CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL REVIEW(S)

CLINICAL REVIEW

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Application Number(s)	761177
Priority or Standard	Standard
Submit Date(s)	June 25, 2020
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Division/Office	Division of General Endocrinology (DGE)/Office of New Drugs (OND)
Reviewer Name(s)	Shivangi Vachhani, MD
Review Completion Date	February 26, 2021
Established/Proper Name	Lonapegsomatropin-tcgd
(Proposed) Trade Name	Skytrofa
Applicant	Ascendis pharma
Dosage Form(s)	Lyophilized powder available in a single-dose, single-use, dual-chamber, prefilled cartridge, containing lonapegsomatropin-tcgd in one chamber and diluent, water for injection, in the other chamber, available in 9 dosage strengths: 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
Applicant Proposed Dosing Regimen(s)	Starting dose of 0.24 mg hGH/kg body weight, injected subcutaneously once weekly. Rounded to the closest cartridge dose.
Applicant Proposed Indication(s)/Population(s)	(b) (4)
Recommendation on Regulatory Action	Approvable from clinical perspective.
Recommended Indication(s)/Population(s) (if applicable)	Treatment of pediatric patients 1 year and older who have growth failure due to inadequate secretion of endogenous growth hormone.

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Glossary

ACTH	Adrenocorticotropic Hormone
ADA	Anti-Drug Antibody
ADH	Antidiuretic Hormone
AE	Adverse Event
AHV	Annualized Height Velocity
ANCOVA	Analysis of Covariance
AUC	Area Under the Curve
BLA	Biologics License Application
BMI	Body Mass Index
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum observed concentration
CMC	Chemistry, Manufacturing, and Controls
COVID-19	Corona Virus Disease-19
CRF	Case Report Form
CSR	Clinical Study Report
CV	Coefficient of Variation
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatric and Maternal Health
ECG	Electrocardiogram
EOP2	End of Phase 2
FDA	Food and Drug Administration
FMQ	FDA Medical Queries
fT3	free Triiodothyronine
fT4	free Thyroxine
GCP	Good Clinical Practice
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GHRH	Growth Hormone Releasing Hormone
HbA1c	Hemoglobin A1c
HDL	high-density lipoprotein
hGH	human Growth Hormone
hGHR	human Growth Hormone Receptor
HV	Height Velocity
ICH	International Council for Harmonization

IGF-1	Insulin like growth factor-1
IGFBP-3	Insulin like growth factor binding protein-3
IND	Investigational New Drug Application
iPSP	Initial Pediatric Study Plan
ITT	Intent To Treat
LDL	low-density lipoprotein
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measurement
mPEG	methoxy Polyethylene Glycol
MRI	Magnetic Resonance Imaging
N/n	number of subjects
NME	New Molecular Entity
NOAEL	No Observed Adverse Effect Level
OBP	Office of Biotechnology Products
oGTT	oral Glucose Tolerance Test
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	Pharmacodynamics
PEG	Polyethylene glycol
PK	Pharmacokinetics
PMC	Post Marketing Commitment
PMR	Post Marketing Requirement
PP	Per Protocol
PT	Preferred Term
REMS	Risk Evaluation and Mitigation Strategy
rhGH	Recombinant Human Growth Hormone
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Standard Deviation
SDS	Standard Deviation Score
SE	Standard Error
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to peak serum concentration
TSH	Thyroid Stimulating Hormone

1. Executive Summary

1.1. Product Introduction

The Applicant (Ascendis pharma) has submitted a Biologic License Application (BLA) for lonapegsomatropin-tcgd, a new biological product, under section 351(a) of the Public Health Act. The Applicant is seeking an approval for lonapegsomatropin-tcgd injection (b) (4)

Lonapegsomatropin-tcgd is a long-acting prodrug of recombinant human growth hormone (rhGH) (somatropin). Lonapegsomatropin-tcgd consists of rhGH that is transiently conjugated to a methoxypolyethylene glycol (mPEG) carrier via a proprietary TransCon linker. The rhGH in lonapegsomatropin-tcgd is obtained from *Escherichia coli* using recombinant technology and has an amino acid sequence that is identical to that of natural human growth hormone (hGH), somatropin. The mPEG carrier prolongs the drug half-life ($t_{1/2}$) by creating a shielding effect that minimizes the renal excretion and receptor-mediated clearance of lonapegsomatropin-tcgd.

