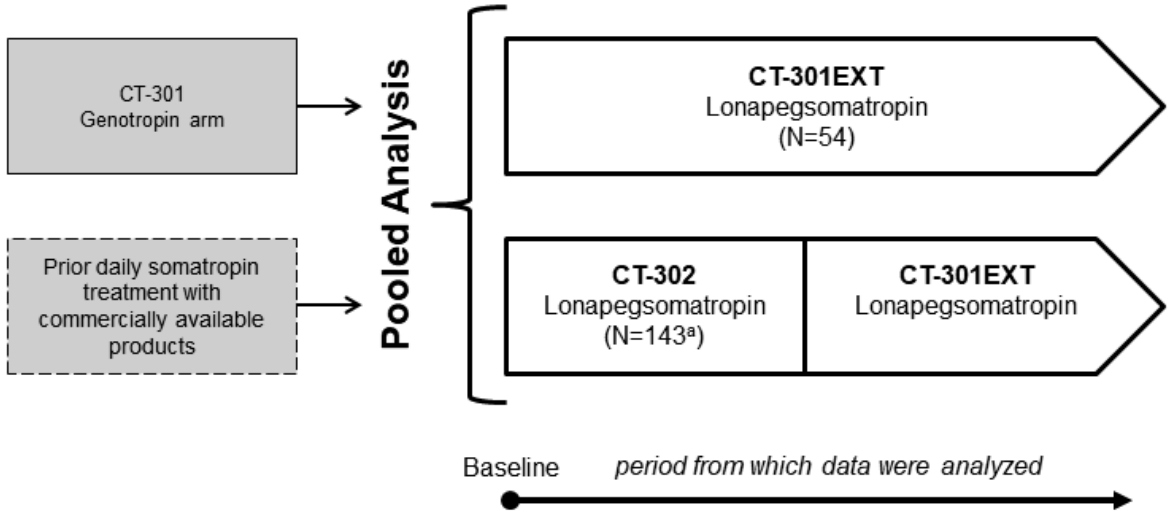
Descriptive summary and model-based analyses were performed to examine efficacy outcomes for efficacy pool I and efficacy pool II using all available data.

Figure 25 Efficacy Pool I: Longitudinal analysis of treatment-naïve patients from CT-301



Source: ISE Table 1.1

Figure 16 Efficacy Pool II: pooled analysis of treatment-experienced subjects from CT-301 and CT-302



[a] Three subjects (all < 3 years old) enrolled in CT-302 did not receive prior treatment with daily somatropin (as permitted by the protocol) and were not included in Efficacy Pool II.
Source: ISE Table 2.1

The definition of baseline in Efficacy pool II varied based on the parent study:

CT-301 somatropin arm enrolled in study CT-301EXT: first lonapegsomatropin dosing date in study CT-301EXT

CT-302 study patients who received prior somatropin therapy: first lonapegsomatropin dosing date in study CT-302

Efficacy endpoints and methodology for longitudinal analyses

In efficacy pool I, annualized height velocity by visit in the lonapegsomatropin and somatropin → lonapegsomatropin groups was analysed. In efficacy pool II, annualized height velocity by visit after the switch to lonapegsomatropin was analysed.

In both efficacy pools, change from baseline in height SDS, the absolute value and change from baseline in average IGF-I, average IGF-I SDS, IGFBP-3 and IGFBP-3 SDS were analysed.

A rolling baseline taking into account data from the prior 52 weeks was used in the aforementioned analyses.

Subgroup analyses

All descriptive efficacy analyses in efficacy pool I and II were repeated on the following subgroups:

- Age (<3 years, ≥3 to <6 years, [≥6 to <11 years for girls, ≥6 to <12 years for boys] and [≥11 years for girls, ≥12 years for boys])
- Gender
- Study baseline growth hormone -stimulation strata (≤5 ng/mL and >5 ng/mL)
- United States (US) vs. Non-US
- 2-year completers (subjects with 2-year efficacy data)

Results efficacy pool I: longitudinal efficacy data for treatment-naïve study patients with growth hormone deficiency

Data were collected and analysed from the beginning of this CT-301 extension study enrolment through the data cut-off date of 30 September 2019.

Subject disposition and key baseline characteristics efficacy pool I

Subject disposition for efficacy pool I is presented in Table 27. Out of the 161 subjects enrolled and dosed in CT-301, 158 (98.1%) continued on to CT-301EXT. Three study patients (1.9%) have withdrawn from CT-301EXT as of the 30 Sep 2019 data cut-off date.

A total of 68 subjects (42.2%) had completed 2 years of therapy across CT-301 and CT-301EXT as of the data cut-off.

Table 27 Efficacy pool I subject disposition

Number of study patients	CT-301 lonapegsomatropin →CT-301EXT (N=105) n (%)	CT-301 somatropin →CT-301EXT (N=56) n (%)	Total (N=161) n (%)
Enrolled and dosed in CT-301	105	56	161
Completed CT-301	104 (99.0)	55 (98.2)	159 (98.8)
Did not continue to CT-301EXT	1 (1.0)	0	1 (0.6)
Continued to CT-301EXT	103 (98.1)	55 (98.2)	158 (98.1)
Completed CT-301EXT	0	0	0
Withdrawn from CT-301EXT	3 (2.9)	1 (1.8)	4 (2.5)
Consent withdrawn	2 (1.9)	0	2 (1.2)
Other	1 (1.0)[a]	1 (1.8)[b]	2 (1.2)

a Parent's decision

b Parental decision due to moving to another region

Source: 120-day Efficacy Table 1.1 and 120-day Efficacy Listing 1.1.1

Key demographic and baseline characteristics for efficacy pool I are the same as for CT-301.

Efficacy pool I results

Efficacy pool I annualized height velocity

At the end of CT-301 (week 52), the annualized height velocity for lonapegsomatropin was 11.2 cm/year. Continued growth was observed with continued lonapegsomatropin treatment beyond the first year, with an annualized height velocity of 9.4 cm/year at week 78 (Table 28, Figure 17).

At the end of CT-301 (week 52), the annualized height velocity for somatropin was 10.3 cm/year. After a treatment switch to lonapegsomatropin, the annualized height velocity at week 78 was 9.3 cm/year (Table , Figure).

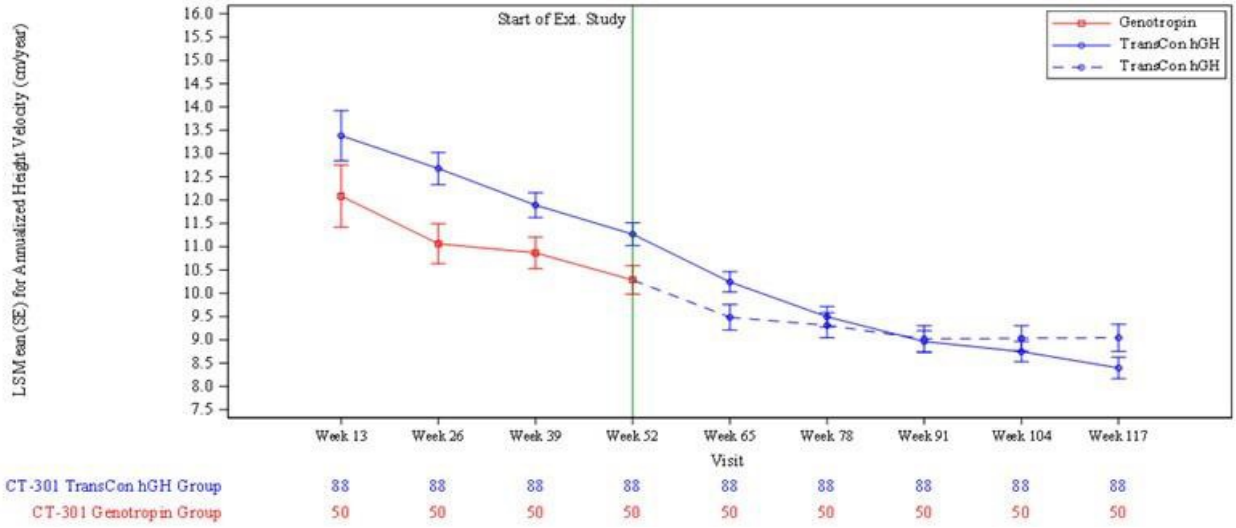
Table 28 Efficacy pool I summary of annualized height velocity (cm/year) by visit (ANCOVA Model)

	CT-301 Lonapegsomatropin →CT-301EXT		**CT-301 Somatropin →CT-301EXT**	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Baseline HV (cm/year)	94	3.93 (2.04)	54	3.93 (1.66)
Visit	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**
Week 13	105	13.28 (0.49)	56	12.22 (0.63)
Week 26	104	12.65 (0.33)	56	11.22 (0.42)
Week 39	104	11.89 (0.26)	56	10.91 (0.33)
Week 52	104	11.16 (0.23)	55	10.31 (0.30)
	Continued lonapegsomatropin		***Switched to lonapegsomatropin***	
Week 65	103	10.10 (0.22)	55	9.46 (0.27)
Week 78	101	9.39 (0.21)	55	9.26 (0.26)
Week 91	100	8.85 (0.21)	53	9.03 (0.27)
Week 104	100	8.65 (0.20)	53	9.00 (0.25)
Week 117	88	8.40 (0.23)	50	9.04 (0.29)

Source: CT-301 CSR Table 14.1.3.1.1 and 120-day Efficacy Table 1.2.

Abbreviations: AHV = annualized height velocity; ANCOVA = analysis of covariance; LS = least squares; SD = standard deviation; SDS = standard deviation score; SE = standard error.
Note: A rolling baseline was used to make sure the baseline was no more than 52 weeks apart. At each postbaseline visit, n is the number of subjects with non-missing rolling baseline and specific postbaseline values. The AHV at each visit was modelled using ANCOVA adjusting for CT301 treatment group, baseline age, peak GH levels (log transformed) at diagnosis, and delta average parental height SDS as covariates and gender as a factor.

Figure 17 Efficacy pool I annualized height velocity up to week 117 (ANCOVA Model)



Source: ISE Figure 1.3.1
Abbreviations: AHV = annualized height velocity; ANCOVA = analysis of covariance; Ext. = extension; GH = growth hormone; hGH = human growth hormone; LS = least square; SDS = standard deviation score; SE = standard error; TransCon hGH = lonapegsomatropin
Note: LS Means (SE) for AHV were estimated from the ANCOVA model adjusting for CT-301 treatment group, baseline age, peak GH levels (log transformed) at diagnosis, and delta average-parental height SDS as covariates and gender as a factor.

Efficacy pool I change from baseline in height SDS

The change from baseline in height SDS by visit for study patients in the efficacy pool I is summarized in Table 29 and illustrated in Figure 18.

At week 78, a persistence in growth effect was observed. Study patients treated with lonapegsomatropin therapy for the first year achieved a LS mean (SE) increase in height SDS of 1.39 (0.05) compared with 1.24 (0.06) for study patients treated with somatropin for the first year of therapy (p = 0.0436). The treatment difference (initial lonapegsomatropin minus initial somatropin) from week 52 (0.14) was maintained at week 78 (0.15).

Study patients switching from somatropin to lonapegsomatropin followed the same growth speed of those originally randomized to lonapegsomatropin, with an increase of approximately 0.29 height SDS from week 52 to week 78 (1.10 to 1.39 for continuous lonapegsomatropin vs. 0.96 to 1.24 for switch to lonapegsomatropin).

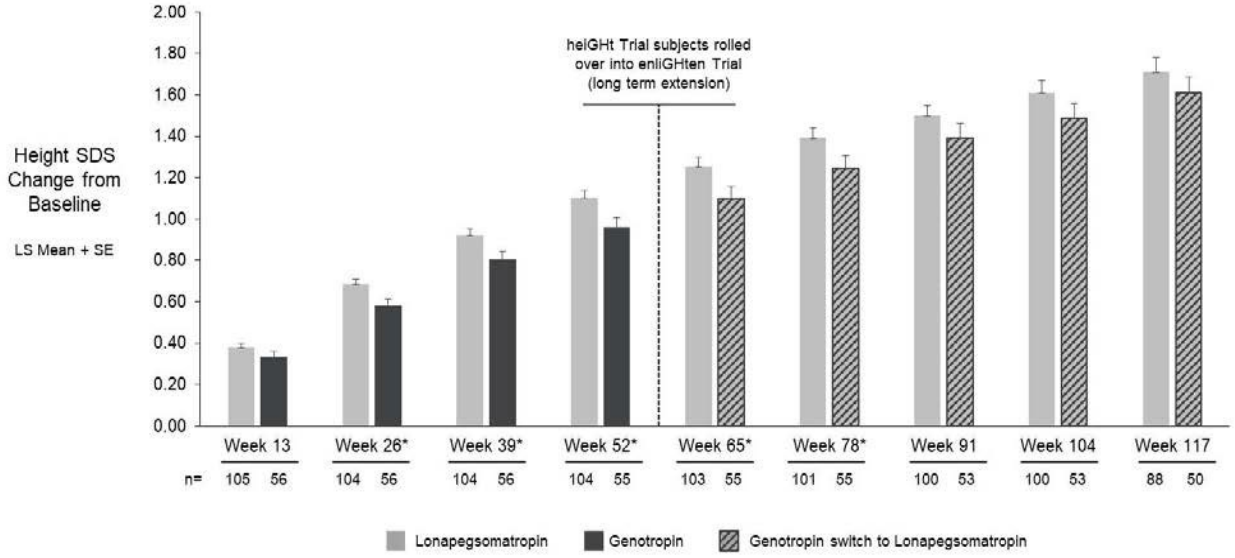
Table 29 Efficacy pool I summary of change from baseline in height SDS by visit (ANCOVA Model)

	CT-301 Lonapegsomatropin →CT-301EXT		**CT-301 Somatropin →CT-301EXT**	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Baseline height SDS	105	-2.89 (0.85)	56	-3.00 (0.90)
Visit	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**
Week 13	105	0.38 (0.02)	56	0.33 (0.03)
Week 26[a]	104	0.68 (0.03)	56	0.58 (0.04)

Week 39[a]	104	0.92 (0.03)	56	0.80 (0.04)
Week 52[a]	104	1.10 (0.04)	55	0.96 (0.05)
	Continued lonapegsomatropin		***Switched to lonapegsomatropin***	
Week 65[a]	103	1.25 (0.05)	55	1.10 (0.06)
Week 78[a]	101	1.39 (0.05)	55	1.24 (0.06)
Week 91	100	1.50 (0.05)	53	1.39 (0.07)
Week 104	100	1.61 (0.06)	53	1.49 (0.07)
Week 117	88	1.71 (0.07)	50	1.61 (0.08)

[a]Treatment difference resulted in a nominal *P* value <0.05.
Source: CT-301 Table 14.1.3.1.1 and 120-day Efficacy Table 1.2.2
Note: At each post-baseline visit, n is the number of subjects with non-missing baseline and specific post-baseline values. The height SDS change from baseline at each visit was modelled using ANCOVA adjusting for study CT-301 treatment group, baseline age, peak GH levels (log transformed) at diagnosis, and baseline height SDS as covariates and gender as a factor.

Figure 18 Efficacy pool I change from baseline in height SDS by visit up to week 117 (ANCOVA Model)



Source: ISE Table 1.2.2
Abbreviations: ANCOVA = analysis of covariance; LS = least square; SDS = standard deviation score; SE = standard error
* Treatment difference resulted in a nominal *P* value <0.05. Source: 120-day Efficacy Table 1.2.2
Note: At each post-baseline visit, n is the number of subjects with non-missing baseline and specific post-baseline. The height SDS change from baseline at each visit was modeled using ANCOVA adjusting for study CT-301 treatment group, baseline age, peak GH levels (log transformed) at diagnosis, and baseline height SDS as covariates and gender as a factor.

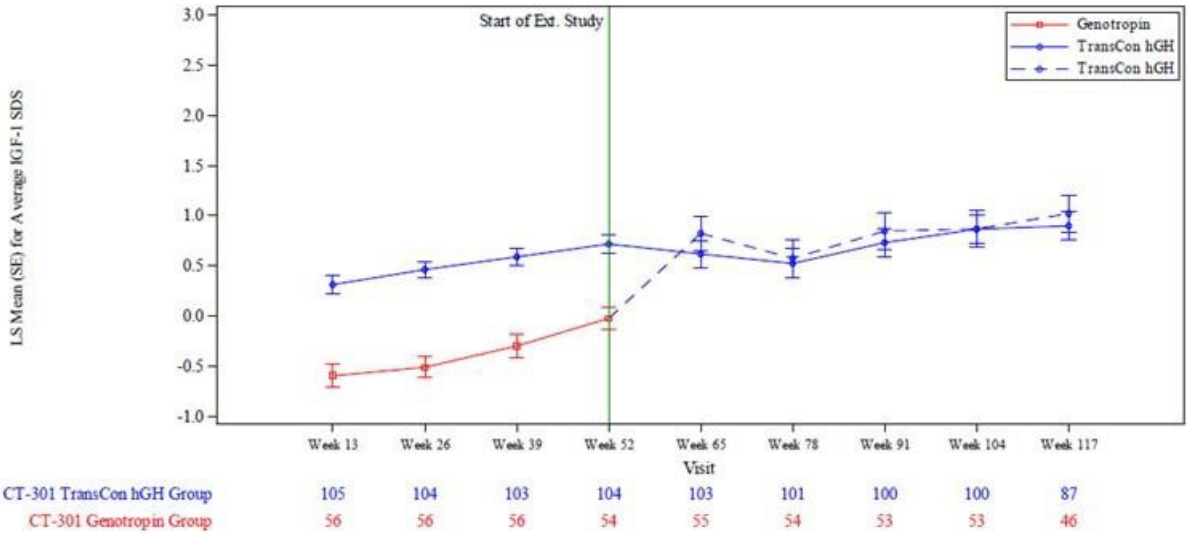
Efficacy pool I average IGF-I SDS and IGFBP-3 SDS

The average IGF-I SDS by visit for study patients in the efficacy pool I is illustrated in Figure 19.

Average IGF-I SDS values tended to be higher for lonapegsomatropin-treated study patients compared with somatropin-treated study patients in study CT-301, paralleling the observed superior growth outcomes. Beyond 52 weeks, for study patients continuing lonapegsomatropin treatment from study CT-301, IGF-I SDS values generally remained stable without further increase. For study patients switching from somatropin treatment in study CT-301 to lonapegsomatropin treatment in study CT-301EXT, an initial increase in IGF-I SDS values with subsequent stabilization was observed.

Overall, the trends for IGFBP-3 SDS mirrored those for IGF-I SDS.

Figure 19 Efficacy pool I average IGF-I SDS by visit up to week 117 (ANCOVA Model)



Source: ISE Figure 1.3.3
Abbreviations: ANCOVA = analysis of covariance; Ext. = extension; GH = growth hormone; hGH = human growth hormone; IGF-I = insulin-like growth factor 1; LS = least square; SDS = standard deviation score; SE = standard error; TransCon hGH = lonapegsomatropin
Note: LS means (SE) were estimated from the ANCOVA adjusting for CT-301 treatment group, baseline age, peak growth hormone levels (log transformed) at diagnosis, and baseline IGF-I SDS as covariates and gender as a factor.

Bone age over time in efficacy pool I

Bone age over time for efficacy pool I is summarized in Table 30. The bone age/chronological age ratios at week 52 and week 104 remained less than 1, representing normal skeletal maturation.

Table 30 Efficacy pool I: summary of bone age (years) up to week 104

Variable	CT-301 Lonapegsomatropin →CT-301EXT (N=105)			CT-301 Somatropin →CT-301EXT (n=56)		
	n	Mean (SD)	Change from Baseline Mean (SD)	n	Mean (SD)	Change from Baseline Mean (SD)
Bone age (years)						
Baseline	105	5.8 (2.6)	-	56	6.0 (2.7)	-
Week 52	104	7.2 (2.7)	1.4 (0.9)	55	7.4 (2.9)	1.4 (0.8)
Week 104	98	8.4 (2.7)	2.6 (1.0)	53	8.5 (3.1)	2.5 (1.1)
Bone age/ chronological age ratio						
Baseline	105	0.7 (0.2)	-	56	0.7 (0.1)	-
Week 52	104	0.7 (0.1)	0.1 (0.1)	55	0.8 (0.1)	0.1 (0.1)
Week 104	98	0.8 (0.1)	0.1 (0.1)	53	0.8 (0.1)	0.1 (0.1)
Delay in bone age (years)						
Baseline	105	2.5 (1.3)	-	56	2.3 (1.1)	-
Week 52	104	2.3 (1.4)	-0.2 (0.9)	55	2.1 (1.1)	-0.2 (0.7)
Week 104	98	2.1 (1.5)	-0.4 (1.0)	53	2.0 (1.2)	-0.4 (1.0)

Source: 120-day Efficacy Table 1.2.8.
Note: At each postbaseline visit, n is the number of subjects with non-missing baseline and specific postbaseline values.

Efficacy pool I subgroup analyses

The change in height SDS at week 78 by subgroup (age, sex, peak stimulated growth hormone, country) for efficacy pool I is summarized in Table 31.

Change in height SDS at week 78 across subgroups was generally consistent with the overall results for efficacy pool I, in which a greater change in height SDS was observed for study patients who were continuously treated with lonapegsomatropin compared to those treated with somatropin for the first 52 weeks.

Table 31 Efficacy pool I change from baseline in height SDS at week 78 by subgroup

Subgroup Category	CT-301 Lonapegsomatropin →CT-301EXT		CT-301 Somatropin →CT-301EXT	
	n	Change in height SDS Mean (SD)	n	Change in height SDS Mean (SD)
Age				
≥3 to <6 years	24	1.62 (0.55)	13	1.40 (0.44)
≥6 to <11 years (girls) ≥6 to <12 years (boys)	61	1.34 (0.57)	36	1.18 (0.60)
≥11 years (girls) ≥12 years (boys)	15	0.74 (0.55)	5	0.85 (0.34)
Sex				
Male	81	1.27 (0.57)	44	1.16 (0.55)
Female	19	1.53 (0.79)	10	1.40 (0.56)

Subgroup Category	CT-301 Lonapegsomatropin →CT-301EXT		CT-301 Somatropin →CT-301EXT	
	n	Change in height SDS Mean (SD)	n	Change in height SDS Mean (SD)
Baseline peak stimulated GH level[a]				
≤5 ng/mL	34	1.47 (0.73)	20	1.28 (0.67)
>5 to ≤10 ng/mL	66	1.23 (0.54)	34	1.15 (0.48)
Country				
United States	25	0.97 (0.53)	14	0.91 (0.62)
Non-United States	75	1.43 (0.61)	40	1.31 (0.50)

[a] Also referred to as the growth hormone stimulation strata group.
Source: ISE Tables 1.3.6, 1.3.7, 1.3.8, and 1.3.9
Abbreviations: GH = growth hormone; SD = standard deviation; SDS = standard deviation score
Note: n is the number of subjects with non-missing baseline and specific post-baseline.

For the 2-year completers subgroup (n = 68), the LS mean (SE) change in height SDS at week 104 was 1.54 (0.08) for study patients who received lonapegsomatropin continuously and 1.53 (0.11) for those who switched to lonapegsomatropin after 52 weeks of somatropin.

Results efficacy pool II: efficacy data for growth hormone treatment-experienced study patients with growth hormone deficiency

Efficacy pool II subject disposition and key baseline characteristics

All 54 somatropin-treated study patients from study CT-301 (100%) and 137/143 treatment-experienced study patients enrolled and dosed in study CT-302 (95.8%) continued on to study CT-301EXT. As of the data cut-off (30 Sep 2019), 5 study patients (2.5%) had withdrawn from study CT-301EXT. Based on this data cut-off, no study patients had completed 2 years of lonapegsomatropin treatment in Efficacy Pool II.

The key demographic and baseline characteristics for efficacy pool II are summarized in Table 32.

Table 32 Efficacy pool II key demographic and baseline characteristics

Characteristic	CT-301 Somatropin →CT-301EXT[a] (N = 54)	CT-302 →CT-301EXT[b] (N = 143)	Total (N = 197)
Age (years)			
Mean (SD), range	9.6 (2.8) [4.2, 13.9]	10.8 (3.7) [2.0, 17.4]	10.4 (3.5) [2.0, 17.4]
<3 years	0	1 (0.7%)	1 (0.5%)
≥3 and <6 years, n (%)	9 (16.7)	20 (14.0)	29 (14.7)
≥6 to <11 years (girls) or ≥6 to <12 years for boys, n (%)	29 (53.7)	55 (38.5)	84 (42.6)
≥11 years for girls or ≥12 years for boys, n (%)	16 (29.6)	67(46.9)	83 (42.1)
Male sex, n (%)	44 (81.5)	109 (76.2)	153 (77.7)
White race, n (%)	51 (94.4)	121 (84.6)	172 (87.3)
US, n (%)	14 (25.9)	136 (95.1)	150 (76.1)
Non-US, n (%)	40 (74.1)	7 (4.9)	47 (23.9)
Height (cm), mean (SD)	122.8 (15.1)	133.6 (21.2)	130.7 (20.3)
Height SDS, mean (SD)	−2.07 (0.81)	−1.40 (0.83)	−1.58 (0.88)
BMI (kg/m^2)	16.4 (2.3)	17.5 (3.0)	17.2 (2.8)
BMI SDS, mean (SD)	−0.41 (1.03)	−0.24 (1.06)	−0.29 (1.06)
Tanner stage, n (%)			
1	44 (81.5)	92 (64.3)	136 (69.0)

Characteristic	CT-301 Somatropin →CT-301EXT[a] (N = 54)	CT-302 →CT-301EXT[b] (N = 143)	Total (N = 197)
2	8 (14.8)	14 (9.8)	22 (11.2)
3	2 (3.7)	30 (21.0)	32 (16.2)
4	0	7 (4.9)	7 (3.6)
5	0	0	0
Average-parental height SDS, mean (SD)[c]	−0.46 (0.80)	−0.28 (0.78)	−0.33 (0.79)
Delta average-parental height SDS, mean (SD)[c]	−2.52 (1.23)	−1.11 (1.00)	−1.51 (1.24)
Bone age (years), mean (SD)d[d]	7.4 (3.0)	8.6 (3.6)	8.3 (3.4)
Delay in bone age (years), mean (SD)e	2.2 (1.1)	1.2 (1.0)	1.4 (1.1)
IGF-I SDS, mean (SD)	−0.02 (1.2)	0.9 (1.3)	0.7 (1.3)
Peak stimulated GH level[e]			
Mean (SD), ng/mL	5.5 (3.0)	5.9 (2.6)	5.8 (2.7)
≤5 ng/mL, n (%)	20 (37.0)	51 (35.7)	71 (36.0)
≥5 ng/mL, n (%)	34 (63.0)	90 (62.9)	124 (62.9)
Missing	0	2 (1.4)	2 (1.0)

[a] Refers to data from study CT-301EXT for study patients who received somatropin for 52 weeks as part of CT-301. [b] Refers to data from study CT-302 and study CT-301EXT for CT-302 study patients who received prior daily somatropin therapy. [c] Average-parental height SDS = (height SDS_{mother} + height SDS_{father})/2; N = 192 for this calculation. [d] Delta average-parental height SDS = (height $SDS_{subject}$ - average-parental height SDS); N = 192 for this calculation. [e] N = 184 for this calculation. [f] Also referred to as peak growth hormone concentration. Source: ISE Table 2.2
Abbreviations: BMI = body mass index; GH = growth hormone; SD = standard deviation; SDS = standard deviation score; US = United States Note: The 15th day of the month was used for age calculation. Years were calculated as total days/365.25.

The mean (SD) prior daily somatropin dose was 0.27 (0.05) mg/kg/week at baseline and the mean (SD) somatropin dose duration since initial GH treatment was 1.1 (0.6) years.

Efficacy pool II results

Efficacy pool II annualized height velocity

A summary of annualized height velocity by visit for efficacy pool II is provided in Table 33.

Overall, for efficacy pool II, the duration of prior daily somatropin treatment was 1.1 years. A trend for continued growth with lonapegsomatropin was observed in these treatment-experienced study patients, with a LS mean (SE) annualized height velocity of 8.36 (0.24) cm/year at week 52.

Table 33 Efficacy pool II summary of annualized height velocity (cm/year) by visit (ANCOVA Model)

Visit	CT-301 somatropin →CT-301EXT[a] (N = 55)	CT-302 →CT-301EXT (N = 143)[b]	LS mean (SE)
	n	n	
Week 13	55	142	8.84 (0.31)
Week 26	55	141	8.67 (0.25)
Week 39	53	134	8.73 (0.20)
Week 52	53	133	8.60 (0.18)
Week 65	50	130	8.46 (0.19)
Week 78	36	126	8.31 (0.20)

[a] Refers to data from CT-301EXT for subjects who received somatropin for 52 weeks as part of study CT-301.
[b] Refers to data from studies CT-302 and CT-301EXT for patients from study CT-302 who received prior daily somatropin therapy. Source: ISE Table 2.2.1
Abbreviations: AHV = annualized height velocity; ANCOVA = analysis of covariance; CI = confidence interval; GH = growth hormone LS = least square; SE = standard error
Note: A rolling baseline was used to make sure the baseline was no more than 52 weeks apart. The rolling baseline was used to calculate the annualized height velocity to make sure there was a 1-year gap. In other words, from the 15-month (65 weeks) visit onwards, the baseline value used for each successive height velocity calculation was the patient's height at the visit 52 weeks previously. At each post-baseline visit, n is the number of subjects with non-missing rolling baseline and specific post-baseline. The annualized height velocity at each visit was modelled using ANCOVA adjusting for parent study, baseline age, peak growth hormone levels (log transformed) at diagnosis, delta average-parental height SDS, prior daily growth hormone dose level (log transformed) and prior daily growth hormone treatment duration (log transformed) as covariates and gender as a factor.

Efficacy pool II change from baseline in height SDS

Following 52 weeks of treatment with lonapegsomatropin, an LS mean (SE) of 0.45 (0.04) increase in height SDS was observed for efficacy pool II (Table 34). While baseline height SDS differed based on the parent study, the change from baseline following lonapegsomatropin therapy was consistent across study patients in efficacy pool II.

Table 34 Efficacy pool II summary of change from baseline in height SDS by visit up to week 78 (ANCOVA Model)

Visit	CT-301 Somatropin→CT-301EXT[a] (N = 55)	CT-302 →CT-301EXT[b] (N = 143)	LS mean (SE)
Week 13	55	142	0.13 (0.01)
Week 26	55	141	0.26 (0.02)
Week 39	53	134	0.39 (0.02)
Week 52	53	133	0.48 (0.03)
Week 65	50	130	0.57 (0.04)
Week 78	36	126	0.69 (0.05)

[a] Refers to data from study CT-301EXT for study patients who received somatropin for 52 weeks as part of study CT-301. [b] Refers to data from studies CT-302 and CT-301EXT for patients from study CT-302 who received prior daily somatropin treatment. Source: ISE Table 2.2.2
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GH = growth hormone; LS = least square; SDS = standard deviation score; SE = standard error
Note: At each post-baseline visit, n is the number of subjects with non-missing baseline and specific post-baseline. The height SDS change from baseline at each visit was modeled using ANCOVA adjusting parent study, baseline age, peak

Visit	CT-301 Somatropin→CT-301EXT[a] (N = 55)	CT-302 →CT-301EXT[b] (N = 143)	LS mean (SE)

GH levels (log transformed) at diagnosis, baseline height SDS, prior daily GH dose level (log transformed) and prior daily GH treatment duration (log transformed) as covariates and gender as a factor.

Efficacy pool II average IGF-I SDS and IGFBP-3

Overall, the average IGF-I SDS remained elevated above pre-treatment levels and was stable over time. The trend for the IGFBP-3 SDS in efficacy pool II mirrored that of the IGF-I SDS.

Efficacy pool II subgroup analyses

Subgroup analyses with respect to the annualized height velocity, delta height SDS, and delta IGF-I SDS for efficacy pool II at week 52 (age, gender, peak stimulated growth hormone level, country) are consistent with the subgroup results from study CT-302.

Comparison of efficacy results of all studies

Bone age

Bone age at each visit was summarized descriptively for each subgroup for efficacy pool I and efficacy pool II.

At baseline, bone age was delayed in both CT-301 arms (mean [SD] 2.5 [1.3] years in the lonapegsomatropin arm and 2.3 [1.1] years in the somatropin arm). In efficacy pool I the mean (SD) change in bone age at week 52 was 1.4 (0.9) years for study patients treated with lonapegsomatropin and 1.4 (0.7) years for study patients treated with somatropin. At week 104, the change in bone age was 2.6 years for both study patients continuously treated with lonapegsomatropin and study patients treated with somatropin followed by lonapegsomatropin.

Patient experience data

Patient experience data with lonapegsomatropin administered using vials with syringe/needle and the DCC and growth hormone auto-injector combination product were collected during studies CT-302 and CT-301EXT.

After subjects began weekly treatment with lonapegsomatropin in study CT-302, the parents' assessment of convenience and satisfaction were 64.6 and 80.9, respectively, at week 6 and 69.0 and 83.0, respectively, at week 13.

After 6 weeks of growth hormone auto-injector use, the majority of study patients strongly or somewhat agreed with the following statements:

1. The growth hormone auto-injector did not cause a lot of pain or discomfort (95.5%)

2. The medicine could be injected without difficulty or making a mistake (100%) in a short amount of time (95.6%), without touching blood (97.8%), and left little to no marks on the skin (95.6%)
3. Study patients could see that it had been properly injected (95.5%) and were easily notified by sound and lights that the medicine was received or if there was a problem (95.6%)

Overall, no study patient experienced an injury caused by the growth hormone auto-injector that required seeing a doctor for help.

Analysis of clinical information relevant for dosing recommendations

Based on the comparable annualized height velocity demonstrated for equivalent weekly doses (0.21 mg/kg/week) of ACP-001 and somatropin in the Phase 2 CT-004 study, a dose of 0.24 mg/kg/week was selected for the lonapegsomatropin and somatropin arms in the global pivotal Phase 3 study CT-001. Studies CT-302 and CT-301EXT also evaluated lonapegsomatropin 0.24 mg/kg/week. The slightly higher dose (0.24 mg/kg/week) relative to the dose evaluated in study CT-004 served to accommodate global somatropin dosing practices (Collett-Solberg 2019) in study CT-301.

The recommended starting dosages of somatropin with lonapegsomatropin, subsequent dose titration, and treatment monitoring are discussed in the sections on pharmacokinetics and pharmacodynamics above. An individualized approach with respect to dosing is mandatory, due to individual differences in sensitivity to somatropin with lonapegsomatropin.

Treatment with lonapegsomatropin should be supervised by a physician who is experienced in the diagnosis and management of paediatric patients with growth failure associated with GHD. The dosage of lonapegsomatropin should be individualized and titrated throughout therapy based on clinical response.

Additionally, compliance should be assessed, and other potential causes of poor growth (e.g., hypothyroidism, under-nutrition, advanced bone age, and antibodies to recombinant human growth hormone) should be evaluated if patients experience failure to increase height velocity, particularly during the first year of treatment.

Once the epiphyses are fused, patients should be clinically re-evaluated for need for treatment with growth hormone.

2.6.5.5. Supportive study(ies)

Study CT-302 (fliGHt study)

Study CT-302 was a Phase 3, global, open-label, single-arm 26-week clinical study that evaluated the clinical effects of once-weekly lonapegsomatropin in 146 paediatric GHD patients aged 6 months up to 17 years. Included patients had (n= 143) or had not received (n=3) prior growth hormone treatment. In respective study, the long-term safety and efficacy of lonapegsomatropin treatment were evaluated.

Methods

Dosing

The initial dose of lonapegsomatropin was 0.24 mg human growth hormone/kg/week for all study patients, regardless of any prior dose of daily human growth hormone. Lonapegsomatropin was administered via vial and syringe/needle.

At visit 2, the lonapegsomatropin dose was adjusted by the investigator based on weight. The goal for IGF-I SDS levels was to be between 0 and +2.0 SDS (unless a different target was identified in consultation with the medical monitor). Thus, if the IGF-I SDS measured at visit 2 (or the Cmax Visit, as applicable) was <0 SDS, and after confirmation of IGF-I level as <0 SDS by a second measurement collected 5 days after dosing (± 1 day) at an unscheduled visit, the dose may have been increased by approximately 20% to the next higher weight bracket by the investigator.

The investigator (with medical monitor preapproval) or medical monitor may have stopped or reduced the dose of trial treatment for an individual study patient at any time during the study in the presence of the symptoms and laboratory abnormalities. If treatment was discontinued, all subsequent visits and assessments were to continue as planned.

Objective

The primary objective was to assess the safety of undergoing the switch from commercially available daily human growth hormone to weekly lonapegsomatropin through the first 6 months of treatment in children with growth hormone deficiency aged 6 months to 17 years.

Endpoints

The efficacy endpoints after 26 weeks of lonapegsomatropin included annualized height velocity, change in height SDS, IGF-I SDS, and the proportion of study patients in each category (cut points of 0 to 2.0, −2.0 to 2.0, and −1.0 to 2.0), and IGFBP-3 SDS. Preference for current once-weekly lonapegsomatropin or prior daily somatropin therapy and treatment burden was assessed in study patients ≥9 years old and their parents. Convenience and satisfaction were also assessed. These outcomes were analysed combined with data from extension study CT-301EXT.

Results

- Participant flow

A total of 162 patients were screened, and 146 patients were enrolled into study CT-302 and received at least one lonapegsomatropin dose. Of the 146 study patients dosed, 144 (98.6%) completed the study and were included in the Full Analysis Set. Two study patients (1.4%) withdrew consent and were withdrawn from the study, one after 2 doses of the study drug and one after 9 doses. The reason why consents were withdrawn were not reported.

- Baseline data

The study patients enrolled in the study spanned a wide range of ages (1.2 to 17.4 years). Four study patients (2.7%) were less than 3 years old. Approximately 65.0% of study patients were pre-pubertal (Tanner stage 1) with the remaining in pubertal transition (Tanner stages 2 to 4). Other key demographic and baseline characteristics are summarized in Table 35.