Lonapegsomatropin-tcgd is available in single dose, single-use, dual chamber cartridges. The proposed dosing is 0.24 mg hGH/kg body weight injected subcutaneously once weekly.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The current submission provides substantial evidence of effectiveness of lonapegsomatropin-tcgd for the treatment of pediatric subjects > 1 year old with growth failure due to growth hormone deficiency (GHD). This evidence was based on the data from pivotal trial CT-301, that demonstrated non-inferiority of lonapegsomatropin-tcgd compared to Genotropin in treatment-naïve subjects with pediatric GHD, with respect to annualized height velocity (AHV) at 52 weeks. Trial CT-301 also demonstrated an improvement from baseline in other parameters such as Insulin like growth factor-1 (IGF-1) levels and height standard deviation score (SDS) at Week 52, in both lonapegsomatropin-tcgd and Genotropin groups.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Lonapegsomatropin-tcgd is a long-acting rhGH (somatropin), administered via a once-weekly subcutaneous injection, and is indicated for the (b) (4) Lonapegsomatropin-tcgd consists of rhGH that is transiently conjugated to a mPEG carrier. The mPEG carrier prolongs the drug half-life by creating a shielding effect that minimizes the renal excretion and receptor-mediated clearance of lonapegsomatropin-tcgd.

GHD is a serious condition. The clinical manifestations of pediatric GHD include short stature, poor height velocity, delayed bone age, delayed puberty, cognitive impairment, and decreased sense of well-being. If left untreated, GHD is associated with a poor growth velocity and a decreased quality of life. The 2016 pediatric endocrine society guidelines recommend Growth Hormone (GH) therapy for children and adolescents with GHD in order to normalize final adult height.

Currently, multiple rhGH therapies are approved by the Food and Drug Administration (FDA) for the treatment of pediatric GHD, all of which require daily subcutaneous injections. These rhGH formulations have a native GH sequence and have been approved by the FDA based on the improvement in height velocity and/or change in height SDS. The earlier long-term studies with rhGH (e.g., Humatrope up to 8 years) also demonstrated that improvement in AHV translates into the improvement in final height. Based on the results of the studies demonstrating the improvement in final height and the fact that short stature in GHD can be traced to a specific hormone deficiency and thus, this short stature can be reversed by hormone replacement at physiologically justified doses, the Agency accepted AHV as an objective primary efficacy endpoint in short term studies (1 year) evaluating efficacy of rhGH formulations with native GH sequence in pediatric patients with delayed proportional growth in the specific settings of hormone deficiency, i.e. GHD.

The safety profile of all rhGH is well established. Labeled adverse effects of GH therapy include severe hypersensitivity, increased risk of neoplasms, glucose intolerance and diabetes, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, scoliosis progression, lipoatrophy, injection site reactions and pancreatitis. Poor adherence is one of the major limitations of the currently approved rhGH therapies. Some of the commonly reported reasons for poor adherence include frequency of injections and route of administration. However, there is no data to date that poor adherence is associated with decreased final adult height.

The clinical development program of lonapegsomatropin-tcgd consisted of three phase 3 trials. Trial CT-301 conducted in treatment naïve subjects with GHD was the primary source of efficacy and safety of lonapegsomatropin-tcgd. Trials CT-302 and CT-301EXT provided additional evidence of safety and efficacy. However, due to the design of these trials, i.e. single arm, designed as safety trial, IGF-1 based titration, relatively short duration (6 months), use of other rhGH formulations, etc., the interpretation of the results of the trials is complicated and is considered as supportive only.

Based on the evidence from the pivotal phase 3 trial CT-301, lonapegsomatropin-tcgd was found to be non-inferior to Genotropin and can be considered as an alternative rhGH therapy for pediatric subjects with GHD. The estimated difference in the mean AHV at Week 52 between lonapegsomatropin-tcgd and Genotropin groups was 0.86 cm/year, which was above the prespecified non-inferiority margin of -2 cm/year. Additionally, given the lower confidence bound was above 0, the Applicant stated that superiority was established. However, (b) (4) (b) (4) the observed difference of 0.86 cm/year in AHV at 12 months between the two treatment groups is small, more than 50% smaller in magnitude than the non-inferiority margin, and of unknown clinical significance. Additionally, statistical significance was not established across all subgroups. (b) (4) The results of the secondary analyses were supportive of the primary analysis. Lonapegsomatropin-tcgd therapy resulted in an improved height SDS compared to baseline as well as a normalization of IGF-1 levels indicating an adequate replacement with missing hormone. At Week 52, the change in mean height SDS from baseline was 1.10 in the lonapegsomatropin-tcgd group and 0.96 in the Genotropin group, whereas IGF-1 SDS levels >0 were observed in 76% of subjects in the lonapegsomatropin-tcgd group and 57% of subjects in the Genotropin group. Height SDS provides important information to the prescribers and patients and should be included in the label. (b) (4)