Table 35 Study CT-302 key demographic and baseline characteristics (Full Analysis Set)

Characteristic	Total (N = 146)
Age (years)	
Mean (SD), [range]	10.6 (3.9) [1.2, 17.4]
<3 years, n (%)	4 (2.7)
≥3 and <6 years, n (%)	20 (13.7)
≥6 to <11 years (girls) or ≥6 to <12 years (boys), n (%)	55 (37.7)
≥11 years (girls) or ≥12 years (boys), n (%)	67 (45.9)
Male, n (%)	110 (75.3)
White race, n (%)	124 (84.9)
Origin, n (%)	
North America	139 (95.2)
Oceania	7 (4.8)
Height (cm), mean (SD)	132.4 (22.5)
Height SDS, mean (SD)	−1.42 (0.84)
BMI (kg/m2), mean (SD)	17.5 (3.0)
BMI SDS, mean (SD)	−0.25 (1.08)
Tanner stage, n (%)	
1	95 (65.1)
2	14 (9.6)
3	30 (20.5)
4	7 (4.8)
5	0 (0)
Delta average-parental height SDS, mean (SD)[c]	−1.14 (1.02)
IGF-I SDS, mean (SD)	0.85 (1.29)
Bone age (years) at GHD diagnosis, mean (SD)[d]	8.2 (3.3)
Delay in bone age (years) at GHD diagnosis, mean (SD)[d]	1.2 (1.1)
Peak stimulated GH level (ng/mL) at GHD diagnosis, mean (SD)[e]	5.9 (2.6)
≤5 ng/mL, n (%)	52 (35.6)
>5 ng/mL, n (%)	91 (62.3)
Missing, n (%)	3 (2.1)
Peak stimulated GH level (ng/mL) at GHD diagnosis, range[f]	0.48, 10.5
Other pituitary deficiencies, n (%)	
Yes	12 (8.2)
No	134 (91.8%)

Characteristic	Total (N = 146)

The 15th day of the month was used for age calculation. Years were calculated as total days divided by 365.25. [c]Delta average-parental height SDS = ($SDS_{subject}$ − average parental height SDS). N = 141 for this calculation. [d]N = 120 for this calculation. [e]Also referred to as peak GH concentration. Source: CT-302 CSR Tables 14.1.2.1, 14.1.2.2, and 14.3.3.1
Abbreviations: BMI = body mass index; GH= growth hormone; GHD = growth hormone deficiency; IGF-I = insulin-like growth factor 1; SD = standard deviation; SDS = standard deviation score.

A total of 143 study patients (97.9%) received daily somatropin treatment before enrolment in study CT-302.

Treatment compliance

Mean treatment compliance (SD) during the study was 98.4% (3.97%), with a range of 76.0 to 104.0%. The majority of study patients (132 study patients, 90.4%) had compliance rates >95%; 8 study patients (5.5%) had compliance rates of ≤90%.

- Outcomes and estimation

Annualized height velocity expressed in LS mean was 9.16 at week 13 and 8.72 at week 26. Height SDS increased during the study. According to the applicant, this indicates that the study patients reduced their growth deficit compared to normal age- and gender-matched children. The applicant indicated that more pronounced growth rates were observed for younger study patients and those with more severe growth hormone deficiency.

CT-302 average IGF-I SDS

At baseline in study CT-302, the mean (SD) IGF-I SDS was 0.85 (1.29). IGF-I SDS across visits based on an ANCOVA model are summarized in Table 36. In study CT-302, IGF-I was sampled on post-dose day 5 ± 1, which corresponds to the average weekly IGF-I value.

Table 1 CT-302 Average IGF-I SDS by visit for study patients who received prior daily somatropin treatment (ANCOVA model, Full Analysis Set)

Visit/Parameter	LS mean (SE)	95% CI
Week 13/IGF-I SDS	1.62 (0.10)	1.43, 1.82
Week 26/IGF-I SDS	1.65 (0.11)	1.43, 1.86
Week 13/IGF-I SDS change from baseline	0.71 (0.10)	0.52, 0.91
Week 26/IGF-I SDS change from baseline	0.74 (0.11)	0.52, 0.95

Source: CT-302 CSR Table 14.2.1.3
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; GH = growth hormone; IGF-I insulin-like growth factor 1; LS = least square; SE = standard error; SDS = standard deviation score
Note: Serum IGF-I measurements were taken at baseline and at 5 ± 1 days after dosing (corresponding to approximately average levels for the week) at Weeks 13 and 26. The absolute value of IGF-I SDS and its change from baseline at each visit was modelled using ANCOVA adjusting for baseline age, peak GH levels (log transformed) at diagnosis, baseline IGF-I SDS, prior GH dose level (log transformed), and prior GH dose duration (log transformed) as covariates and gender as a factor. Subjects who did not take prior GH treatment were not included in the model.

Upon switching from commercially available daily somatropin products to once-weekly lonapegsomatropin, average IGF-I SDS increased by approximately 0.7.

- Ancillary analyses

Subgroup analyses according to annualized height velocity

Subgroup analyses for annualized height velocity in study CT-302 at week 26 (age, gender, peak stimulated GH level, Tanner stage, prior exposure to somatropin therapy, duration of prior exposure to somatropin therapy) are summarized in Table 37.

Table 2 CT-302 Subgroup analyses according to annualized height velocity at week 26 (Full Analysis Set)

Subgroup Category	**AHV (cm/year)**	**ΔHSDS**	**ΔIGF-I SDS**
Age			
<3 years, n	4	4	4
Mean (SD)	16.24 (2.32)	0.96 (0.43)	1.72 (1.26)
≥3 to <6 years, n	20	20	20
Mean (SD)	9.99 (1.96)	0.41 (0.25)	0.93 (1.33)
≥6 to <11 years (girls), ≥6 to <12 years (boys), n	55	55	55
Mean (SD)	8.21 (2.21)	0.26 (0.18)	0.39 (1.27)
≥11 years (girls), ≥12 years (boys), n	65	65	63
Mean (SD)	9.02 (2.60)	0.23 (0.21)	0.97 (0.93)
Gender			
Male, n	109	109	107
Mean (SD)	9.04 (2.53)	0.28 (0.22)	0.84 (1.16)
Female, n	35	35	35
Mean (SD)	9.05 (3.25)	0.31 (0.31)	0.52 (1.19)
Peak stimulated GH levels[a]			
≤5 ng/mL, n	52	52	50
Mean (SD)	9.59 (2.85)	0.34 (0.26)	0.95 (1.21)
>5 ng/mL, n	89	89	89
Mean (SD)	8.63 (2.50)	0.24 (0.22)	0.63 (1.15)
Tanner stage			

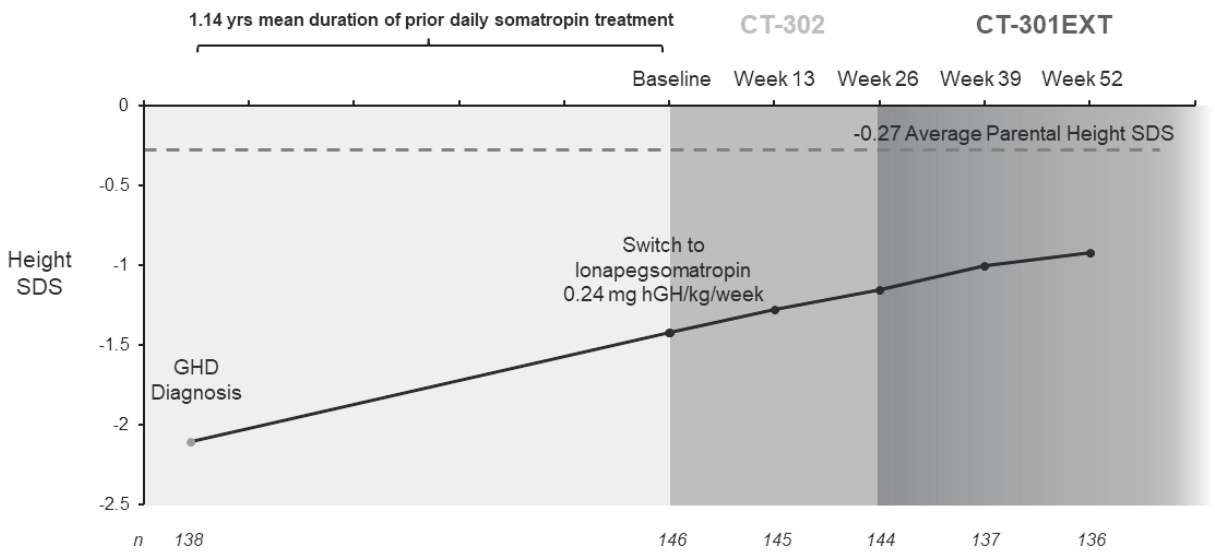
Subgroup Category	AHV (cm/year)	ΔHSDS	ΔIGF-I SDS
Stage 1, n	95	95	95
Mean (SD)	8.91 (2.76)	0.29 (0.27)	0.68 (1.25)
Stage 2, n	13	13	13
Mean (SD)	9.12 (3.19)	0.25 (0.27)	0.94 (1.44)
Stage 3, n	30	30	28
Mean (SD)	9.64 (2.42)	0.28 (0.19)	0.83 (0.77)
Stage 4, n	6	6	6
Mean (SD)	8.04 (2.14)	0.30 (0.15)	1.28 (1.00)
Prior daily somatropin treatment duration[g]			
<0.5 years, n	40	—	40
Mean (SD)	9.74 (2.11)	—	0.74 (1.01)
≥0.5 and <1 year, n	32	—	32
Mean (SD)	8.87 (2.34)	—	0.58 (1.03)
≥1 and <1.5 years, n	28	—	27
Mean (SD)	8.42 (3.13)	—	0.75 (1.26)
≥1.5 years, n	41	—	40
Mean (SD)	8.33 (2.13)	—	0.82 (1.36)

Subjects were stratified at study entry based on results of at least 2 prior growth hormone stimulation tests. This subgroup also referred to as the baseline peak growth ho stimulation strata group. g Ad-hoc analyses of AHV and ΔIGF 1 SDS by subgroup categories of prior daily human growth hormone treatment duration at baseline. Source: CT-302 CSR Tables 14.2.2.1, 14.2.2.2, 14.2.2.3, 14.2.2.5, 14.2.2.6, 14.2.2.7, 14.2.2.13, 14.2.2.14, 14.2.2.15, 14.2.2.17, 14.2.2.18, 14.2.2.20, ad hoc Table 14.2.2.17.2, and ad hoc Table 14.2.2.19.2 Abbreviations: ΔHSDS = change from baseline in height standard deviation score; ΔIGF-I SDS = change from baseline in insulin-like growth factor 1 standard deviation score; AHV = annualized height velocity;
hGH = human growth hormone; SD = standard deviation; SDS = standard deviation score Note: Subgroup categories are reflective of the point of CT-302 enrollment.

CT-301EXT data in study patients who had been included in study CT-302

Evaluation of height SDS at the time of growth hormone deficiency diagnosis, during study CT-302, and throughout ongoing study CT-301EXT (Figure 20) showed continued improvement as study patients approached their genetic potential (average parental height SDS). After 52 weeks of lonapegsomatropin treatment, height SDS improved by mean (SD) 0.51 (0.33).

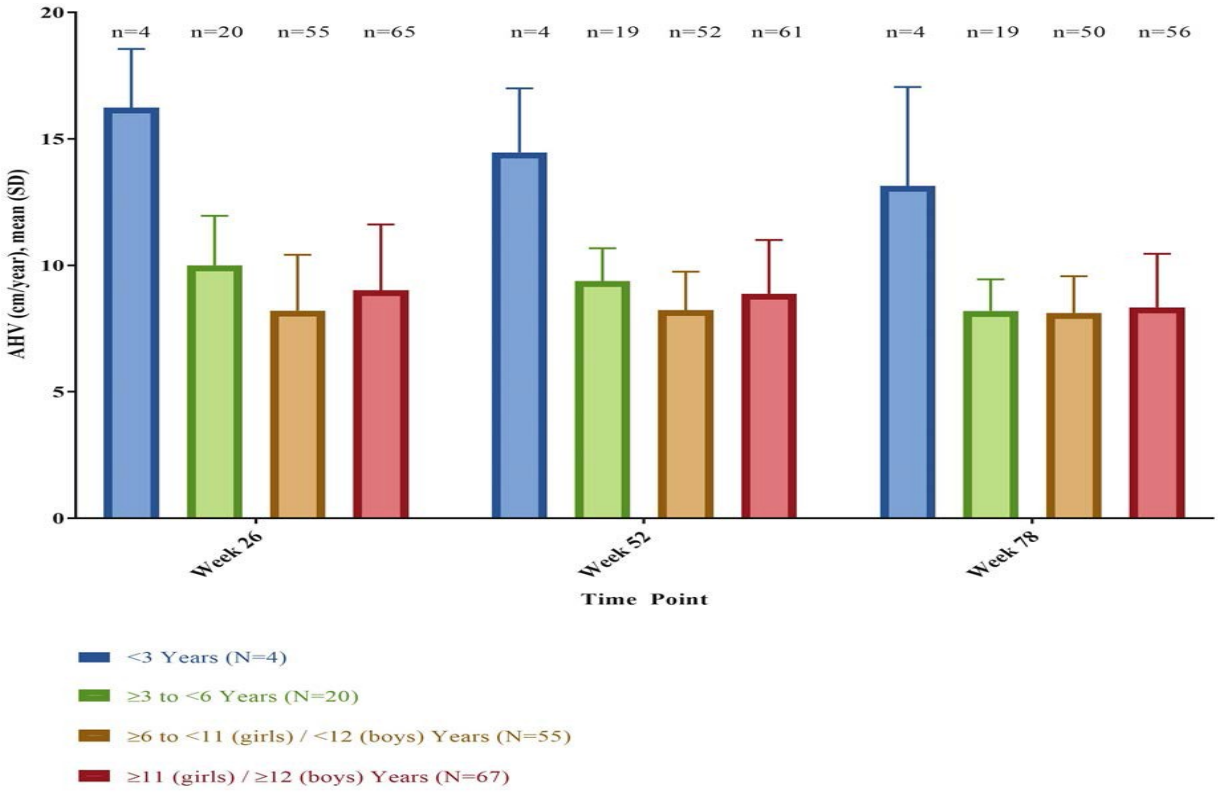
Figure 20 Height SDS for CT-302 study patients, incorporating CT-301EXT data



Source: CT-302 CSR Tables 14.1.2.1, 14.1.2.2, and 14.2.1.2; CT-301EXT CSR Table 14.2.1.2
Abbreviations: GHD = growth hormone deficiency; hGH = human growth hormone; SDS = standard deviation score; yrs = years. Note: Height SDS data from time of GHD diagnosis collected from medical records.

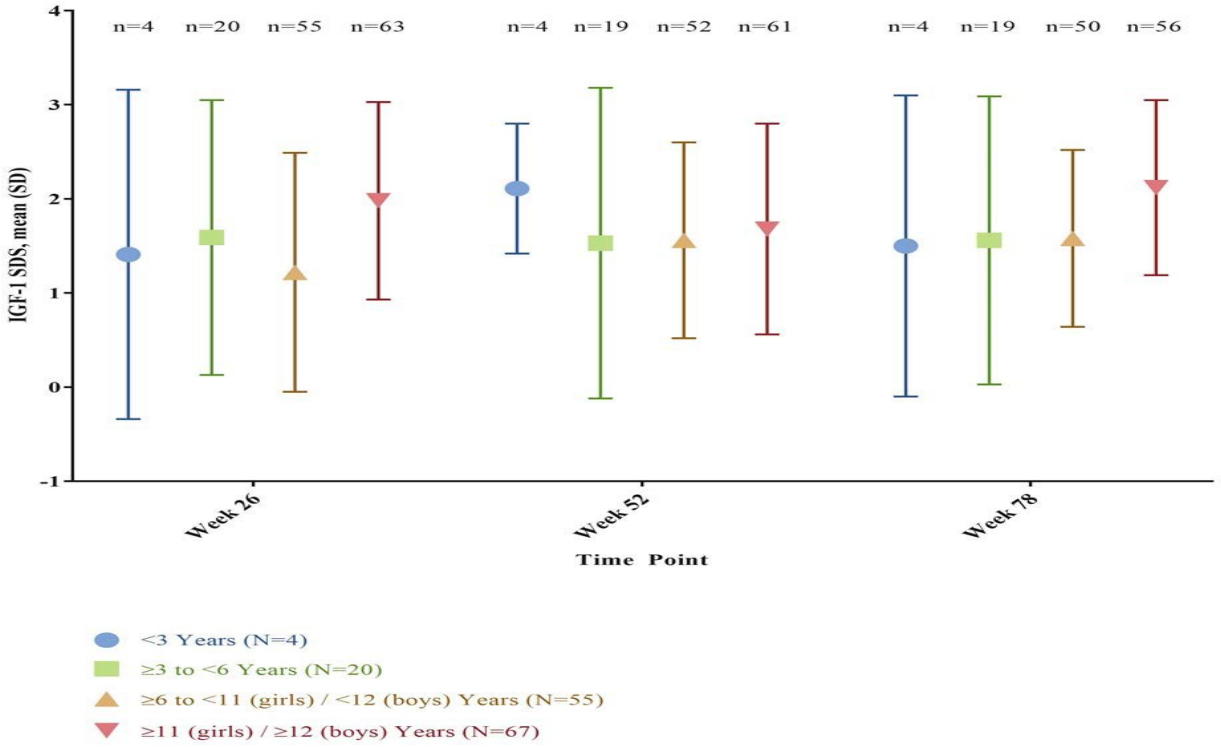
The annualized height velocity by visit and age subgroups in study CT-302 and CT-301EXT through week 78 is presented in Figure 21. The annualized height velocity tended to be larger in paediatric GHD patients under 3 years of age (n= 4) compared to those aged 3 years and above (n= 138). Similar trends were observed with respect to height SDS in these subgroups. However, observed IGF-I SDS levels were comparable in these age groups (Figure 22).

Figure 21 Annualized height velocity by visit and age subgroup in study CT-302 and CT-301EXT through week 78



Abbreviations: SD = standard deviation
Note: n denotes that number of subjects with data at a given time point. Age was at the start of CT-302 trial. Source: EMA D120 Prep Table 3.1.2.99.14

Figure 22 Average IGF-I SDS levels by visit and age subgroup in study CT-302 and CT-301EXT through week 78



Abbreviations: IGF-I = insulin-like growth factor 1; SD = standard deviation; SDS = standard deviation score. Note: n denotes that number of subjects with data at a given time point. Age was at the start of CT-302 trial. Source: EMA D120 Prep Table 3.1.2.99.12

Study CT-301EXT (enliGHten study)

Study CT-301EXT is an ongoing, global, open-label, single-arm, Phase 3, long-term extension clinical study. This study is conducted to evaluate the long-term efficacy and safety data for once-weekly lonapegsomatropin (0.24 mg hGH/kg/week) in eligible paediatric patients with growth hormone deficiency who had previously participated in study CT-301 or study CT-302.

Key results as available at the data cut-off date of 30 September 2019 have been included in the presented analyses across studies.

2.6.6. Discussion on clinical efficacy

Clinical efficacy of lonapegsomatropin treatment in paediatric patients with growth hormone deficiency (GHD) was evaluated in one Phase 2 dose-finding study (study CT-004) and three Phase 3 studies (studies CT-301, CT-302, and CT-301EXT). Study CT-301 is the pivotal study in the current application; studies CT-302 and CT-301EXT are supportive studies.