Overall, the safety profile of lonapegsomatropin-tcgd was well characterized in the clinical development program. AEs observed with lonapegsomatropin-tcgd were consistent with the AEs associated with rhGH therapy class. These include potential increased risk of neoplasm, glucose intolerance, hypoadrenalism, hypothyroidism, injection site reactions and hypersensitivity reactions. Treatment with lonapegsomatropin-tcgd was not associated with increased risk of well-known AEs and was not associated with any new significant safety signals. The most common (≥5%) AEs that occurred with higher frequency in the lonapegsomatropin-tcgd group compared to Genotropin group were pyrexia (15.2% vs 8.9%), hemorrhage (6.7% vs, 1.8%), viral infection (15.2% vs. 10.7%), arthralgia and arthritis (5.7% vs. 1.8%), cough (10.5% vs. 7.1%), nausea and vomiting (10.5% vs. 7.1%), abdominal pain (5.7% vs. 3.6%) and diarrhea (5.7% vs. 5.4%). Lonapegsomatropin-tcgd was associated with a greater rate of IGF-1 SDS ≥ +2 compared to Genotropin (35.2% vs 3.6%). However, overall, IGF-1 SDS ≥ +2 was not associated with an increased risk of adverse events. GH therapy is associated with an increase in phosphate and alkaline phosphate levels. Treatment with

lonapegsomatropin-tcgd was associated with a greater rate of phosphate and alkaline phosphate elevation compared to Genotropin. More subjects treated with lonapegsomatropin-tcgd shifted from normal baseline levels to elevated phosphate and alkaline phosphate levels at Week 52 compared to Genotropin group (44.2% vs. 30.2% for phosphate levels and 19.2% vs. 9.4% for alkaline phosphate levels).

During the non-clinical studies of lonapegsomatropin-tcgd, immunohistochemical staining of mPEG and vacuolation were observed in the brain tissues of rats and monkeys in the highly vascularized areas of the blood-brain barrier and blood-CSF barrier. Additionally, after the 27-week recovery period in rats, and 52-week recovery period in monkeys, there was a persistence of mPEG association with several cell types and vacuolation of the choroid plexus, indicating only a partial recovery upon withdrawal of lonapegsomatropin-tcgd. However, mPEG staining and vacuolation were not associated with a distortion of the cytoplasmic or nuclear compartments, degeneration, necrosis, or inflammation. Second, there was no evidence of signs of neurotoxicity such as tremors, convulsions, reactivity to handling or unusual behavior in animal studies. Third, the predicted median steady state level of mPEG in the choroid plexus of children at the proposed dose of 0.24 mg hGH/kg/week is 2-fold lower than the predicted steady state levels in the choroid plexus of monkeys at the NOEL of 0.4 mg/hGH/kg/week, whereas the test article-related microscopic findings in the brain (vacuolation of epithelial cells and/or macrophages within the choroid plexus) were observed in male and female monkeys dosed at ≥1.6 mg hGH/kg/week for 52 weeks. Lastly, during the clinical studies of lonapegsomatropin-tcgd, treatment with lonapegsomatropin-tcgd was not associated with an increased risk of central nervous system related adverse events compared to Genotropin. Headaches were the only adverse events in the nervous system disorders or psychiatric disorders System Organ Class, that were observed in ≥2% of subjects, and were present at a similar rate in both lonapegsomatropin-tcgd (12.3%) and Genotropin (14.3%) groups. Hence, the anticipated risks of mPEG at the proposed therapeutic dose of 0.24 mg hGH/kg/week may be considered minimal.

In summary, the Applicant has provided substantial evidence that lonapegsomatropin-tcgd is an effective treatment of growth failure associated with pediatric GHD when given at the proposed dose, and that observed improvement in AHV is expected to translate into the improvement of final adult height. Additionally, the safety profile of lonapegsomatropin-tcgd was well characterized in the clinical development program. Overall, the AEs observed are predictable, well-known class effects of GH therapies, and can be adequately identified and managed by the health care providers. The safety profile of lonapegsomatropin-tcgd is acceptable given its potential benefits and the expected class effects will be mitigated through the labeling.

Thus, this medical reviewer recommends the approval of lonapegsomatropin-tcgd from a clinical perspective, (b) (4) pending Center for Devices and Radiological Health

(CDRH) review and Office of Pharmaceutical Quality (OPQ) review. At the time of this review completion, CDRH review of human factors validation study was still ongoing. CDRH identified multiple study methodology deficiencies during the initial review and recommended that the Applicant conducts another human factor validation study, that is currently pending. The inspection of manufacturing site is delayed during to Corona Virus Disease-19 (COVID-19) pandemic.