Design and conduct of clinical studies

Study design. Study CT-301 was a pivotal, 52-week, randomized, open-label, Phase 3 clinical study in paediatric GHD patients in which the clinical effects of once-weekly lonapegsomatropin compared with those of daily treatment with somatropin product Genotropin, both at a total dosage of 0.24 mg/kg/week. Included study patients were centrally allocated to lonapegsomatropin or somatropin, at a 2:1 ratio.

Though study CT-301 was an open-label study, a blinding procedure was set in order to assess endpoints without knowing a patient's treatment. However, an unspecified number of failures in the blinding procedure were reported. An appropriate reporting of unblinded study patients would have helped to better apprehend the level of bias in the study.

Supportive study CT-302 was a Phase 3, open-label, single-arm 26-week clinical study that evaluated the clinical effects of once-weekly lonapegsomatropin in 146 paediatric GHD patients with growth hormone deficiency aged 6 months up to 17 years. As 143/146 (97.9%) of included patients had (n= 143) received (n=3) prior growth hormone treatment, the design of study CT-302 is suitable to evaluate the clinical effects of lonapegsomatropin in paediatric GHD patients who had received prior growth hormone treatment.

Study patients who completed study CT-301 or CT-302 were eligible to participate in open-label extension study CT-301EXT. This is in line with the CHMP recommendation to evaluate the clinical effects of lonapegsomatropin in paediatric GHD patients for more than one year in both EMA scientific advice (EMA/CHMP/SAWP/588843/2016 and EMA/CHMP/SAWP/711581/2017). In study CT-301EXT all study patients were treated with weekly lonapegsomatropin at a dosage of 0.24 mg/kg/week. In some patients in study CT-301EXT, the safety and ease of use of lonapegsomatropin administration by means of a dual-chamber cartridge and growth hormone auto-injector were evaluated after initial administration with a syringe. This is acceptable.

Due to the open-label design of Phase 3 studies CT-301, CT-302, and CT-301EXT, the study results of these studies may be affected by bias to some extent. However, growth parameters which concern key endpoints in these studies can be measured objectively.

Study population. In pivotal study CT-301 treatment-naïve pre-pubertal paediatric GHD patients aged 3-17 years were included. These study patients were generally selected in line with general EMA guidance in this respect (EMEA/CHMP/BMWP/94528/2005 Rev. 1) and EMA scientific advice on lonapegsomatropin (EMA/CHMP/SAWP/588843/2016).

In study CT-302, paediatric GHD patients aged 6 months up to 18 years were included. These patients had to have received prior growth hormone treatment, except from those aged 6 months up to 3 years. GHD Was diagnosed according to criteria mentioned in guidelines on growth hormone deficiency.[5,6] In addition, many in- and exclusion criteria were in line with those in pivotal study CT-301. Overall, respective criteria were endorsed by the CHMP in the scientific advice.

[5] GH Research Society. Consensus guidelines for the diagnosis and treatment of growth hormone (GH) deficiency in childhood and adolescence: summary statement of the GH Research Society. The Journal of Clinical Endocrinology & Metabolsim. Vol. 85 (11). 2000: 3990-3993.

[6] Grimberg et al. Guidelines for growth hormone and insulin-like growth factor-I treatment in children and adolescents: growth hormone deficiency, idiopathic short statures, and primary insulin-like growth factor-I deficiency. Hormone research in paediatrics 2016; 86: 361-397.

Comparator. In study CT-301, clinical effects of weekly lonapegsomatropin were compared with those of daily dosed somatropin product Genotropin, both at a total weekly dose of 0.24 mg/kg/week. The selected dosage of the somatropin product Genotropin is in line with the recommended posology of this product in the SmPC of Genotropin. It is acknowledged that a weekly lonapegsomatropin dosage of 0.24 mg/kg/week was accepted by the CHMP in the EMA scientific advice. The recommended starting dose in paediatric GHD patients who received prior growth hormone treatment, as well as the dose titration and treatment monitoring ((based on IGF-I SDS levels, auxological parameters, safety, gender, prior treatment with daily GH) and the frequency of this monitoring in particular circumstances (e.g. after a dose change, change of Tanner stage, or adverse events) in lonapegsomatropin-treated paediatric GHD patients irrespective of any prior growth hormone treatment, were substantiated. The applicant proposed for naïve and non-naïve children acceptable recommendations of dose titration and treatment evaluation in the SmPC according to IGF-I SDS levels and puberty status. The gender has no impact on the dose. In line with this, the somatropin dosing recommendations with lonapegsomatropin are the same for boys and girls with GHD (see also above clinical pharmacology section).

Endpoints. The primary efficacy endpoint in study CT-301 was the annualized height velocity at week 52. Secondary efficacy endpoints in this study included the annualized height velocity over 52 weeks, the change in height SDS over 52 weeks, and serum IGF-I and IGFBP-3 levels. Aforementioned primary and secondary endpoints are relevant for the evaluation of the clinical effects of growth hormone treatment and were considered acceptable in EMA scientific advice EMA/CHMP/SAWP/588843/2016.

The CHMP advised in 2016 (EMA/CHMP/SAWP/588843/2016) that increased adherence compared to daily injections and PROs should be considered as secondary outcome measures for pivotal study CT-301. Although these endpoints were not included in study CT-301, such endpoints were included in studies CT-302 and study CT-301EXT.

Studies CT-302 and CT-301EXT had similar endpoints. Considering the aforementioned scientific advice, the respective endpoints in these studies are also acceptable.

Statistical analysis. For the comparison of clinical effects with respect to the primary endpoint annualized height velocity at week 52 in study CT-301, a non-inferiority margin of 2.0 cm/year was chosen. A test for superiority would be conducted if non-inferiority was demonstrated. In the EMA scientific advices it was indicated that this non-inferiority margin could be acceptable upon appropriate substantiation.

Efficacy in studies CT-302 and CT-301EXT was evaluated in a descriptive manner, since no comparisons between study arms can be made between study arms in these open-label studies.

Dynamic allocation (minimization rule) was used for randomization in study CT-301. When dynamic allocation is used the type 1 error control is not always ensured with conventional statistical methods, as indicated in the EMA Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013). The impact and implications of dynamic allocation methods on the statistical analysis were initially unclear. A re-randomization test provided comparable results, indicating that dynamic allocation unlikely has led to a much-inflated Type I error.

Eighteen major protocol deviations were reported in study CT-301. It was initially unknown to which extent obtained study results will change if study patients with major protocol deviations would be excluded. The applicant showed that upon exclusion of all study patients with major deviations, non-inferiority of lonapegsomatropin as compared to somatropin was still demonstrated in the per-protocol population.

From conducted geographical subgroup analysis concerning the primary endpoint in study CT-301, the obtained results in EU countries were unclear. The applicant demonstrated later in a primary subgroup analysis restricted to EU countries consistent results with the overall analysis. Though the EU population was a small fraction of the total study population (~12%), the CHMP agrees that non-inferiority was also confirmed in this subgroup.

Efficacy data and additional analyses

Patient disposition. 162 Study patients were randomized in study CT-301. 104 of 106 (98.1%) study patients randomized to lonapegsomatropin and 55 of 56 (98.2%) study patients randomized to somatropin completed the study. Hence, premature study dropout was well-balanced between study treatment groups.

Of the 146 study patients dosed in study CT-302, 144 (98.6%) completed the study.

Baseline characteristics. In study CT-301, the demographics and baseline data between the treatment groups were balanced. At baseline, study patients had diminished growth with a mean height velocity of 3.93 cm/year and a mean height SDS of -2.93. These data indicate a serious growth retardation. The majority of study patients (65.2%) had isolated, idiopathic aetiology of growth hormone deficiency.

The proportion of men of the total study population that was included in studies CT-004, CT-301 and CT-302 were respectively 71.7%, 82.0% and 75.3%. These proportions exceed the male proportion of growth hormone deficiency patients of 66.7%, i.e. a male: female ratio of 2:1, reported in the literature (e.g. Grimberg et al. 2005). The relatively high proportions of male GHD study patients in the clinical studies hamper comparisons between the studies on lonapegsomatropin and studies on other growth hormone medicinal products.

The impact of gender on the lonapegsomatropin dosing recommendations was initially unclear. The applicant indicated later that currently available results on key efficacy endpoints are similar for male and female GHD patients. In line with this, the somatropin dosing recommendations with lonapegsomatropin are the same for boys and girls with GHD (see also above clinical pharmacology section).

In study CT-302, no European patients were included. Like in study CT-301, the proportion of men (75.3% of study patients) was relatively high. Only four GHD patients under 3 years of age were included in study CT-302 and they appeared to be more sensitive to the clinical effects of lonapegsomatropin compared to older paediatric GHD patients. During the assessment process, the applicant decided not to seek an indication for lonapegsomatropin in paediatric GHD patients under 3 years of age due to limited data in this group of patients.

Compliance. The compliance in study CT-301 was between >95% and ≤100% for 99% of lonapegsomatropin-treated study patients and 94.6% of somatropin-treated study patients. In study CT-302 mean treatment compliance (SD) during study CT-302 was 98.4% (3.97%) with a range of 76.0 to 104.0%. The majority of study patients (132 study patients, 90.4%) had compliance rates >95%. The aforementioned data show that the compliance rates of lonapegsomatropin were acceptable in paediatric GHD patients who either had or had not received prior growth hormone treatment. However, it is unclear whether the compliance rates in the trial can also be expected in clinical practice.

Primary endpoint – Annualized height velocity at week 52. For observed cases in study CT-301, the mean (SD) annualized height velocity at week 52 was 10.90 (2.29) cm/year for lonapegsomatropin and 10.22 (2.37) cm/year for somatropin. The LS mean (SE) of annualized height velocity at week 52 was 11.17

(0.23) cm/year for lonapegsomatropin compared with 10.31 (0.30) cm/year for somatropin, with a difference in LS means (SE) of 0.86 (0.33) cm/year (95% CI: 0.22 to 1.50). Since the lower confidence bound was above the non-inferiority margin of -2.0 cm/year, non-inferiority was demonstrated. In addition, the treatment difference was statistically significant in favour of lonapegsomatropin (P = 0.0088); therefore, statistical superiority has been demonstrated but not clinically. Indeed, the upper bound of the 95% confidence interval (0.22, 1.50) is inferior to the +2 cm limit of non-inferiority. Consistent results were obtained from sensitivity analyses with different analysis models and missing data handling methods. As in clinical practice, paediatric GHD patients are titrated on growth (velocity) for efficacy and IGF-I (above the +2 SDS) for safety and adherence to treatment. The observed results suggest a difference in titration in both arms. Therefore, although the superiority of lonapegsomatropin over somatropin was demonstrated statistically, it is unclear whether comparable IGF-I levels would also provide a (clinically relevant) better response. Hence, there is insufficient evidence to conclude that the clinical effects of weekly lonapegsomatropin are superior to those of daily somatropin.

Secondary endpoints are in line with the primary outcome.

A statistically significant treatment-by-age interaction was observed in study CT-301. This finding is consistent with the known effects of daily somatropin, where larger annualized height velocities are observed for younger children.[7] The larger treatment difference in favour of lonapegsomatropin for younger children reflects greater treatment benefit for patients with greater growth potential compared to older GHD patients. It is well-known that older children have less growth benefit potential from growth hormone treatments. Because of this, the expected clinical response to lonapegsomatropin concerning growth will be more limited and not relevant after achieving final height in older GHD patients.

In study CT-302, annualized height velocity in LS mean was 9.16 at week 13 and 8.72 at week 26. Observed height velocities tended to be somewhat lower compared to those observed in study CT-301. These observations are in line with literature indicating that growth in paediatric GHD patients continues at a lower, more constant rate after an initial catch-up growth in treatment- non-naïve paediatric GHD patients.[8]

Secondary endpoint - Change in height SDS compared to baseline. In study CT-301, changes in height SDS compared to baseline tended to increase for both lonapegsomatropin (LS means week 5: 0.13, LS means week 52: 1.10) and somatropin (LS means week 5: 0.12, LS means week 52: 0.96) during follow-up. Treatment differences with respect to this endpoint were statistically significant from week 26 onwards.

In line with the annualized height velocity, change from baseline in height SDS at week 26 upon lonapegsomatropin treatment tended to be larger in growth hormone treatment naïve patients in study CT-301 (LS mean 0.68) compared to those in study CT-302 (LS mean 0.25).

Secondary endpoint – Average IGF-I SDS levels. In study CT-301, average IGF-I SDS levels tended to increase for both lonapegsomatropin and somatropin from week 13 (LS mean lonapegsomatropin: 0.31, LS mean somatropin: -0.60) up to week 52 (LS mean lonapegsomatropin: 0.72, LS mean somatropin: -0.02). The average IGF-I SDS levels were higher for lonapegsomatropin as compared to somatropin throughout the study. In line with this pharmacodynamic effect, the clinical effects of lonapegsomatropin with respect to growth were larger than those of somatropin.

[7] Bakker B, Frane J, Anhalt H, Lippe B, Rosenfeld RG. Height velocity targets from the national cooperative growth study for first-year growth hormone responses in short children. J Clin Endocrinol Metab. 2008 Feb;93(2):352-7.

[8] Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr. 2013;79(2):51-67.

At baseline in study CT-302, the mean IGF-I SDS was +0.85. Upon switching from commercially available daily somatropin products to once-weekly lonapegsomatropin, average IGF-I SDS increased by approximately 0.7. These data support improved growth parameters in these patients, as reported above.

In the clinical studies, the average IGF-I SDS levels increased over time with a significant proportion of paediatric GHD patients with average IGF-I SDS levels above +2 (i.e. 7.6% in CT-301, 56.8% in CT-302 and 48.6% in CT-301 EXT at any point) and above +3 (i.e. 25.3% in CT-302 and 19.6% in CT-301 Ext at any point), especially in non-naïve patients who switched from daily somatropin to weekly lonapegsomatropin. Chronically elevated IGF-I SDS levels may increase particular safety risks such as neoplasms, diabetes mellitus type 2, and brain hemorrhages. The patient characteristics of study patients in whom elevated IGF-I SDS levels were observed were initially unclear. In *post hoc* univariate logistic regression analyses, age, weight, and more advanced Tanner stages (3, 4, and 5) were significantly associated with IGF-I SDS levels above +2. Especially in these patients, regular monitoring of IGF-I SDS levels and dose adjustments in case of IGF-I SDS levels outside the normal range between -2 and +2 are mandatory (the IGF-I SDS target should be close to 0 SDS according to Collett-Solberg et al. 2019[9]). Upon request, the applicant included practical guidance with respect to somatropin starting doses with lonapegsomatropin, treatment monitoring including evaluation of IGF-I SDS levels, and somatropin dose adjustment in the SmPC. A more specific discussion about these aspects is available in the clinical pharmacology section above.

Subgroup analyses. According to a subgroup analysis in study CT-301, several baseline characteristics seem to be associated with a more pronounced favourable response to lonapegsomatropin as compared to somatropin treatment. These baseline characteristics include age < 6 years, a growth hormone level > 5 ng/ml during a growth hormone stimulation test, male gender, and a patient origin outside the United States of America.

The difference in effects between lonapegsomatropin and somatropin treatment with respect to the annualized height velocity at week 52 tended to be smaller in US patients compared to non-US patients in study CT-301. The reason for this trend was first unclear. It was reported in literature that annualized height velocity in the first year is influenced by demographic variables, such as chronological age, bone age, height, height velocity, and IGF-I prior to initiating treatment, as well as severity of GHD.[10] The US patients had older chronological age, older bone age, higher baseline height SDS, higher baseline IGF-I SDS, and higher baseline height velocity. In addition, the imprecision due to the small sample size in the US (n= 42) could explain the wider confidence interval in US patients as compared to non-US patients. It is likely that differences in baseline characteristics ma explain (part of) the observed difference. There is no evidence that the underlying treatment effect of lonapegsomatropin is different for US patients as compared to non-US patients.

Ancillary analyses. An integrated analysis was conducted across studies CT-301, CT-302, and CT-301EXT. Efficacy across studies was evaluated in two pools:

- **Efficacy pool I**: a longitudinal review of a treatment-naïve study population that received lonapegsomatropin or somatropin in study CT-301 and subsequently lonapegsomatropin in study CT-301EXT.

[9] Collett-Solberg PF, Ambler G, Backeljauw PF, et al. Diagnosis, Genetics, and Therapy of Short Stature in Children: A Growth Hormone Research Society International Perspective. Horm Res Paediatr. 2019;92(1):1-14.
[10] Ranke MB, Lindberg A, Chatelain P, Wilton P, Cutfield W, Albertsson-Wikland K, Price DA. Derivation and validation of a mathematical model for predicting the response to exogenous recombinant human growth hormone (GH) in prepubertal children with idiopathic GH deficiency. KIGS International Board. Kabi Pharmacia International Growth Study. J Clin Endocrinol Metab. 1999 Apr;84(4):1174-83.

- **Efficacy pool II**: a pooled review of efficacy data in study CT-301EXT in study patients who had received treatment with somatropin product Genotropin in study CT-301, and study patients in study CT-302 who had received prior somatropin treatment.

The results of efficacy pool analyses should be interpreted with caution due to differences between particular studies. This especially applies to efficacy pool II, in which GHD patients from different studies were included. Efficacy pool analyses may therefore only be used for explorative purposes.

The rationale for a rolling baseline was initially not understood. The applicant later clarified that the annualized height velocity concerns the annualized height velocity calculated based on the available data within the first year of follow-up or the annualized height velocity over the last year from follow-up week 65 onwards. Hence, the annualized height velocity concerns the annualized height velocity within the last year.

Some study patients prematurely discontinued study participation in studies CT-301, CT-302, and CT-301EXT. Limited information about this is available. The applicant later indicated that three out of five study patients who had participated in study CT-302 withdrew their consent in study CT-301EXT because of reaching satisfactory height, according to the investigator.

Efficacy pool I. At the end of study CT-301 (week 52), the annualized height velocity for lonapegsomatropin was 11.2 cm/year. Continued growth was observed with continued lonapegsomatropin treatment beyond the first year, with an annualized height velocity of 8.7 cm/year at week 104. At the end of CT-301 (week 52), the annualized height velocity for somatropin was 10.3 cm/year. After a treatment switch to lonapegsomatropin, the annualized height velocity at week 104 was 9.0 cm/year. At week 104, the annualized height velocity of study patients who had received lonapegsomatropin (8.7 cm/year) and those who had received somatropin (9.0 cm/year) in study CT-301 was comparable. Data mentioned above indicate that after a switch from somatropin to lonapegsomatropin a similar annualized height velocity can be obtained as compared to patients who had been treated with lonapegsomatropin. Similar trends were observed for height increases and IGF-I levels.

The aforementioned observations are in line with literature indicating that growth in paediatric GHD patients continues at a lower, more constant rate after an initial catch-up growth in treatment-naïve paediatric GHD patients.[11]

Efficacy pool II. In efficacy pool II, the annualized height velocity was relatively constant (LS mean 8.6 up to 8.8 cm/year) from week 13 up to 52 in paediatric GHD patients who have received prior growth hormone treatment. This also applied to the average IGF-I SDS and IGFBP-3 levels. Changes in height SDS tended to increase with time (LS mean week 13: 0.13, LS mean week 52: 0.48).