However, the Applicant proposes to indicate this drug for all pediatric patients with opened epiphysis, whereas, the clinical program included subjects 1.2 to 17.4 years old. Given subjects <1-year-old were not enrolled in the clinical development program of lonapegsomatropin-tcgd and pharmacokinetic (PK) profile of this long-acting drug is different from other approved rhGH formulations, the safety of this drug, including the use of mPEG is unknown in this patient population at this time. Growth failure due to GHD is rarely diagnosed in children < 2 years old and the most common causes of growth failure during the first year of life are small for gestational age or genetic causes. Thus, this Medical Officer recommends approval of this drug in pediatric patients with growth failure due to GHD who are > 1 years old only.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• GHD is a condition characterized by insufficient production of GH by the pituitary gland. • Clinical signs and symptoms of GHD in children include short stature, poor height velocity, delayed bone age and delayed puberty. Neonates with GHD can present with hypoglycemia, prolonged jaundice, microphallus or craniofacial midline abnormalities. GHD can also lead to cognitive impairment and decreased sense of well-being. • The 2016 Pediatric Endocrine Society (PES) guidelines recommend GH therapy for children and adolescents with GHD in order to normalize final adult height and prevent extreme shortness.	Pediatric GHD is a serious condition that, if left untreated, is associated with a poor growth velocity. Children with GHD who are not treated with GH therapy are unlikely to reach normal adult height and can also experience a decreased quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Currently, multiple daily rhGH formulations are available for the treatment of pediatric patients with growth failure due to GHD and are considered first line therapy. These short-acting rhGH formulations with a native GH sequence have been approved by the FDA based on the improvement in final height, height velocity and/or change in height SDS. • GH therapy is overall well tolerated. Labeled adverse effects of GH therapy include increased risks of neoplasms, impaired glucose intolerance and diabetes, intracranial hypertension, severe hypersensitivity, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphysis, scoliosis progression, lipoatrophy, and pancreatitis. • Poor adherence is one of the major limitations of the current GH therapy, with frequency of injections and route of administration as one of the reasons for non-adherence. However, there is no data to date that poor adherence has an effect on final adult height.	Currently, all the rhGH replacement therapies that are available for the treatment of pediatric GHD require daily subcutaneous injections. The current treatment armamentarium may benefit from GH therapy that require less frequent injections.
Benefit	• Lonapegsomatropin-tcgd is effective in improving AHV in PGHD as demonstrated in Trial CT-301, the pivotal, randomized, active-controlled trial of 52 weeks duration in 161 pre-pubertal, treatment-naïve subjects with GHD when given at a dose of 0.24 mg hGH/kg/week. • The estimated difference in mean AHV between the lonapegsomatropin-tcgd and Genotropin groups was 0.86 cm/year, which was above the prespecified non-inferiority margin of -2 cm/year. Additionally, statistical superiority was established given the lower bound of the confidence interval was >0. However, the difference in	• Improvement in AHV at 52 weeks is an objective efficacy endpoint in trials of short duration in pediatric patients with GHD. Height velocity during the first year of treatment with GH products with native GH sequence has been accepted by the Agency as an important predictor of subsequent growth and the Agency has used AHV endpoint to establish efficacy of other GH therapies

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	AHV at 52 weeks between the two groups is small and of unknown clinical significance. • The results of the secondary analyses were supportive of the primary analysis. However, secondary endpoints were not adjusted for multiplicity. o Lonapegsomatropin-tcgd therapy resulted in an improvement in height SDS compared to baseline. At Week 52, the change in mean height SDS from baseline was 1.10 in the lonapegsomatropin-tcgd group and 0.96 in the Genotropin group. o Lonapegsomatropin-tcgd therapy also resulted in normalization of IGF-1 levels, indicating an adequate replacement with missing hormone. At Week 52, IGF-1 SDS levels >0 were observed in 76% of subjects in the lonapegsomatropin-tcgd group and 57% of subjects in the Genotropin group. • The efficacy of lonapegsomatropin-tcgd was confirmed in all subgroups analyzed. Subgroup analysis confirmed the known better response to GH therapy in pediatric subjects of younger age or with severe GHD. Subjects who were <6 years old had a slightly greater AHV at 52 weeks compared to subjects who were ≥ 6 years old (12.41 cm/year vs 10.72 cm/year); subjects with peak stimulated GH response of ≤5 ng/mL had a slightly greater AHV at 52 weeks compared to subjects with peak stimulated GH response of >5 ng/mL (11.98 cm/year vs. 10.56 cm/year); and subjects with multiple pituitary hormone deficiency had a greater AHV at 52 weeks compared to subjects with isolated	in pediatric patients with proportional short stature due to GHD. • Overall, there is substantial evidence of effectiveness of lonapegsomatropin-tcgd for the treatment of short stature associated with GHD based on the improvement in AHV. The changes in secondary endpoints, i.e. in height SDS and IGF-1 are supportive of the drug efficacy. • (b) (4) a single study comparing the effect of two drugs on a surrogate endpoint of AHV, and the observed difference of 0.86 cm/year in AHV at 52 weeks between the two groups is of little clinical significance (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	idiopathic GHD (12.68 cm/year vs. 10.4 cm/year)	
Risk and Risk Management	• The safety database of lonapegsomatropin-tcgd included 252 subjects who were exposed to lonapegsomatropin-tcgd for ≥52 weeks, which is consistent with the International Council for Harmonization (ICH) guidelines. • There were no deaths or discontinuations due to adverse events (AEs) during the clinical development program of lonapegsomatropin-tcgd. The incidence of serious adverse events (SAEs) and severe AEs was low, and similar between the lonapegsomatropin-tcgd and Genotropin groups. • The most common (≥5%) AEs that occurred with higher frequency in the lonapegsomatropin-tcgd group compared to Genotropin group were pyrexia (15.2% vs 8.9%), hemorrhage (6.7% vs, 1.8%), viral infection (15.2% vs. 10.7%), arthralgia and arthritis (5.7% vs. 1.8%), cough (10.5% vs. 7.1%), nausea and vomiting (10.5% vs. 7.1%), abdominal pain (5.7% vs. 3.6%) and diarrhea (5.7% vs. 5.4%). • AEs that are associated with GH therapy such as increased risk of neoplasm, glucose intolerance, hypoadrenalism, hypothyroidism, lipoatrophy and injection site reactions, severe hypersensitivity and progression of pre-existing scoliosis occurred at a low frequency overall, and at a similar frequency in the lonapegsomatropin-tcgd and Genotropin groups. • Other AEs that are associated with GH therapy such as intracranial	Overall, the safety profile of lonapegsomatropin-tcgd was well characterized in the clinical development program. The pattern of AEs observed with lonapegsomatropin-tcgd was similar to the AEs associated with rhGH therapy class and no new safety signals including immunogenicity were detected. AEs observed during the clinical program (pyrexia, GI adverse events, arthralgia) are monitorable AEs and will be mitigated through the appropriate labeling. Other AEs associated with rhGH therapy class that were observed during the clinical development program of lonapegsomatropin-tcgd with low frequency or not observed at all (e.g., neoplasm, glucose intolerance, hypoadrenalism, hypothyroidism, lipoatrophy ,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hypertension, fluid retention, slipped capital femoral epiphyses, and pancreatitis were not observed during the phase 3 development program of lonapegsomatropin-tcgd. • Lonapegsomatropin-tcgd was associated with a greater rate of elevation in IGF-1 SDS above +2 compared to Genotropin (35.2% vs 3.6%). However, overall, IGF-1 levels above the range of +2 SDS were not associated with an increased risk of adverse events. • GH therapy is associated with an increase in phosphate and alkaline phosphate levels. Treatment with lonapegsomatropin-tcgd was associated with a greater rate of phosphate and alkaline phosphate elevation compared to Genotropin. An elevation in phosphate levels for >50% of the times was observed in 86.4% of subjects in lonapegsomatropin-tcgd group and 14.5% of subjects in Genotropin group. Similarly, an elevation in alkaline phosphate of >50% of times was observed in 15.4% of subjects in lonapegsomatropin-tcgd group and 7.1% of subjects in Genotropin group. • In non-clinical studies of lonapegsomatropin-tcgd in rats and monkeys, mPEG staining in brain tissues and vacuolization of the choroid plexus were observed. However, compared to the mPEG exposures in children at the proposed clinical dose of 0.24 mg hGH/kg/week, the exposure margins at the No Observed Adverse Effect Level (NOAEL) in the animal studies were as follows: 3.5x in the 26-week study in rat, 35x in the 26-week study in monkey, and 34x in the 52-week study in monkey. Also, the predicted median steady state level of mPEG in the choroid plexus of children at the proposed dose of 0.24 mg hGH/kg/week is 2-fold lower than the predicted steady state levels in the choroid plexus of	injection site reactions, hypersensitivity, progression of pre-existing scoliosis intracranial hypertension, fluid retention, slipped capital femoral epiphyses, pancreatitis) are mechanistically anticipated and will be adequately mitigated through the labeling as well.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	monkeys at the NOEL of 0.4mg/hGH/kg/week, whereas the test article-related microscopic findings in the brain (vacuolation of epithelial cells and/or macrophages within the choroid plexus) were observed in male and female monkeys dosed at ≥1.6 mg hGH/kg/week for 52 weeks. Thus, the overall risk associated with mPEG in children at the proposed dose can be considered low.	