In a subgroup analysis of efficacy pool II younger paediatric GHD patients and those with more severe growth hormone deficiency (peak stimulated growth hormone ≤5 ng/ml) displayed more pronounced rates of growth as measured by the annualized height velocity and change from baseline in height SDS. The potential implications of the subgroup analysis for efficacy pool II for lonapegsomatropin treatment in clinical practice were initially unclear. The applicant indicated later that the subgroup analyses in efficacy pool II support the efficacy of lonapegsomatropin treatment in clinical practice across the ages, and spectrum of peak stimulated GH levels, among other variables in the Phase 3 studies. It is also agreed that the efficacy results in efficacy pool II also support the broad clinical efficacy of weekly lonapegsomatropin in patients who switched from daily somatropin treatment.

[11] Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr. 2013;79(2):51-67.

Growth hormone treatment may, at least in theory, result in earlier than expected closure of growth plates, leading to premature cessation of growth effects (Kang 2019). This was not observed for lonapegsomatropin. **Bone age** in years was similar at baseline, week 52 and week 104 in study patients who had been treated with either lonapegsomatropin or somatropin in study CT-301 and who received lonapegsomatropin in study CT-301EXT.

The **treatment burden** as evaluated by the Child Sheehan Disability Scores for both the paediatric study patients and (their) parents decreased from baseline in study patients treated with lonapegsomatropin in studies CT-302 and CT-301EXT. This also applies to study patients who used the dual-chamber cartridge and growth hormone auto-injector combination product in study CT-301EXT.

A consistent **preference** for once-weekly lonapegsomatropin relative to daily somatropin treatment was reported by children and parents at week 6 and 13 in studies CT-302 and CT-301EXT. This preference increased with continued lonapegsomatropin treatment. Acceptable convenience (≥ 69) and satisfaction (≥ 80) scores of the TSQM-9 questionnaire were obtained in parents of study patient upon the use of lonapegsomatropin in efficacy pool II. This also applies to parents of study patients who switched to the dual-chamber cartridge and growth hormone auto-injector combination product in study CT-301EXT.

Available data indicate that the use of the dual-chamber cartridge and growth hormone-auto injector combination product was safe and easy to use in the majority of study patients.

Study data of ongoing study CT-301EXT were initially submitted until the data cut-off in September 2019. Later, additional clinical efficacy data of ongoing study CT-301EXT were submitted until the data cut-off in June 2020.

Long-term data on the clinical effects of lonapegsomatropin are yet unavailable. Growth on lonapegsomatropin treatment may decrease or even stop prematurely. It is yet unknown whether paediatric GHD patients on lonapegsomatropin treatment can achieve a similar final height as those who were treated with somatropin. For this reason, both the PDCO (P/0275/2020) and CHMP (scientific advice EMA/CHMP/SAWP/588843/2016 and EMA/CHMP/SAWP/711581/2017) indicated that long-term efficacy data on the clinical effects of lonapegsomatropin should be obtained. The PDCO requested data on the final heights of included paediatric GHD study patients. These data will be obtained as part of a requested PASS.

Assessment of paediatric data on clinical efficacy

Lonapegsomatropin has been developed for treatment of paediatric GHD patients. All Phase 3 studies were conducted in these patients. A paediatric investigational plan was approved and completed (see above).

2.6.7. Conclusions on the clinical efficacy

Submitted clinical studies support the clinical efficacy of lonapegsomatropin treatment in paediatric GHD patients who have or have not received prior growth hormone treatment. In the pivotal study CT-301, the mean annualized height velocity in growth hormone treatment naïve study patients at week 52 was 10.90 cm/year for lonapegsomatropin and 10.22 cm/year for somatropin. The LS mean of annualized height velocity at week 52 was 11.17 cm/year for lonapegsomatropin compared with 10.31 cm/year for somatropin, with a difference in LS means of 0.86 cm/year (95% CI: 0.22 to 1.50). Non-inferiority was demonstrated. In addition, the treatment difference was statistically significant in favour of lonapegsomatropin (P = 0.0088). Taking into account the differences in IGF levels, there is, however, insufficient evidence to conclude

therapeutic superiority of lonapegsomatropin over somatropin.

Lonapegsomatropin is also effective in paediatric GHD patients who have received prior growth hormone treatment, but the clinical effects of lonapegsomatropin tend to be less pronounced in these patients than those who are naïve to growth hormone treatment.

The clinical effects of long-term lonapegsomatropin treatment should be evaluated further.

Long-term efficacy data, i.e. data on final height, will be generated as part of the secondary objectives of the PASS.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

A total of 379 individuals (306 children with GHD and 73 healthy adult subjects) have been exposed to at least 1 dose of lonapegsomatropin. At the 01 June 2020 data cut, of the 306 children included in the clinical programme 290 were exposed to lonapegsomatropin for more than one year. Lonapegsomatropin treatment was initiated under 3 years of age in four paediatric GHD patients.

In the safety pool II 160 patients were mentioned to have a follow-up of ≥2 year.

Overall, the mean duration of lonapegsomatropin treatment was 100.3 weeks, and the mean number of actual doses of study drug was 499.3.

2.6.8.2. Adverse events

Overall, 29 study patients (9.5%) experienced treatment-related treatment-emergent adverse events. Respective adverse events were reported at a comparable frequency among study patients who had (8.6%) and those who had not one or more IGF-I SDS levels above +2 (10.8%). Commonly reported (≥2 subjects overall) treatment-related treatment-emergent adverse events were secondary hypothyroidism (2.6%), headache (2.0%), increased IGF-I (1.3%), growing pains and injection site atrophy (0.7% each). Strabismus and hypermetropia were also considered related to lonapegsomatropin treatment, but all cases were reported from the same investigator who had doubts about a possible relationship with drug products. The review of cases of strabismus and hypermetropia did not provide sufficient level of evidence of a causal relationship with lonapegsomatropin.

2.6.8.3. Serious adverse event/deaths/other significant events

There have been no deaths reported in the clinical development program for lonapegsomatropin.

In Safety Pool II, 12 (3.9%) experienced 20 serious adverse events: 6 study patients (5.7%) in the CT-301 lonapegsomatropin/CT-301EXT group, 3 study patients (5.5%) in the CT-301 somatropin/CT-301EXT group, and 3 study patients (2.1%) in the CT-302/CT-301EXT group. Besides the single patient in study CT-301 treated with daily somatropin who reported a serious adverse event, several study patients treated with lonapegsomatropin experienced serious adverse events of epilepsy (including generalized tonic-clonic seizure; N=2), pyrexia (N=1), gastrointestinal viral infection (N=1), vomiting (N=1), cyclic vomiting syndrome (N=1), adenoidal hypertrophy (N=1), appendicitis (N=1), atrioventricular block (N=1), chest pain

(N=1), tonsillitis (N=1), humerus fracture (N=1), pneumonia (N=1), headache (N=1), upper limb fracture (N=1), serum sickness-like disorder (N=1), and rash (N=1). None of these serious adverse events was assessed by the Investigator as related to the study drug or resulted in changes in study drug dose.

2.6.8.4. Laboratory findings

Although there were occasional excursions for individual subjects, the mean and median values of all haematology, chemistry, lipid panel (cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides) and hormone and glycaemic parameters remained within the reference ranges at all time points.

2.6.8.5. In vitro biomarker test for patient selection for safety

No such studies were conducted, which is agreed by the CHMP.

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

2.6.8.7. Immunological events

Anti-drug antibody findings following lonapegsomatropin exposure and its potential impact on clinical efficacy and safety were evaluated. The evaluation was conducted for all analysed samples up to the interim data cut date of 01 June 2020.

Overall, transient positive results for anti-hGH binding antibodies were seen after baseline in a total of 14 subjects (4.7%). Treatment-emergent anti-hGH antibodies were detected in 13 subjects, while 1 subject had a treatment-boosted positive result.

Twelve subjects (4.0%) had treatment-emergent positive anti-lonapegsomatropin binding antibody results. Antibodies were transient in 6 subjects (2.0%) and persistent in 6 subjects (2.0%).

Two subjects (0.7%) had treatment-emergent, transient positive results for anti-mPEG binding antibodies.

The impact of persistent antibodies against lonapegsomatropin on clinical efficacy was initially unclear. The applicant later showed that the IGF-I SDS levels and height SDS of the six study patients with antibodies against lonapegsomatropin were within the range of study patients without such antibodies. Hence, observed persistent antibodies against lonapegsomatropin are non-neutralising, i.e. they do not affect efficacy.

For safety, the applicant analysed the relation between injection site reactions and ADA. Of the 4 patients with injection site reactions (on lonapegsomatropin), only 1 was positive for ADA. Given the limited analysis and the low number of events, no firm conclusions can be drawn. This will be evaluated further as part of routine pharmacovigilance.

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

No formal drug-drug interaction studies have been conducted with lonapegsomatropin. This is agreed by the CHMP.

2.6.8.9. Discontinuation due to adverse events

There have been no treatment-emergent adverse events that led to the discontinuation of the study drug during any of the phase 3 studies of lonapegsomatropin.

2.6.8.10. Post marketing experience

Lonapegsomatropin was approved in the United States on 25 August 2021 for the treatment of paediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone (GH). 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

In the safety assessment information from Safety Pool II (consisted of integrated data from the three phase 3 studies in children with GHD (CT 301, CT 302, and CT 301EXT)) was used.

Exposure

The number of patients (N=306) is limited for a safety database and does not fulfil the requirements of the ICH-E1 (at least 1500 patients exposed). However, as growth hormone is a well-known active substance, as is the PEG used, the safety database is considered sufficient to compare the safety profile with the known profile of growth hormone and the PEG.

In Safety Pool II, 290 children were exposed to lonapegsomatropin for more than one year. Further, 160 children were treated for ≥2 years. The mean exposure (SD) was 100.3 (29.5) weeks. This exposure is sufficient for the assessment of acute safety (within one year). For long-term safety, this follow-up time is considered insufficient as there is an ongoing discussion on the carcinogenic effect of GH (and/or IGF-I) and possible induction of type 2 diabetes mellitus. It is anticipated that long-term safety risks of lonapegsomatropin treatment are more likely in the case of IGF-I SDS levels above +2. As indicated in the pharmacodynamic section, such IGF-I SDS levels were increasingly observed upon lonapegsomatropin treatment with time, especially in non-naïve patients. From the available scientific information, it is unclear what are the characteristics of paediatric GHD patients in whom such IGF-I SDS levels were observed. A follow-up measure regarding conducting a PASS is proposed.

The PASS should not only collect information on malignancies and cases of diabetes mellitus type 2 but also should evaluate the – theoretical – adverse events induced by the PEG molecule (see non-clinical part of the dossier). Due to the absence of specific markers for safety risks of mPEG exposure, it is difficult to demonstrate that particular safety risks are due to long-term mPEG exposure. However, evaluation of renal, hepatic, immunologic, and neurologic adverse events, neurological examination (e.g. cranial nerves, motor and sensory function, gait, coordination and language), and laboratory parameters (e.g. serum creatinine, transaminases, bilirubin, alkaline phosphatase) are useful to evaluate potential safety risks due to mPEG exposure. Similar evaluations are conducted in ongoing PASS of medicinal products indicated for treatment of

patients with haemophilia A.

As the concerns are based on the ongoing discussion in the scientific community (malignancies and type 2 diabetes mellitus) or non-clinical observations (PEG related issues) the PASS should be considered a category 3.

The indications of several PEGylated medicinal products are limited to patients aged 12 years and above due to uncertainties concerning the long-term safety risks of mPEG exposure. Considering lonapegsomatropin is transiently pegylated, mPEG clearance is expected to be faster with lonapegsomatropin compared to permanently PEGylated compounds for long-term use. In line with this, observed non-clinical and clinical data on therapeutic lonapegsomatropin doses thus far do not indicate increased safety risks in paediatric GHD patients aged 3-12 years. Hence, currently available data suggest that the safety risks of mPEG exposure are acceptable in paediatric GHD patients aged 3-18 years in the short-term. Based on the currently available data, the possibility of prolonged mPEG accumulation in the choroid plexus and other tissues and organs is considered to be small at the expected exposure range. Safety risks of long-term mPEG exposure with lonapegsomatropin will also be evaluated in a PASS.

Patient and baseline characteristics

Subjects were predominantly male (78.8%), the mean (SD) age for subjects who initiated lonapegsomatropin treatment was 9.7 (3.5) years. Of the patients, 69.7% were prepubertal (Tanner stage I) upon starting lonapegsomatropin treatment, particularly study patients who started in CT-301, which required study patients to be in Tanner stage I at enrolment. In the safety pool II 64.7% of study patients had prior human growth hormone treatment experience (198/306 study patients), and the mean (SD) duration of prior human growth hormone therapy was 1.10 (0.63) years (range: 0.25 to 3.97 years). The most frequent mentioned medical conditions are endocrine disorders.

The male predominance is well-known, with an almost 2:1 male to female ratio. Therefore the 78.8% male patients in safety pool II and the 81.9% male patients in study CT-301 might induce some bias. The mean age for study patients who initiated lonapegsomatropin treatment was similar to the age of treatment initiation for the general paediatric GHD population. Traditionally, in studies evaluating growth in children, all patients included are pre-pubertal. Given the fact that 30.6% of the patients is not prepubertal, the effects of sex hormones introduce a bias; therefore, a comparison with literature should be made with caution.

Overall, the most common (≥10%) concomitant medications were painkillers/ antipyretics (propionic acid derivatives, 38.9%; anilides, 33.7%); penicillins with extended-spectrum (19.3%), antihistamines for systemic use (17.0%); glucocorticoids (15.7%); plain multivitamins (15.0%), piperazine derivatives (14.4%); thyroid hormones (13.7% each); centrally acting sympathomimetics (13.1% each); selective beta-2 adrenoreceptor agonists (12.1%) corticosteroids and expectorants (11.4% each); and opium alkaloids and derivatives (10.5%). This is not unexpected for patients suffering from GHD.

Overall, the type and frequency of concomitant treatments were balanced across patient study groups.

Adverse events

Overall, over three-quarters of subjects experienced at least 1 **treatment-emergent adverse event** (235/306; 76.8%). The incidence of treatment-emergent adverse events considered by the investigator to be related to the study drug was 9.5%.

The most common treatment-emergent adverse events (≥10%) were upper respiratory tract infection

(23.2%), pyrexia (16.3%), nasopharyngitis (15.4%), headache (12.7%), and cough (12.1%). The occurrence of pyrexia was associated with adverse events pertaining to the system organ class Infections or infestations or with other adverse events commonly associated with pyrexia such as headache, vomiting and nausea in most cases which provide a more probable explanation. Moreover, interpretation of the imbalance of incidence of pyrexia observed between somatropin, and lonapegsomatropin groups is difficult considering the low number of patients enrolled. Therefore, there is not sufficient evidence of a causal relationship between pyrexia and lonapegsomatropin.

Overall, most subjects experienced treatment-emergent adverse events that were mild (44.4%) or moderate (29.1%); 10 subjects (3.3%) experienced treatment-emergent adverse events that were severe.

Overall, 29 subjects (9.5%) experienced **treatment-related emergent adverse events**. Commonly reported (≥2 subjects overall) treatment-related treatment-emergent adverse events were secondary hypothyroidism (2.6%), headache (2.0%), increased IGF-I (1.0%), growing pains, scoliosis, and injection site atrophy (0.7% each). Three treatment-emergent adverse events strabismus and hypermetropia were considered related to lonapegsomatropin treatment by the same investigator who had doubts about a possible relationship with drug products. However, the review of these 3 cases (2 with lonapegsomatropin and 1 with somatropin) did not provide sufficient evidence for a causal relationship with lonapegsomatropin since strabismus and hypermetropia are not expected adverse reaction of growth hormone therapy.

Except for injection site atrophy the safety profile of lonapegsomatropin was consistent with that of daily somatropin products evaluated in a clinical study setting.

There have been no **deaths** reported in the clinical development program for lonapegsomatropin.

Serious adverse events were experienced by 12 subjects (3.9%) overall; none of these serious adverse events were assessed by the investigator as related to the study drug or resulted in changes in study drug dose.

Based on few available data on **laboratory findings** and multiple causes for reported excursions, no dose adjustments or specific warnings can be proposed in the product information.

During the clinical program, there were no remarkable findings for vital signs.

Local tolerability is of special interest with once-weekly preparations. In comparison with somatropin (study CT-301), the incidence reported 15 minutes after the administration of study patients was greater in the lonapegsomatropin group (redness (20% vs 3.6%), swelling (5.7% vs 0.0%), or other injection-related symptoms (1.0% vs 0.0%)). The incidence of bruising was comparable between both arms. In the open-label study (study CT-302) 15 minutes after the administration, study patients reported symptoms of redness (47.3%), swelling (12.3%) or pain (3.5%). In the lonapegsomatropin treated patients reporting of injection-related symptoms decreased over subsequent weeks. Injection side atrophy was mentioned for 3 patients (of the 306 in the pool). In one patient, the atrophy resolved. In the somatropin group, injection site atrophy was not reported. Although anecdotally mentioned as an adverse event during daily growth treatment, injection site atrophy in 0.7% of the patients is surprising. In this aspect, it is reassuring that the frequency of lipoatrophy is more or less the same between daily growth hormone (1.2%) and the lonapegsomatropin when using the auto-injector (1.5%). To further reduce the injection site reactions, it is advised in the SmPC to vary the administration site to prevent lipoatrophy (this is a class warning). Based on these results and additional literature showing that growth hormone itself may cause the observed lipoatrophy, this adverse event is not thought to negatively impact the compliance to the lonapegsomatropin as compared to the daily somatropin treatment.

Dose reductions were mostly due to high IGF-I levels. In 1 subject this was temporary. In 3 subjects, the dose was reduced for the remainder of the study. Two subjects had their dose of study drug reduced due to headache. Temporarily dose reductions were due to coxitis, abdominal pain and viral gastroenteritis. One subject had a dose reduction while on somatropin treatment. The dose was reduced due to facial oedema. Doses of growth hormone treatment may need to be adjusted due to abnormal IGF-I levels and/or an inappropriate clinical response of a patient, as stated in the SmPC.

In study CT-301 a **QTcF change** >60 msec was observed in one patient during lonapegsomatropin treatment, and a total of 14 study patients (13.3%) and 5 study patients (8.9%) in the lonapegsomatropin and somatropin arms, respectively, recorded a QTcF change >30 msec. A comparable trend was observed in study CT-004 performed with ACP-001 (predecessor molecule to lonapegsomatropin). Notwithstanding the observed increase in QTc the actual QTc was – after 26 weeks treatment -well within the normal range (sex and age-corrected).

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

Overall, transient positive results for **anti-hGH binding antibodies** were seen after baseline in 4.7% of the patients. In one patient, a boost in anti-hGH antibodies was observed.

Treatment-emergent positive anti-lonapegsomatropin binding antibodies were reported for 4.0% of patients. Treatment-emergent, transient positive results for anti-mPEG binding antibodies were reported for 0.7% (safety pool II) and 1.9% (study CT301) of the patients. Antibodies against lonapegsomatropin were persistent in 6 subjects (2.0%). It was shown later that there is no evidence that these antibodies neutralize the clinical efficacy of lonapegsomatropin treatment.

No formal drug-drug interaction studies have been conducted with lonapegsomatropin. However, the pharmacodynamic interactions of lonapegsomatropin can be derived from literature.

No discontinuations due to adverse events were reported.

Overall, there were no unexpected clinical safety findings, including any renal, hepatic, immune, or neurologic signals, potentially attributable to PEG accumulation across the phase 3 clinical development program in children with GHD.