2. Therapeutic Context

2.1. Analysis of Condition

Growth hormone deficiency (GHD) is a condition characterized by insufficient production of growth hormone (GH) by the pituitary gland.[1] GHD can either be of childhood onset or adult onset. The prevalence of childhood onset GHD is estimated to be 1:1533 to 1:30,000 worldwide, and 1:3480 in the U.S., with boys outnumbering girls by a 2.7:1 ratio.[2]

Childhood onset GHD can be divided into GHD due to an organic cause and GHD for which cause is unknown (idiopathic GHD).[3] Most children with GHD have idiopathic GHD, and these children often have a normal GH response when tested in adulthood. In patients for whom an organic cause for GHD is known, the causes for GHD include congenital causes (genetic, associated with structural defects of the brain or associated with midline facial defects) or acquired causes (trauma, infection, central nervous system tumors, Langerhans cell histiocytosis, post cranial irradiation, post chemotherapy, pituitary infarction, neurosecretory dysfunction, psychosocial deprivation or hypothyroidism).[4] Genetic causes include mutations in genes that encode GH, growth hormone releasing hormone (GHRH), and transcription factor defects.[5]

Clinical signs and symptoms of GHD in children include hypoglycemia, prolonged jaundice, microphallus or craniofacial midline abnormalities in neonates, and short stature, poor height velocity and delayed bone age.[6,7] Diagnosis of GHD involves a multistep approach, and is based on the combination of clinical and auxological assessment, biochemical tests and radiological

[1] Grimberg A, et al. Guidelines for Growth Hormone and Insulin-like Growth Factor-I Treatment in Children and Adolescents: Growth Hormone Deficiency, Idiopathic Short Stature, and Primary Insulin-like Growth Factor-I Deficiency. *Hormone Research in Pediatrics.* 2016; 86:361-397
[2] Lindsay R, et al. Utah Growth Study: Growth standards and the prevalence of growth hormone deficiency. *The Journal of Pediatrics*. 1994;125:29-35
[3] Molitch M, et al. Evaluation and Treatment of Adult Growth Hormone Deficiency: An Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology and Metabolism.* 2011; 96:1587-1609
[4] Dattani M, et al. Growth hormone deficiency and related disorders: insights into causation, diagnosis, and treatment. *The Lancet*. 2004; 363:1977-1987
[5] Alatzoglou K, et al. Genetic causes and treatment of isolated growth hormone deficiency – an update. *Nature Reviews Endocrinology*. 2010; 6:562-576.
[6] Stanley T. Diagnosis of Growth Hormone Deficiency in Childhood. *Current Opinion in Endocrinology, Diabetes and Obesity.* 2012; 19:47-52
[7] Southern C, et al. Somatotropin in the treatment of growth hormone deficiency and Turner syndrome in pediatric patients: a review. *Clinical Pharmacology: Advances and Applications*. 2010; 2:111-122

evaluation.[8] Prior to commencing evaluation of GHD in a patient with short stature, other causes of growth failure such as hypothyroidism, chronic systemic disease, Turner syndrome, or skeletal disorder should be excluded.

GHD should be investigated in children with following features: 1) severe short stature (height <-3 standard deviation (SD) below mean); 2) height < -1.5 SD below mid-parental height; 3) height < -2 SD below mean and either height velocity <-1 SD below mean over past year or decrease in height SD of more than 0.5 SD over past year; 4) in the absence of short stature, height velocity <-2 SD below mean over 1 year or <-1.5 SD below mean over 2 years; 5) signs of an intracranial lesions; 6) signs of multiple pituitary hormone deficiency; and 7) neonatal symptoms and signs of GHD.[9]

Radiological evaluation includes bone age estimated from an x-ray of the left wrist and hand for all children over 1 year and x-ray of knee and ankle for infants less than 1 year.[10] The degree of delay in bone age is dependent on the severity and duration of GHD.

Diagnosis also involves measurement of Insulin like growth factor-1 (IGF-1) and Insulin like growth factor binding protein-3 (IGFBP-3) levels. IGF-1 and IGFBP-3 absolute values should be standardized for age and sex, or SD should be used. IGF-1 and/or IGFBP-3 values <-2 SD suggest GHD in a patient in whom other causes of low IGF have been excluded. However, some patients with GHD can have normal IGF-1 and IGFBP-3 levels. Thus, GH provocation tests are used.

Inadequate response to two GH provocation tests is required to diagnose GHD in most patients. GH provocation tests can be conducted using arginine, clonidine, glucagon, insulin, L-dopa or GHRH.[11] A peak GH concentration of <10 mcg/L in a patient with clinical criteria for GHD has been used to support the diagnosis of GHD. Sex steroid priming with 2 mg (or 1 mg/kg for children <20 kg) of β-estradiol taken orally on each of the two evenings preceding the test is recommended in pre-pubertal boys >11 years old and pre-pubertal girls >10 years old with adult height prognosis within -2 SD of the reference population mean to differentiate true GHD from delayed growth.