The experience with 141 patients using the GH auto-injector for 30.9 weeks (range: 1-42 weeks) did not reveal serious or unexpected safety issues.

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

Additional expert consultations

The Safety Working Party (SWP) and the Non-clinical Working Group (NcWG) of the PDCO were consulted regarding the potential safety risks of long-term mPEG exposure in paediatric GHD patients. A joint meeting was held in July 2021.

Afterwards, a CHMP request for consultation to the Modelling and Simulation Working Party (MSWP) was adopted and the MSWP has provided an answer in September 2021.

Safety working party (SWP) and non-clinical working group (NcWG) of the PDCO

General questions

1. Has the overall view concerning the risk of PEG induced vacuolization and subsequent long-term safety concerns changed based on newly available preclinical information since the SWP response to the PDCO regarding the use of PEGylated drug products in the paediatric population (EMA/CHMP/SWP/6475258/2012)?

In a recent joint SWP/NcWG meeting, an overview of the toxicity findings (i.e vacuolation in the ependymal cells of the choroid plexus) regarding the latest known pegylated products since 2012 was presented and discussed. At that meeting it was concluded that "The recent collected data could be used to update the SWP response of 2012 and provide meaningful information for a more harmonised approach in the evaluation of pegylated products." (SWP/NcWG minutes, 2020, Bonn).

More specifically, the following conditions for the occurrence of vacuolisations, as described in the SWP response to PDCO (2012), could likely benefit from an update:

- cynomolgus monkeys as sole test species
- size of PEG moiety ≥ 40kDa
- study duration ≥ 6 weeks
- threshold for CP vacuolation at PEG exposure of ≥ 0.4 µmol/kg/month

Since then, PEG-related vacuolations have been observed in other species, with smaller PEG moieties <40 kDa, in studies with a duration shorter than 6 weeks and with a lower monthly PEG exposure than 0.4 µmol/kg/month.

The non-clinical data for PEGylated products causing vacuolations continue to support a lack of adverse (neurologic or other) clinical signs and effects on CNS development related to these vacuolations or PEG exposure, even at supra-therapeutical dose levels.

At the same SWP/NcWG meeting, it was however also reiterated that "No new evidence regarding the mechanism of formation of vacuolation has been generated since 2012 and there is a need to have more clinical data to establish the clinical relevance of these findings." (SWP/NcWG minutes, 2020, Bonn).

If no,

2. Which toxicological manifestations (i.e. signs and symptoms) might be expected following long-term PEG exposure in children and/or adolescents and/or adults, especially with respect to the central nervous system, kidney, liver and immune system in case of possible accumulation of PEG? Are the manifestations, if any, expected to be age-dependent?

In the non-clinical studies available to date, findings were limited to histopathological evidence of PEG containing macrophages and vacuoles among others at the level of the choroid plexus, kidney, spleen and lymph nodes. Depending on the localization, vacuoles can persist even after a long period of recovery. Although cellular changes may adversely affect the function of the cells [redacted – non-public details on specific product], and thereby organ functioning, functional PEG-related effects have not been observed in any of the studies. The clinical impact in children and adults remains unknown.

Whereas the observed vacuolations are not considered age-dependent – vacuolations have been observed in adult and juvenile animals - a thorough risk assessment for use of pegylated products is needed before allowing chronic use in young children in view of the immature status of the CNS, the role of the choroid plexus in CNS homeostasis and the increased potential for accumulation in case of life-long use.

There is no biological rationale for differentiating between children above or below a certain age cut-off. The choroid plexus is fully developed before birth (Dziegielewska 2001, Liddelow 2015, Lun 2015). Also, the BBB and B-CSF-B are developed in the targeted paediatric population from 6 months onwards.

Specific questions on lonapegsomatropin;

3. Are there any valid reasons to consider that the elaborations above with respect to PEG induced vacuolization do not apply to lonapegsomatropin (which contains 40 kDa mPEG)?

The experts consider that the conclusions on PEG vacuolation are applicable to Lonapegsomatropin too. Uptake of mPEG via somatropin receptor-mediated uptake does not take place, differentiating lonapegsomatropin from other PEGylated biopharmaceuticals that may undergo receptor-mediated uptake, via receptor binding of the active moiety, and thereby co-transport of PEG into the cell.

However, in view of the occurrence of vacuolation in the CP in animal studies for this product and the observation that non-drug bound PEG can also result in CP vacuolation, a risk assessment for lonapegsomatropin as for other PEGylated products before authorizing chronic use in children is equally justified.

This concerns a branched chain 4 x 10 kDa PEG, and thus in terms of conformation distinct from linear 40 kDa PEG or banched 2x20 kDa PEG. The exact impact of the PEG conformation and size on the threshold for vacuolation is yet unknown. To our knowledge, PEG-related vacuoles have been observed with different types of PEG structures and sizes down to 2 kDa.

4. Taking into consideration the available non-clinical (and lack of clinical) information, especially the fact that the mPEG concentration during lonapegsomatropin treatment remains below the 0.4 µmol/kg/month, do the experts agree with the non-clinical assessment of lonapegsomatropin and conclusions regarding an expected negligible effect on long term safety in paediatric GHD patients (potentially treated for up to 15 years)?

If no;

a. Can these long-term safety issues be (partially) addressed non-clinically, and would an optimized animal PK (PD) -model be of help to assess the clinical relevance of non-clinical observations for humans?

b. Which biomarkers, functional testing or even medical imaging, could be assessed to prevent/minimalize potential safety consequences of mPEG accumulation in paediatric GHD patients?

The experts agree with the non-clinical assessment of Lonapegsomatropin.

Reference is made to the NcWG advice for the paediatric investigation plan for lonapegsomatropin (EMEA-002692-PIP01-19), concluding that the overall risk in this case was considered to be low.

The most important arguments for reaching that conclusion were:

- The availability of a comprehensive non-clinical package including a 'long-term' (52-week) monkey study using juvenile animals. Evaluation of PEG vacuoles was performed with a sensitive staining

method. In addition, mPEG in the CSF was quantified and the study included detailed clinical CNS observations[12].

- The absence of adverse clinical signs, including tremors, in either rat or monkey studies.
- Although the expected vacuolation in CP epithelial cells has been observed in the NC studies with lonapegsomatropin, the vacuoles were small and the integrity of the cells was unaffected (no evidence of distortion of cytoplasmic or nuclear compartments, degeneration, necrosis or inflammation), even at supra-therapeutical dose levels. As a consequence, these vacuoles are unlikely to impact cell or organ function.
- The applicant has demonstrated that the product does not undergo active transport across the blood-CSF barrier (absence of mPEG in the CSF).
- The presence of a small safety margin between the dose of mPEG in the 52-week toxicity study in juvenile cynomolgus monkeys where no H&E stain vacuoles were seen (800 µg mPEG/kg/week) and the mPEG dose at the clinical therapeutic dose level of 0.24 mg hGH/kg/week (480 µg mPEG/kg/week)
- The exposure margin of 7.7 between the measured steady state mPEG concentrations in children (13 µg/mL, age range: 1.2 - 17.4 years) administered lonapegsomatropin as part of the extension trial, CT-301EXT, relative to the mPEG exposure/vacuolation threshold of 100 µg/mL (Jacobsen and Bjørnsdottir, 2017). Of interest, steady state mPEG levels for the 4 children below the age of 3 years were found to be comparable to the overall population and ranged between 2.4 and 13.4 µg/mL.

4a. Cf. NcWG advice for the paediatric investigation plan for lonapegsomatropin (EMEA-002692-PIP01-19). Additional non-clinical studies are not expected to generate any added value. In this regard, the experts agreed that a consultation of MsWP is considered most useful.

4b. Question outside the scope of NcWG expertise.

As part of previous discussions for other pegylated compounds, applicants have consistently responded that there are no markers for PEG accumulation in the choroid plexus or choroid plexus functioning. Input from clinical experts could be obtained regarding the sensitivity and feasibility of e.g. CNS imaging.

SWP and the NcWG of PDCO discussed whether new methodologies, such as metabolomics, might have added value for the detection of new biomarkers. This is not a formal request in the context of the current procedure. However, input from the Applicant on the feasibility of using metabolomics to detect new biomarkers which are linked to the dysregulation of the choroid plexus and CNS homeostasis might reveal new possibilities for biomarkers with added value for future assessments of pegylated products.

<u>Modelling and simulation working party (MSWP)</u>

1. Is the semi-physiologically based PK MODHGH001 study to the MSWP's opinion suitable for estimation of the mPEG exposure in human, as concluded by the Applicant, in light of the above-mentioned preclinical margin?

[12] Detailed clinical observations intended to detect pharmacological or toxicological side effects. Often, these observations are timed in relation to time of administration: prior to and just after administration, a couple of hours later etc. They generally consist of cage observations, handling observations, and observations of reaction to manipulation.

The MSWP acknowledged that the Applicant has made a serious effort to predict the mPEG exposure in human choroid plexus. However, the concentration predictions (i.e. PK model) relies on multiple assumptions such as: a) biodistribution between serum and choroid plexus is the same across species as in rats (allometrically scaled), b) pharmacokinetics of mPEG and PEG40(N9-GP) are scalable all species, and c) the formation of vacuoles are similar across species. In the absence of data, it is important to highlight that the underlying assumptions of the modelling exercise can never be verified and therefore uncertainties will remain. Thus, although mPEG concentrations in human serum is sufficiently well captured, the predictions of human mPEG concentrations in choroid plexus should be interpreted with caution.

2. Previously, the MSWP concluded: "the predicted CP/CSF concentrations are not reliable and should not even be considered as supportive evidence in combination with the safety data". Is the MSWP of the opinion that – in the light of the additional information – the PK MODHGH001 study can be considered sufficiently reliable to substantiate the safety profile of product in terms of mPEG exposure?

Given the model assumptions mentioned in response to question 1, the opinion of MSWP is that the predicted human mPEG concentrations in choroid plexus should be interpreted with strong caution. The MSWP considers the current modelling analyses at best supportive for the hypothesis that mPEG levels in the human choroid plexus are non-toxic with respect to vacuolization as the model is mainly based on theoretical considerations and no data to verify the assumptions are available. Realizing that, without new data, uncertainties on the model assumptions will remain, the Applicant can only increase confidence in the model by collecting additional data on the pharmacokinetics of mPEG in the choroid plexus in different species. In addition, the Applicant could consider developing a PBPK model that may provide more granularity on the PK processes involved in the distribution to the CP. This exercise will be quite elaborative since in addition to using a standard PBPK software the Applicant will need to conduct literature research on systems data related to PK in CP. Uncertainties will however always remain as the choroid plexus mPEG concentration cannot be determined in paediatrics and therefore the final decision should be made on the totality of evidence.

Assessment of paediatric data on clinical safety

Paediatric GHD patients have been included in submitted studies. The safety data from these studies have been discussed above.

2.6.10. Conclusions on the clinical safety

The safety profile of somatropin within lonapegsomatropin across the phase 3 program was consistent with that of daily somatropin products evaluated in a clinical study setting. The safety risks associated with long-term exposure of long-acting growth hormone lonapegsomatropin in GHD patients aged 6 months and above are unclear.

The indications of several PEGylated medicinal products are limited to patients aged 12 years and above due to uncertainties concerning the long-term safety risks of mPEG exposure. Considering lonapegsomatropin is transiently pegylated, mPEG clearance is expected to be faster with lonapegsomatropin compared to permanently PEGylated compounds for long-term use.

At present, there is no clear evidence that the risk of mPEG accumulation in choroid plexus in paediatric GHD patients aged from 3 to 12 years is higher than in older children during short-term lonapegsomatropin treatment.

In addition, observed non-clinical and clinical data on therapeutic lonapegsomatropin doses thus far do not indicate increased safety risks in animals and paediatric GHD patients aged 3-12 years.

A PASS is planned to evaluate the occurrence of potential long-term safety risks such as the occurrence of diabetes mellitus type 2, malignancies, and adverse events due to long-term (i.e. 10 years and beyond) exposure to long-acting somatropin and mPEG associated with lonapegsomatropin.

The planned PASS will provide more insight into the combined long-term safety risks of long-acting somatropin and mPEG with lonapegsomatropin in paediatric GHD patients.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Neoplasms (benign, malignant, unspecified) • Diabetes mellitus type 2 • Medication errors
Missing information	• Long-term safety (including adverse drug reactions potentially related to mPEG exposure)

2.7.2. Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
A prospective, non-interventional, long-term, safety study of patients treated with "TRADENAME" (lonapegsomatropin) Planned	The overarching goal of this study is to further characterise the potential long-term safety risks of "TRADENAME" in patients treated with "TRADENAME" under real-world conditions in the	Neoplasms (benign, malignant, unspecified) Diabetes mellitus type 2 Medication errors Long-term safety (including adverse drug reactions potentially related to mPEG exposure)	Submission of study protocol for PRAC approval	March 2022
			Approval of study protocol by PRAC	July 2022
			Registration in EU PASS Register	July 2022

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	post-marketing setting		Start of data collection/first patient enrolled	January 2023
			Last patient enrolled	January 2028
			End of data collection	January 2032
			Study progress report(s)	With PBRERs
			Interim report(s) of study results	April 2027 April 2031
			Final report of study result	July 2033

2.7.3. Risk minimisation measures

Safety Concern	Risk Minimisation Measures
Neoplasms (benign, malignant, unspecified)	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8.* *In order to inform patients of this risk, corresponding text is also present in the package leaflet.* *There is a contraindication in section 4.3 of the SmPC.* *According to section 4.4 of the SmPC, in patients with previous malignant disease, special attention should be given to signs and symptoms of relapse. Patients with pre-existing tumours or GHD secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process.* *In order to warn patients about this risk, corresponding text is also present in the package leaflet.*

Safety Concern	Risk Minimisation Measures
	Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Diabetes mellitus type 2	Routine risk minimisation measures: *SmPC sections 4.4 and 4.8.* *In order to inform patients of this risk, corresponding text is also present in the package leaflet.* *According to section 4.4 of the SmPC, growth hormone may reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after somatropin therapy is instituted. Patients with diabetes mellitus, glucose intolerance, or additional risk factors for diabetes mellitus should be monitored closely during lonapegsomatropin therapy.* *In order to warn patients about this risk, corresponding text is also present in the package leaflet.* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Medication errors	Routine risk minimisation measures: *According to section 4.2 of the SmPC, treatment should be initiated and monitored by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. The amount and concentration of lonapegsomatropin is always expressed in terms of mg somatropin referring to the content of the somatropin moiety and not including mPEG-linker in order to prevent medication errors when patients switch from daily somatropin therapy. The posology and administration should be individualised for each patient. The recommended starting dose of "TRADENAME" is 0.24 mg somatropin/kg body weight, given once weekly. "TRADENAME" is intended to be administered after reconstitution of the powder for solution for injection with the enclosed solvent. "TRADENAME" should be administered by means of the GH Auto-Injector. The patient and caregiver should receive training to ensure understanding of the administration procedure by means of the device in order to be allowed to (self)-inject lonapegsomatropin.* *In order to warn patients about this risk, corresponding text is also present in*

Safety Concern	Risk Minimisation Measures
	the package leaflet. Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*
Long-term safety (including adverse drug reactions potentially related to mPEG exposure)	Routine risk minimisation measures: *None* Other routine risk minimisation measures beyond the Product Information: *Legal status: Restricted medical prescription.* Additional risk minimisation measures: *None.*

2.7.4. Conclusion

The CHMP and the PRAC consider that the risk management plan version 0.4 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 25.08.2021. 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. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.1 of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

Regarding the omission of particulars on the cartridge label, the Group considered the invented name as an important aspect to be stated on the label and should be displayed.

Given the space constraints on the DDC label and the technical problems to increase the size of the label without compromising the performance of the combination product with the device, the QRD group exceptionally endorsed the use of "injection" as a linked term to the combined pharmaceutical dose form "powder and solvent for solution for injection". EDQM was also consulted on the matter.

Regarding expression of strength/INN, the Group agreed that there should be alignment on the expression of the strength with the INN. Medication errors have been reported when the INN does not correlate with the quantity declared in the strength. Section 2 of the SmPC and Annex IIIA should include information on the equivalence and interchangeability between pro-drugs and active moiety.

The MAH has requested the omission of the pharmaceutical form from the DDC label. However, "injection" is displayed on the DDC label as a linked term to the combined pharmaceutical dose form "powder and solvent for solution for injection".

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shaded to show that they will not be included on the printed materials.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lonapegsomatropin Ascendis Pharma (lonapegsomatropin) 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

Lonapegsomatropin is proposed for growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient secretion of growth hormone (growth hormone deficiency or GHD).

Growth hormone deficiency (GHD) is characterised by too low systemic levels of growth hormone. Growth hormone (GH) is produced by the somatotroph cells of the anterior pituitary gland. The secretion of growth hormone from the pituitary gland is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, both produced by the hypothalamus. Therefore, growth hormone deficiency (GHD) is often associated with defects in the pituitary gland or the hypothalamus.

The typical symptom of GHD in children is growth failure. Growth failure is suspected if the growth of paediatric subjects develops at a slower rate than expected based on the growth chart of the local geographic area. In this case, further diagnostic evaluations can be considered to find the cause of the growth failure.[13]

The incidence of growth failure associated with GHD has been estimated to be approximately 1:4000 to 1:10,000.[14,15] Once GHD is diagnosed, the aim of growth hormone treatment is to normalise the growth rate during childhood and attainment of normal adult height.

3.1.2. Available therapies and unmet medical need

Available therapies

The aim of GHD treatment is the normalization of the growth rate during childhood and attainment of normal adult height. The effects of human growth hormone replacement in children can be evaluated by assessing the increase in height velocity and related auxological parameters as well as bone maturation. For over 30 years, GHD has been treated with daily recombinant human growth hormone. Examples of such medicinal products concern Omnitrope (EU/1/06/332) and Nutropin Aq (EU/1/00/164). Weekly growth hormone treatment is available for the treatment of adult GHD (Sogroya (EU/1/20/1501)).

With current treatment algorithms paediatric recombinant human growth hormone doses 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.

Unmet medical need

While daily human growth hormone is both safe and effective, its frequency of administration can be

[13] Collett-Solberg et al. Diagnostics, genetics and therapy of short stature in children: a growth hormone research society international perspective. Horm Res Paediatr 2019; 92:1-14.
[14] Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016 Jan; 101(1):96-100. Epub 2015 Jul 7.
[15] Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016 Jan; 101(1):96-100. Epub 2015 Jul 7.

burdensome for both paediatric population and their caregivers. Although children with GHD treated with daily growth hormone replacement have the potential to achieve normal adult height, real-world outcomes have not matched expectations. Due to nonadherence rates ranging from 5 to 82% (Fisher 2013), most do not reach their target genetic height (Guyda 1999, Lustig 2004), leaving an opportunity to improve treatment outcomes in paediatric GHD.

While there are multiple therapeutic goals of human growth hormone therapy in treating GHD, including achievement of normal growth patterns, lean/fat body composition, bone mass, glucose homeostasis, cognition and improved quality of life, the most readily measured indicator of efficacy is linear growth according to the applicant.

3.1.3. Main clinical studies

In 26-week Phase 2 multicentre, randomized, open-label dose-finding **study CT-004**, the clinical effects of three different dosages (0.14 (n= 12), 0.21 (n= 14), and 0.30 (n= 14) mg/kg/week) of weekly ACP-001, a predecessor of lonapegsomatropin, have been compared with those of daily administration of somatropin product Genotropin at a dosage of 0.21 mg/kg/week (n=13) in 53 pre-pubertal paediatric GHD patients aged 3-12 years in Tanner stage I. Included study patients were naïve to growth hormone treatment.

In 52-week pivotal Phase 3 multicentre, randomized, open-label **study CT-301**, the clinical effects of weekly lonapegsomatropin (n= 105) and daily somatropin product Genotropin (n= 56), both at a total weekly dosage of 0.21 mg/kg/week were compared in 161 pre-pubertal paediatric GHD patients aged 3-12 years in Tanner stage I. Included study patients were naïve to growth hormone treatment.

In 26-week Phase 3 multicentre, single-arm, open-label **study CT-302**, the clinical effects of lonapegsomatropin were evaluated in 146 paediatric GHD patients aged 6 months up to 18 years. The vast majority (97.9%) of included study patients had received prior daily growth hormone treatment.

GHD study patients who had completed study CT-301 or CT-302 were eligible to enrol in Phase 3 multicentre, long-term, single-arm open-label **study CT-301EXT**. In an ongoing study CT-301EXT, all included study patients received lonapegsomatropin at a dosage of 0.21 mg/kg/week. At the data cut-off date of 01 JUN 2020, 298 study patients had been included in study CT-301EXT.

In the conducted studies, study treatment was administered subcutaneously by means of a syringe with needle. In 46 study patients in study CT-301EXT lonapegsomatropin was not only administered by means of a syringe with needle but also by means of a dual chamber cartridge and growth hormone auto-injector combination product in order to evaluate safety and ease of use of the latter product.

Efficacy across studies was evaluated in two pools:

- **Efficacy pool I**: a longitudinal review of a treatment-naïve study population that received lonapegsomatropin or somatropin in study CT-301 and subsequently lonapegsomatropin in study CT-301EXT. Study patients in this pool were randomized and received at least one dose of study treatment in study CT-301.
- **Efficacy pool II**: a pooled review of efficacy data in study CT-301EXT in study patients who had received treatment with somatropin product Genotropin in study CT-301, and study patients in study CT-302 who had received prior somatropin treatment.

3.2. Favourable effects

Annualized height velocity, height SDS, and IGF-I SDS increased upon initiation of lonapegsomatropin treatment in paediatric GHD patients who were naïve or non-naïve to lonapegsomatropin treatment.

Annualized height velocity. In pivotal study CT-301, mean height velocity at baseline for both lonapegsomatropin (n= 105) and somatropin (n= 56) treated paediatric GHD patients was 3.93 cm/year. At week 52, the mean annualized height velocity for lonapegsomatropin (10.90 cm/year) was higher than that of somatropin (10.22 cm/year) (LS means respectively 11.2 and 10.3; difference in LS means 0.86 (95% CI: 0.22 – 1.50); p= 0.009). Non-inferiority and subsequently statistical superiority of lonapegsomatropin above somatropin were demonstrated. Clinical effects of lonapegsomatropin were more pronounced than those of somatropin at all study visits. Differences were observed from week 26 onwards.

After inclusion in study CT-301EXT after completing study CT-301, mean annualized height velocities at week 78 were similar for study patients who had received lonapegsomatropin (9.4 cm/year) and somatropin (9.3 cm/year) in study CT-301.

In study CT-302, the LS mean of the annualized height velocity at week 26 was 8.72 (95% CI 8.24- 9.20). A comparable annualized height velocity was observed at week 52 (LS mean 8.36 cm/year) in efficacy pool II.

Height SDS. In pivotal study CT-301, mean height at baseline for lonapegsomatropin (n= 105) and somatropin (n= 56) treated paediatric GHD patients were respectively 112.9 and 112.2 cm. Mean height SDS at baseline for these study treatments was respectively -2.89 and -3.00. Height SDS increased progressively for both lonapegsomatropin and somatropin treatment during study CT-301. Increases in height SDS were larger for GHD study patients treated with lonapegsomatropin compared to those treated with somatropin. Observed differences were statistically significant from week 26 onwards. At week 52, the estimated treatment difference expressed in LS mean for the difference in height SDS between lonapegsomatropin (LS mean 1.10) and somatropin (LS mean 0.96) was 0.14 (95% CI: 0.03-0.26) (p= 0.01).

Study patients treated with lonapegsomatropin in study CT-301 achieved a LS mean (SE) increase in height SDS at week 78 of 1.39 (0.05) compared with 1.24 (0.06) for study patients treated with somatropin in study CT-301 (p = 0.0436). Thus, the treatment difference (initial lonapegsomatropin minus initial somatropin) from week 52 (0.14) was maintained at week 78 (0.15).

Study patients switching from somatropin to lonapegsomatropin followed the same growth speed of those originally randomized to lonapegsomatropin, with an increase of approximately 0.29 height SDS from week 52 to week 78 (1.10 to 1.39 for continuous lonapegsomatropin vs 0.96 to 1.24 for a switch to lonapegsomatropin).

In study CT-302, the mean difference between a subject's height SDS and the average parental height SDS was -1.14. This difference decreased upon lonapegsomatropin treatment. After 52 weeks, height SDS was improved by a mean (SD) 0.51 (0.33).

In efficacy pool II, the change from baseline in height SDS increased consistently with time (LS mean week 13: 0.14, LS mean week 52: 0.45).

IGF-I SDS. In pivotal study CT-301, mean IGF-I SDS at baseline for lonapegsomatropin (n= 105) and somatropin (n= 56) treated paediatric GHD patients was respectively -2.08 and -1.96. IGF-I SDS increased progressively for both lonapegsomatropin and somatropin treatment during study CT-301. Increases in IGF-I SDS tended to be larger for GHD study patients treated with lonapegsomatropin compared to those treated with somatropin. Observed differences were statistically significant from week 13 onwards. At week 52, the

estimated treatment difference expressed in LS mean for the difference in IGF-I SDS between lonapegsomatropin (LS mean 0.72) and somatropin (LS mean -0.02) was 0.74 (95% CI: 0.49-1.00) (p <0.0001).

Beyond 52 weeks, for study patients continuing lonapegsomatropin treatment from study CT-301, IGF-I SDS values generally remained stable without further increase. For study patients switching from somatropin treatment in study CT-301 to lonapegsomatropin treatment in study CT-301EXT, an initial increase in IGF-I SDS values with subsequent stabilization was observed. At week 78, IGF-I SDS levels of both groups were in the upper normal range, i.e. between 0 and +2.

In study CT-302, mean IGF-I SDS level at baseline was 0.85. After initiation of lonapegsomatropin treatment a LS mean of 1.65 (95% CI 1.43- 1.86) was observed at week 26.

In efficacy pool II, the average IGF-I SDS level remained elevated above pre-treatment levels (≤ 0.9 SDS) and was stable in the IGF-I SDS range between 0 and +2 over time. The trend for the IGFBP-3 SDS in efficacy pool II mirrored that of the IGF-I SDS.

Compliance. In pivotal study CT-301 the compliance was between >95% and ≤100% for nearly all subjects (lonapegsomatropin: 104 subjects [99.0%], somatropin: 53 subjects [94.6%]).

Mean treatment compliance to lonapegsomatropin treatment in study CT-302 (n= 146) was 98.4%.

Bone age. In efficacy pool I the mean (SD) change in bone age at week 52 was 1.4 (0.9) years for study patients treated with lonapegsomatropin and 1.4 (0.7) years for study patients treated with somatropin. At week 104, the change in bone age was 2.6 years for both study patients continuously treated with lonapegsomatropin and study patients treated with somatropin followed by lonapegsomatropin.

Patient/parent reported outcomes

Treatment preference. A consistent preference for once-weekly lonapegsomatropin relative to daily somatropin treatment was reported by children and parents at week 6 and 13 in studies CT-302 and CT-301EXT. This preference increased upon continued lonapegsomatropin treatment.

The **treatment burden** as evaluated by the Child Sheehan Disability Scores for both the paediatric study patients and (their) parents decreased from baseline in study patients treated with lonapegsomatropin in studies CT-302 and CT-301EXT. This also applies to study patients who used the dual chamber cartridge and growth hormone auto-injector combination product in study CT-301EXT.

Convenience and satisfaction were evaluated among parents of all study patients in study CT-302, in study CT-301EXT among parents of study patients who received somatropin in study CT-301, and among parents of study patients who switched to the growth hormone auto-injector in study CT-301EXT. In all these groups, evaluated study treatments were considered convenient (≥ 69) and satisfactory (≥ 80). Available data indicate that the use of the dual-chamber cartridge and growth hormone-auto injector combination product was safe in the majority of study patients.

In summary, the clinical effects of weekly lonapegsomatropin with respect to growth-related parameters (i.e. annualized height velocity, change in height SDS compared to baseline, IGF-I SDS levels) were statistically larger than those of daily somatropin in pivotal study CT-301. The results from supportive studies indicate that lonapegsomatropin also promotes growth in paediatric GHD patients who have received prior somatropin treatment. Growth was maintained in GHD patients irrespective of whether they were naïve to growth hormone treatment. The efficacy of lonapegsomatropin was also supported by several patient/reported outcomes.

3.3. Uncertainties and limitations about favourable effects

Although the superiority of lonapegsomatropin over somatropin was demonstrated statistically, it was not demonstrated clinically. Indeed, the upper bound of the 95% confidence interval (0.22, 1.50) is inferior to the +2 cm limit of non-inferiority.

The male predominance among paediatric GHD patients is well-known with an almost 2:1 male to female ratio.[16] This male preponderance was even higher in submitted studies. Therefore, the 78.8% male patients in safety pool II and the 81.9% male patients in study CT-301 might induce some bias. The potential impact of bias on the overall results due the preponderance of male paediatric GHD patients was evaluated. The impact of the male preponderance on obtained results and the recommended lonapegsomatropin doses is still unclear.

The results on key efficacy endpoints indicate similar responses to study treatment in children of both sexes. However, as men are more sensitive to growth hormone treatment, an increasing sensitivity to growth hormone (expressed as change in IGF-I per growth hormone dose) over time may be observed, particularly in boys and could lead to safety concerns. It is unclear whether there were more dose adjustments in boys than girls during the conducted clinical studies.

A limited number of GHD patients under 3 years of age (n= 4) were included in submitted clinical studies. Based on submitted graphical data, observed effect sizes with respect to growth parameters tended to be larger compared to paediatric GHD patients aged 3 up to 18 years and above. Considering lonapegsomatropin dosing per body weight was similar for all paediatric GHD patients, younger paediatric GHD patients tend to be more sensitive to lonapegsomatropin compared to older GHD patients.

In dose-finding study CT-004, the annualized height velocity (mean 11.93 vs 11.64 cm/year), the difference in height SDS compared to baseline (0.68 vs. 0.62), and the proportions of study patients with IGF-I SDS levels in the range -2 up to +2 (81.8 vs. 76.9%) were comparable for ACP-001 at a dosage of 0.14 mg growth hormone/kg/week and somatropin at a dosage of 0.21 mg growth hormone/kg/week. The applicant, however, considered the clinical effects of ACP-001 and somatropin comparable at a dosage of 0.21 mg growth hormone/kg/week. Based on this, lonapegsomatropin at a growth hormone dosage of 0.24 mg growth hormone/kg/week was chosen for further clinical development. The clinical effects of a lower somatropin growth hormone dosage for lonapegsomatropin have not been evaluated. Respective effects remain therefore unknown. However, the applicant's choice for a different dosing regimen is acknowledged, although the chosen somatropin dosage for lonapegsomatropin corresponds to the maximal recommended dose for the treatment of GHD in the somatropin based medicines which have a marketing authorization currently.

Observed IGF-I SDS levels tended to be higher for lonapegsomatropin as compared to those of somatropin in pivotal study CT-301, while both study treatments were administered at a total weekly dose of 0.24 mg/kg/week. The implications of supratherapeutic IGF-I SDS levels on the long-term clinical effects of lonapegsomatropin are yet unclear.

The proportions of GHD study patients with IGF-I SDS levels above +2 upon lonapegsomatropin treatment tended to be lower in study CT-301 (7.6%) as compared to extension study CT-301EXT (48.6%) and study CT-302 (56.8%). The fact that monitoring of IGF-I SDS levels was more deliberate in studies CT-301EXT and CT-302 as compared to CT-301 may partially explain these findings. Hence, regular monitoring and potential

[16] Grimberg et al. Sex differences in patients referred for evaluation of poor growth. The Journal of Pediatrics 2005; 146: 212-6.

dose adjustments based on IGF-I SDS levels during lonapegsomatropin treatment appear to be important to achieve appropriate IGF-I SDS levels.

The study patient/parents reported outcomes were in favour of lonapegsomatropin treatment in study CT-302. Administration of lonapegsomatropin by a dual-chamber cartridge and growth hormone auto-injector device was also considered acceptable. If patients and their parents were kept blinded for the received study treatment, observed results might have been more favourable.

Blinding was not appropriately reported in study CT-301. The fact that the primary endpoint measurement is objective did not exempt the applicant from making an accurate reporting of these unanticipated unblinding situations. This would have helped to better apprehend the level of bias in study CT-301.

Study data of study CT-301EXT have been presented until the data cut-off of 01 June 2020. It is unclear which final heights can be achieved upon long-term lonapegsomatropin treatment in paediatric GHD patients and whether these final heights are appropriate. This will be evaluated in a PASS.

3.4. Unfavourable effects

A total of 378 individuals (305 children with GHD and 73 healthy adult subjects) have been exposed to at least 1 dose of lonapegsomatropin. Of the 305 children included in the clinical programme, 252 were exposed to Lonapegsomatropin for more than one year. Further, 44 patients had a follow-up of ≥2 years. The mean exposure (SD) was 70.2 (25.2) weeks.

Overall, 26 subjects (8.5%) experienced treatment-related emergent adverse events. Commonly reported (≥2 subjects overall) treatment-related emergent adverse events were secondary hypothyroidism (2.6%), headache (2.0%), increased IGF-I (1.3%), and growing pains and injection site atrophy (0.7% each).

There have been no deaths reported in the clinical development program for lonapegsomatropin.

Serious adverse events were experienced by 7 subjects (2.3%) overall; none of the serious adverse events were considered related to the study drug by the investigator. Subjects experienced serious adverse events of epilepsy (including generalized tonic-clonic seizure; N=2), pyrexia (N=1), gastrointestinal viral infection (N=1), vomiting (N=1), adenoidal hypertrophy (N=1), and rash (N=1). None of these serious adverse events was assessed by the investigator as related to the study drug or resulted in changes in study drug dose.

Although there were occasional excursions for individual subjects, the mean and median values of all haematology, chemistry, lipid panel and hormone and glycaemic parameters remained within the reference ranges at all time points.

No remarkable findings for vital signs (weight, BMI, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and body temperature) or during physical examination (except for those observations related to infections and growth hormone treatment) were noted with lonapegsomatropin therapy in the clinical program. None of the subjects with abnormal findings had any signs of intracranial hypertension.

In comparison with somatropin (study CT-301) the incidence reported 15 minutes after the administration of subjects was greater in the lonapegsomatropin group (redness (20% vs 3.6%), swelling (5.7% vs 0.0%), or other injection-related symptoms (1.0% vs 0.0%)). The incidence of bruising was comparable between both arms. In the open-label study (study CT-302) 15 minutes after the administration subjects reported symptoms of redness (47.3%), swelling (12.3%) or pain (3.5%). In the lonapegsomatropin treated patients reporting of injection-related symptoms decreased over subsequent weeks. Injection side atrophy was

mentioned for 3 patients (of the 305 in the pool). In one patient, the atrophy resolved. In the somatropin group, injection site atrophy was not reported.

Dose reductions were mostly due to high IGF-I levels. In 1 subject, this was temporary. In 3 subjects the dose was reduced for the remainder of the study. Two subjects had their dose of study drug reduced due to headache. Temporarily dose reductions were due to coxitis, abdominal pain and viral gastroenteritis. One subject had a dose reduction while on somatropin treatment. The dose was reduced due to facial oedema.

In study CT-301 a QTcF change >60 msec is observed in one patient during lonapegsomatropin treatment, and a total of 14 subjects (13.3%) and 5 subjects (8.9%) in the lonapegsomatropin and somatropin arms, respectively, recorded a QTcF change >30 msec. A comparable trend was observed in study CT-004 performed with ACP-001 (predecessor molecule to lonapegsomatropin). Notwithstanding the observed increase in QTc the actual QTc was – after 26 weeks of treatment -well within the normal range (sex and age-corrected).

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.

Overall, transient positive results for anti-growth hormone-binding antibodies were seen after baseline in 4.3% to 6.7% of the patients. In 2 patients, a boost in anti-growth hormone antibodies was observed.

Treatment-emergent positive anti-lonapegsomatropin binding antibodies were reported for 3.6% - 3.8% of the patients. Antibodies were persistent in 6 subjects, but respective antibodies were non-neutralising.

Treatment-emergent, transient positive results for anti-mPEG binding antibodies were reported for 0.7% - 1.9% of the patients. No clear and consistent effect was seen on some selected safety issues (injection site reactions, hypersensitivity).

No discontinuations due to adverse events were reported.

Overall, there were no unexpected clinical safety findings, including any renal, hepatic, immune, or neurologic signals, potentially attributable to PEG accumulation across the phase 3 clinical development program in children with GHD.

The experience with 45 patients using the growth hormone auto-injector for 10.1 weeks (range: 6-14 weeks) did not reveal serious or unexpected safety issues.

3.5. Uncertainties and limitations about unfavourable effects

The number of patients (N=305) is limited for a safety database and does not fulfil the requirements of the ICH-E1 (at least 1500 patients exposed). However, somatropin itself is a well-known active substance, and the safety database is considered sufficient from this perspective to compare the safety profile with the known profile of growth hormone. However, there is a high degree of uncertainty regarding the long-term safety risks -i.e. for 10 years and beyond- of lonapegsomatropin, particular concerning the long-acting properties of lonapegsomatropin and the mPEG exposure associated with lonapegsomatropin.

Somatropin dosing for lonapegsomatropin

Somatropin dosing for lonapegsomatropin is targeted to achieve IGF-I SDS levels within the normal range between -2 and +2 (preferably close to 0 SDS) apart from clinical benefit. Though IGF-I SDS levels within this target range were achieved in the majority of study patients in conducted studies, the proportions of

GHD study patients with IGF-I SDS levels above +2 increased with time, especially in the youngest non-naïve patients. This is of concern, since the safety risks of long-acting lonapegsomatropin (e.g. malignancies, diabetes mellitus type 2) are expected to be higher with higher IGF-I SDS levels. This underscores the importance of regular evaluation of paediatric GHD patients including IGF-I SDS levels, and somatropin dose adjustments based on such evaluations if necessary. Additional recommendations on somatropin starting doses with lonapegsomatropin, dose adjustments, and treatment monitoring have later been included in the product information according to IGF-I SDS levels and puberty status for naïve and non-naïve patients. The long-term safety risks associated with the long-acting lonapegsomatropin medicinal product will be evaluated in a PASS.

mPEG exposure

An uncertainty with respect to clinical safety is the theoretical vacuolisation of mPEG in cells of the choroid plexus (CP) based on non-clinical observations. At 6.7 times the human dose of mPEG, a slight vacuolisation was seen in the CP-cells of juvenile cynomolgus monkeys after 52 weeks of treatment with lonapegsomatropin. After a treatment-free period of 52 weeks, the vacuolisation was partly recovered. At higher doses, this vacuolisation expands to more cells and more vacuoles. In a recent paper, at a dose of 360 times the human dose, alterations in tissue architecture that could potentially lead to dysfunction are shown in the CP of cynomolgus monkeys after three months of treatment (Fletcher, 2019). However, still no signs were shown in the behaviour of these animals.