GHD diagnosis does not require provocative tests in patients who meet auxological criteria, have

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[8] GH Research Society, Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescense: Summary Statement of the GH Research Society. *The Journal of Clinical Endocrinology and Metabolism.* 2000; 85:3990-3993

[9] Murray P, et al. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. *Archives of Disease in Childhood*. 2016; 101:96-100

[10] Sizonenko P, et al. Diagnosis and management of growth hormone deficiency in childhood and adolescence. *Growth Hormone and IGF Research*. 2001; 11:137-168

[11] Chinoy A, et al. Diagnosis of growth hormone deficiency in the pediatric and transitional age. *Best Practice and Research Clinical Endocrinology and Metabolism*. 2016; 30:737-747.

hypothalamic-pituitary defect (such as major congenital malformation, tumor, or history of irradiation), and deficiency of at least one additional pituitary hormone. Additionally, newborns with hypoglycemia, who have serum GH concentration <5 mcg/L and a deficiency of at least one additional pituitary hormone and/or classic imaging triad (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk) also do not need to undergo GH provocative testing to establish the diagnosis of GHD due to congenital hypopituitarism.

2.2. Analysis of Current Treatment Options

GH therapy is recommended and approved therapy in pediatric patients with GHD. Primary objective of treatment of GHD in children is normalization of height during childhood, and attainment of normal adult height that is consistent with the patient's genetic potential.[12]

GH replacement therapy was first approved by the FDA in 1985. Since then, multiple short-acting rhGH formulations with native GH sequence have been approved for the treatment of pediatric patients with growth failure due to GHD[13]. All approved GH products require daily subcutaneous administration. The rhGH formulations with native GH sequence were approved by the FDA for the treatment of children with growth failure due to GHD based on an improvement in final height, height SDS and/or height velocity (Table 1). The rhGH-induced changes in annualized growth velocity ultimately translate into increased final adult height; this evidence is supported by a clear mechanistic rationale (replacement therapy in patients with GHD) and clinical data from the trials with short acting GH formulations where some patients had been treated to final adult height (Table 1) and demonstrated that improvement in annualized growth velocity was associated with an improvement in final adult height.

Table 1: Examples of FDA-approved GH therapies for pediatric GHD

GH product (Company)	Year of Approval	Approved dosing	Duration of studies, number of patients and endpoints
Humatrope (Lilly)	1987	0.18 to 0.3 mg/kg/wk divided into equal daily doses	• Up to 8 years, 314 treatment-naïve children • Open-label, uncontrolled trial • Primary efficacy endpoint: height velocity (3.6 ± 1.9 cm/year at baseline to 8.8 ± 2.3 cm/year at 1 year • Height velocity of 6.3 ± 2.5 cm/year at year 8 in a small subset of patients (n=12) who remained on extension trial

[12] Richmond E, et al. Treatment of growth hormone deficiency in children, adolescents and at the transitional age. *Best Practice and Research Clinical Endocrinology and Metabolism.* 2016; 749-755
[13] *https://dailymed.nlm.nih.gov*

GH product (Company)	Year of Approval	Approved dosing	Duration of studies, number of patients and endpoints
Nutropin (Genentech)	1994	Up to 0.3 mg/kg/wk divided into equal daily doses	• Mean duration of 2.7 ± 1.2 years, 97 treatment-experienced pubertal patients (Tanner stage ≥2) • Open label, randomized trial comparing two dosages of Nutropin (0.3 mg/kg/wk and 0.7 mg/kg/wk) • Primary efficacy endpoint: last measured height • Mean height SDS was -1.3 at baseline, and -0.7 ± 1 in 0.3 mg/kg/wk group and -0.1 ± 1.2 in the 0.7 mg/kg/wk group at the last measured height
Zomacton (Ferring)	1995	0.18 to 0.3 mg/kg/wk divided into equal daily doses	• 2 years, 164 treatment-naïve and treatment-experienced patients • Open-label • Primary efficacy endpoint: increase in height velocity from baseline • After 12 months of treatment, the mean cumulative increase in height velocity from baseline was 5.7 cm/year in Naïve Type I (GH < 10 ng/mL in response to provocative tests), of 4.4 cm/year in Naïve Type II (integrated GH < 3.5 ng/mL ± at least one GH ≥ 10 ng/mL) and 5.3 cm/year in Non-Naïve patients
Norditropin (Novo Nordisk)	2000	0.17 to 0.24 mg/kg/wk divided into equal daily doses	• 2 years, 111 treatment naïve patients • Open-label, randomized trial comparing 3 doses of Norditropin (0.025 mg/kg/day, 0.05 mg/kg/day, 0.1 mg/kg/day) • Primary efficacy endpoint: mean increase in height SDS over the 2-year period (0.81 in 0.025 mg/kg/day, 1.57 in 0.05 mg/kg/day and 1.73 in 0.1 mg/kg/day groups) • Height velocity and height velocity SDS also increased, with greatest response during the first year of treatment