The applicant made it plausible that the vacuolisation is driven by a non-specific transport process (fenestrated capillaries) probably independent of human age, and as the choroid plexus anatomy and function are highly conserved, the distribution of mPEG between plasma and choroid plexus is expected to be comparable between species. Although the results of the popPK model used for prediction of mPEG levels in the choroid plexus in patients 3-12 years of age should be used with caution, the model suggests that steady-state (SS) for mPEG in the choroid plexus in GHD children may be reached, and the model-predicted median SS level of mPEG in the CP of GHD children at 0.24 mg hGH/kg/week was ~2-fold below the SS levels in CP of monkeys at the NOEL (0.4 mg/kg/week). Because a mild vacuolisation in cells is not an adverse effect in itself, and the exposure to mPEG in GHD children will probably be below the vacuolisation limit, the risk for adverse effects in children caused by vacuolation is regarded as minimal from a non-clinical viewpoint.

Based on the provided information from literature, it can be agreed that mPEG distribution in/out the choroid plexus is most likely solely driven by non-specific mechanisms, some of the mechanisms requiring energy (active) some not (passive), but solely non-specific. It is agreed that these mechanisms are likely preserved over different species, in contrast to such specific transporters, which may be species-specific. Therefore, the assumption that the biodistribution coefficient for distribution of mPEG between serum and choroid plexus can in principle be extrapolated from one to another species is now considered acceptable, and this is assumed to apply in the provided popPK model intended for bridging of the preclinical safety data to the human situation. Although this consideration may reduce the chance that mPEG distribution from serum to choroid plexus in humans is completely different from that obtained in other species, and this appears numerically confirmed by the predictions from the popPK choroid plexus model, actual strength of the support for that assumption from the model is limited. Therefore, the risk of prolonged mPEG accumulation in the human CP may not formally be excluded, but it seems to be unlikely.

Although there are still uncertainties on the extrapolation of the mPEG exposure from animals to human GHD patients, the non-clinical data with lonapegsomatropin are considered reassuring as no significant deleterious effects with lonapegsomatropin were observed in cynomolgous monkeys despite vacuolisation of choroid plexus cells upon mPEG exposure. Furthermore, no specific effects possibly related to the vacuolisation of mPEG in the choroid plexus were highlighted in animals and during the clinical studies in human paediatric GHD patients. Though there was a concern of mPEG accumulation upon long-term use of lonapegsomatropin, there is no clear evidence that the short-term risk of mPEG accumulation in the choroid plexus and other tissues and organs of human paediatric GHD patients aged 3 up to 12 years is higher than in older children.

The applicant agreed to evaluate potential long-term safety risks of lonapegsomatropin in a PASS because of current uncertainties with respect to long-term clinical safety. Long-term safety risks that will be evaluated include safety risks due to mPEG exposure and somatropin within lonapegsomatropin.

Lonapegsomatropin safety in subgroups

The inclusion of paediatric patients <3 years of age is based on data from 4 patients, which is considered very limited. It is unclear whether the clinical safety of long-acting lonapegsomatropin is comparable for GHD patients under 3 years of age, and those aged 3-18 years. Of the four patients included in the clinical study under 3 years of age, all experienced IGF-I SDS levels above +2. Apart from this, lonapegsomatropin may only be administered in paediatric GHD patients weighing 11.5 kg or more due to device restrictions. In line with above issues, the applicant decided to restrict the indication to GHD patients aged 3 years and above.

No studies were submitted in which the teratogenic effects and effects on the placenta of lonapegsomatropin have been evaluated. However, in a peri- and postnatal developmental study in rats, there were no adverse effects on the pregnant/lactating female or on development of the conceptus and the offspring following exposure of the female from implantation through weaning to doses up to 13-fold the clinical dose of 0.24 mg somatropin/kg/week.

Other uncertainties

No formal drug-drug interaction studies have been conducted with lonapegsomatropin. However, the pharmacodynamic interactions of lonapegsomatropin (i.e. growth hormone) can be derived from literature.

3.6. Effects Table

Table 3 Effects Table of lonapegsomatropin for paediatric GHD patients (data cut-off: 30 September 2019).

Effect	Short Description	Unit	Lonapegsomatropin (A)	Somatropin (B)	Uncertainties/ Strength of evidence	References
Favourable Effects						
AHV	Mean annualized height velocity at week 52	cm/ year	10.90	10.22	**SoE:** Δ LS mean A (11.17) vs. B (10.31) 0.86 (95% CI 0.22-1.50) p= 0.0088, superiority A vs. B demonstrated **Unc:** AHV tends to decrease with time and age, open-label treatment, Long-term efficacy unclear	Study CT-301
Height SDS	LS mean height SDS at week 52 compared to baseline	NA	1.10	0.96	**SoE:** Δ A vs. B 0.14 (95% CI 0.03-0.26) p= 0.01 Increase with time	
IGF-I SDS	LS mean insuline-like growth factor-I SDS	NA	0.72	-0.02	**SoE:** Δ A vs. B 0.74 (95% CI 0.49-1.00) p< 0.0001 IGF-I SDS levels increase with time, also proportions of patients with IGF-I SDS levels above +2	
Compliance		%	99.0	94.5	**Unc:** Compliance may decrease with time	
Treatment preference	Treatment preference child week 13	%	83.8	9.1[a]	**SoE:** 7.1% no preference	Study CT-302
Unfavourable Effects						
Injection site atrophy	Adverse event	%	0.7		**Unc:** In 1 out of 146 patients, might impact the compliance	Study CT-302/EXT301
Long-term safety GH	Missing data				**Unc:** Ongoing discussion on carcinogenicity and development of type 2 diabetes mellitus. Safety risks may increase with long-term increased IGF-I levels.	
Long-term safety PEG	Missing data				**Unc:** Ongoing discussion on detrimental effects on kidney, liver, immune system and CNS	

Abbreviations: Δ: difference, CI: confidence interval, LS: least squares, SDS: standard deviation score, vs.: versus

Notes:a: prior somatropin treatmen

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The typical symptom of GHD in children is growth failure, and consequently, the main aim of treatment is the normalization of the growth rate during childhood and attainment of normal adult height. The effects of growth hormone replacement in children can best be evaluated by assessing the increase in height velocity and related auxological parameters as well as bone maturation.

The study results of conducted clinical studies support the efficacy of lonapegsomatropin in paediatric GHD patients. Results with respect to growth-related parameters were in line with each other, also across different studies. Lonapegsomatropin also promotes growth in paediatric GHD patients who have received prior somatropin treatment. Growth was maintained in GHD patients irrespective whether they were naïve to growth hormone treatment at baseline. Bone age was similar in study patients treated for one year with either lonapegsomatropin or somatropin. The efficacy of lonapegsomatropin was also supported by several patient/parent-reported outcomes.

Altogether, the efficacy data provide robust evidence for the clinical efficacy of weekly lonapegsomatropin treatment in paediatric GHD patients. Practical guidance with respect to starting doses, dose titration, and treatment monitoring is available in the SmPC for treatment-naïve and non-naïve patients.

Although the safety database is limited, the short-term safety profile of lonapegsomatropin across the Phase 3 program was consistent with that of daily somatropin medicinal products evaluated in a clinical study setting. The overall occurrence of treatment-related treatment-emergent adverse events (e.g. headache, injection site atrophy) was low (8.5% of subjects). The experience with the growth hormone auto-injector did not reveal serious or unexpected safety issues.

Safety risks associated with long-term exposure in recommended somatropin doses for long-acting growth hormone lonapegsomatropin in paediatric GHD patients are unclear. Potential carcinogenic effects of growth hormone (and/or IGF-I), and possible induction of type 2 diabetes mellitus will be evaluated in the planned PASS. Respective evaluations are also important to further characterize the long-term safety profile -i.e. for 10 years and beyond up to epiphyseal closure or growth plate fusion- of lonapegsomatropin in paediatric GHD patients. Since the safety concerns are based on the ongoing discussion in the scientific community (malignancies and type 2 diabetes mellitus) and non-clinical aspects (PEG related issues, see below), the PASS should be considered a category 3 PASS.

The safety risks concern especially paediatric GHD patients under three years of age, since these patients are more responsive to the clinical effects of lonapegsomatropin. Of the four patients included in the clinical study under 3 years of age, all experienced IGF-I SDS levels above +2. This is of importance since the medical need in this population is not considered high. Treatment adherence to daily growth hormone injections is not an issue. In addition, the faster titration possibility with daily dosing is considered an advantage over weekly dosing in this vulnerable patient population. Apart from this, lonapegsomatropin may only be administered in paediatric GHD patients weighing 11.5 kg or more due to device restrictions. In line with above issues, the applicant decided to restrict the indication to GHD patients aged 3 years and above.

Concerning the potential safety risks of vacuolization and mPEG accumulation due to long-term mPEG exposure with lonapegsomatropin in GHD patients aged 3 up to 18 years, it should be noted that it seems to be highly unlikely that the observed vacuolisation in animals might result in any observable toxicity (at the exposure used in clinical studies) and that the current (short-term) safety information in children does not indicate any safety issues that could be attributed to mPEG. In a 1-year monkey study, the no observed effect level (NOEL) for vacuolisation in choroid plexus cells was found at 1.7 times the human dose (the effect is an adaptive response). In a 3-month study in monkeys (Fletcher et al, 2019), the no observed adverse effect level (NOAEL) was found at 260 times the human dose (exaggerated adaptive response or toxic effect was found at 356 times the human dose). Though it is not absolutely clear which level of exposure is relevant for the safety assessment for humans; the NOEL or the NOAEL, from a mechanistic point of view, it is considered sufficiently justified that in- and outward cellular mPEG transport occurs via non-specific mechanisms and is highly preserved over various species. This provides reassurance that the non-clinical lonapegsomatropin safety data are relevant for the human situation. The non-clinical data on lonapegsomatropin support that, next to the presence of an uptake mechanism, also excretion mechanisms are in place for mPEG. In addition, the presence of a dynamic equilibrium, i.e., uptake of mPEG by pinocytosis, is balanced by excretion by, e.g. exocytosis and cell turnover, even in a theoretical situation where uptake is against a concentration gradient also sufficiently supported by the provided non-clinical data. Therefore, at the expected exposure range obtained with lonapegsomatropin, no prolonged mPEG accumulation, to a level inducing vacuoles, is expected to occur in choroid plexus, liver or kidney. Also, the non-clinical mPEG related findings in CP epithelial cells do not worsen over time, following up to 2 years of continuous mPEG exposure, which supports a dynamic equilibrium that balances cellular uptake and elimination.

The long-term implications of observed vacuolisation in cynomolgous monkeys triggered by mPEG exposure with lonapegsomatropin in paediatric GHD patients are from a clinical perspective unknown and need further evaluation in a PASS. In this context, previous regulatory discussions and conclusions concerning other PEGylated medicinal products about indications, applicable patient populations, and clinical safety of long-term mPEG exposure need to be considered for the current marketing authorization application. PEG accumulation has been discussed thoroughly by the Committee for Medicinal Products for Human Use (CHMP) and the Paediatric Committee (PDCO), as well as the Safety Working Party.

The long-term safety risks of mPEG exposure with lonapegsomatropin may be higher in younger GHD patients since the time to closure of the epiphyses is longer in these patients. Alternative growth hormone medicinal products are available for paediatric patients under 12 years of age (e.g. Omnitrope (EU/1/06/332), and Nutropin Aq (EU/1/00/164)). Based on observed vacuolisation in choroid plexus cells in cynomolgus monkeys, there was a concern about potential safety risks due to vacuolisation and mPEG accumulation in choroid plexus cells and other tissues and organs in human GHD patients upon long-term mPEG exposure with lonapegsomatropin. Considering this concern, the applicant attempted to predict the choroid plexus mPEG levels in children 3-18 years of age, including those aged 3-12 years by means of a popPK model, in which mPEG choroid plexus exposure in children was predicted based on extrapolation of measured choroid plexus PEG levels in the rat and the known serum mPEG exposure leading to vacuolisation in the monkey. It is considered plausible that mPEG transport into the choroid plexus is mediated by non-specific transport processes, a process which is conserved in the various species. Active transport of mPEG, when linked to lonapegsomatropin via e.g. the growth hormone receptor, seems unlikely since the somatropin part of lonapegsomatropin is shielded from this growth hormone receptor by mPEG. Though the popPK model may support the proposed extrapolation of the mPEG choroid plexus data in rats to humans, the outcome of the popPK model should be considered with caution since a number of assumptions

underlying the choroid plexus model cannot be confirmed. Though the actual steady state serum mPEG levels in children is well below the steady state serum levels leading to vacuolisation in monkeys, further relief of concerns towards the possibility of vacuolisation and mPEG accumulation based on comparison of predicted choroid plexus mPEG levels in the monkey and children is thus limited, but the possibility of prolonged mPEG accumulation in the choroid plexus and other tissues and organs is considered to be small. Vacuolisation and accumulation after mPEG exposure in different tissues and organs has not been evaluated specifically in human GHD patients.

Considering the above, and based on additional expert consultations with SWP, the NcWP of the PDCO and MSWP, non-clinical observations with respect to mPEG exposure may in principle be extrapolated to paediatric GHD patients under 12 years of age, though the assumptions underlying this potential extrapolation cannot be verified based only on the PopPK modelling. Safety risks of long-term lonapegsomatropin exposure will be evaluated in a PASS.

Transient positive results for anti-growth hormone-binding antibodies were observed in a limited proportion of study patients. Antibodies were persistent in some subjects, but a clear and consistent effect on height velocity was not observed. Currently, available data do not indicate increased safety risks compared to antibody formation upon exposure to other growth hormone medicinal products.

3.7.2. Balance of benefits and risks

Efficacy of once-weekly lonapegsomatropin has been demonstrated in paediatric GHD patients who are naïve or non-naïve to growth hormone treatment. Results with respect to different growth-related parameters were in line with each other, consistent over time, also across different studies, and non-inferior compared to somatropin. The treatment difference between lonapegsomatropin and somatropin with respect to the primary endpoint annualized height velocity was statistically significant in favour of lonapegsomatropin (p= 0.088) but there was insufficient evidence for clinical superiority. Indeed, taking into account the differences in IGF-I SDS levels, there is insufficient evidence to conclude a therapeutic superiority of lonapegsomatropin over somatropin. The results of the clinical studies were in line with literature indicating that growth in paediatric GHD patients continues at a smaller, more constant rate after an initial catch-up growth in treatment- non-naïve paediatric GHD patients.[17]

An improvement with respect to different patient/parent-reported outcomes was also demonstrated. The majority of GHD study patients preferred weekly lonapegsomatropin above daily somatropin treatment.

From the limited population, the short-term safety profile of lonapegsomatropin appears to be in line with the known growth hormone-containing medicinal products. Injection site reactions, and antibody formation against lonapegsomatropin are the most important short-term safety risks.

There is some uncertainty regarding the clinical consequences of potential vacuolization in the choroid plexus due to long-term mPEG exposure with lonapegsomatropin. The extent in which non-clinical data with respect to mPEG exposure in the choroid plexus can be extrapolated to paediatric GHD patients is unknown. The acceptable margin between the steady state serum mPEG levels in paediatric GHD patients and preclinical serum levels leading to vacuolisation cannot convincingly be translated to the choroid plexus by model-predicted choroid plexus mPEG exposure in the monkey and children due to uncertainties towards the assumptions for the PopPK model. However, the assumed margin in serum exposure between animals and

[17] Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr. 2013;79(2):51-67.

human GHD patients and the fact that no indications regarding mPEG related safety issues are apparent during short-term follow-up in any part of the dossier, supports a positive benefit-risk balance in paediatric GHD patients aged 3-18 years of age, i.e. intended target population.

Previously, pegylated medicinal products for long-term use were indicated in paediatric patients aged 12 years and above. In this respect, an important observation in the case of lonapegsomatropin was that vacuolization in the choroid plexus of juvenile cynomolgus monkeys did not affect the cell integrity and was not associated with clinical signs and symptoms at multiple times the mPEG exposure for therapeutic doses of lonapegsomatropin. As part of these studies, the applicant has also argued that mPEG, either linked to somatropin or released, does not undergo specific active transport across the blood-cerebrospinal fluid barrier, but is transported via non-specific mechanisms. These non-specific transport mechanisms appear more conserved over species, thus increasing trust in the relevance of the preclinical mPEG toxicity data for the human situation. Further, the applicant, SWP, and NcWG of the PDCO indicated that the blood-brain barrier and blood-cerebrospinal fluid barrier in humans are fully developed at an age of 6 months. In the conducted clinical studies in paediatric GHD patients, the clinical efficacy and safety of lonapegsomatropin were similar in younger and older paediatric GHD patients.

Based on aforementioned discussion and available data, it is concluded that there is thus far no evidence for an increased risk of development of clinical signs and symptoms upon mPEG exposure and accumulation in the choroid plexus and other tissues and organs, at therapeutic doses of lonapegsomatropin in paediatric GHD patients, even in GHD patients under 12 years of age.

No prolonged mPEG accumulation, to a level inducing vacuoles, is expected to occur in the choroid plexus, liver or kidney. Although the risk of prolonged mPEG accumulation in the human CP seems to be unlikely, this risk will be closely followed in the PASS.

The totality of evidence supports a positive benefit/risk balance in paediatric GHD patients aged 3-18 years. The long-term clinical effects of lonapegsomatropin treatment in paediatric GHD patients aged 3-18 years will be further evaluated in a PASS.

3.7.3. Additional considerations on the benefit-risk balance

Somapacitan medicinal product Sogroya (EU/1/20/1501) is indicated for the replacement of endogenous growth hormone in adults with GHD. Long-term safety risks of somapacitan are to be evaluated in a PASS.

Previously, two growth hormone-containing depots for use in children were submitted for assessment (somatropin Biopartners and Nutropin depot). The Nutropin depot was withdrawn by the applicant before a final position could be reached by the CPMP.

The other product somatropin Biopartners (EMEA/H/C/2196) was approved. Observed clinical effects with respect to this medicinal product were comparable with those observed for lonapegsomatropin. The applicant agreed on a PASS to elucidate the long-term risks of the observed exposure with growth hormone and IGF-I. The marketing authorisation ceased to be valid due to the sunset clause.

Conclusions

The overall benefit/risk balance of Lonapegsomatropin Ascendis Pharma 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 Lonapegsomatropin Ascendis Pharma 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 Lonapegsomatropin Ascendis Pharma is favourable in the following indication(s):

Growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD]).

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 (see Annex I: Summary of Product Characteristics, section 4.2).

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 review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that lonapegsomatropin active substance (biological of the applicant) in comparison to somatropin (biological approved) previously authorised as a medicinal product in the European Union is to be qualified as a new active substance as it differs significantly in properties with regard to safety and/or efficacy from the previously authorised substance.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0275/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.