Source: Approved labels at: https://dailymed.nlm.nih.gov

GH therapy is overall well tolerated. Labeled adverse effects of GH treatment include intracranial hypertension, slipped capital femoral epiphysis, scoliosis progression, pancreatitis, impaired glucose intolerance and diabetes, prepubertal gynecomastia, arthralgia, and edema. GH treatment can unmask underlying adrenal insufficiency and hypothyroidism. Patients should thus be assessed for adrenal and thyroid axes after initiation of GH therapy. Treatment with GH therapy is contraindicated in patients with active malignancy, as due to the mitogenic and antiapoptotic activity of GH and IGF-1, there is a theoretical concern for neoplasia development with GH therapy.[14] However, at this time, there is no clear evidence that GH therapy leads to

[14] Chae HW, et al. Growth hormone treatment and risk of malignancy. *Korean Journal of Pediatrics*. 2015; 52:41-46

tumor development in children with or without a history of prior malignancy.[15,16,17, 18] Doses up to 0.3 mg/kg/week have been approved by the FDA as safe and effective doses for the treatment of pediatric patients with growth failure due to GHD. However, the lowest effective dose is recommended[1] since high dosing of GH may be associated with increased IGF-1 levels above normal range and long-term adverse effects associated with elevated IGF-1 levels above normal.

Patients should be monitored closely for growth response to GH treatment. In general, in pediatric patients, IGF-1 levels are monitored for safety, not for evaluation of the response to therapy. High IGF-1 levels suggest over treatment and should prompt dose reduction. Lastly, it is recommended that treatment with rhGH of pediatric growth failure due to GHD should be discontinued once the epiphyses are closed and patient should be reevaluated.

Poor adherence is one of the major limitations of the current GH therapy, and can be seen in up to 43% to 64% of pediatric patients.[19,20,21] The reasons for non-adherence are extensive and inconsistent across the observational studies, but include perceived ineffectiveness, side effects, frequency and route of administration, issues with device/supply/insurance, or cognitive/emotional issues. There is no data to date that poor adherence has an effect on final adult height.

3. Regulatory Background

[15] Wilton P, et al. Growth hormone treatment in children is not associated with an increase in the incidence of cancer: Experience from KIGS. *The Journal of Pediatrics*. 2010; 157:265-270

[16] Tuffli GA, et al. Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. *Journal of Clinical Endocrinology and Metabolism*. 1995; 80:1416-1422

[17] Moshang T, et al. Brain tumor recurrence in children treated with growth hormone: the National Cooperative Growth Study experience. *The Journal of Pediatrics*. 1996; 128:S4-S7

[18] Swerdlow A, et al. Growth Hormone treatment of children with brain tumors and risk of tumor recurrence. *The Journal of Clinical Endocrinology and Metabolism*. 2000; 85:4444-4449

[19] Mohseni S, et al. Adherence to growth hormone therapy in children and its potential barriers. *Journal of Pediatric Endocrinology and Metabolism.* 2017; 31:13-20

[20] Rosenfeld RG, et al. Compliance and persistence in pediatric and adult patients receiving growth hormone therapy. *Endocrine Practice*. 2008; 14:143-54

[21] Rees L. Compliance with growth hormone therapy in chronic renal failure and post transplant. *Pediatric Nephrology*. 1997; 11:752-754

3.1. U.S. Regulatory Actions and Marketing History

Lonapegsomatropin-tcgd is a new molecular entity (NME), and is not currently marketed in the U.S.

3.2. Summary of Presubmission/Submission Regulatory Activity

On May 4, 2010, the Agency had a pre-Investigative New Drug (IND) meeting with the Sponsor to discuss the development plan for ACP-001 (a predecessor molecule for lonapegsomatropin-tcgd containing an (b) (4) kDa mPEG carrier), for the treatment of GHD (b) (4) The Agency recommended that the phase 3 trial should be designed as a non-inferiority trial in children with GHD using height velocity of 2 cm/year as the non-inferiority margin (refer to meeting minutes in DARRTS from July 8, 2010, under IND (b) (6))
On December 16, 2010, the Sponsor opened IND (b) (6) for ACP-001 for the treatment of GHD (b) (4) The opening study was a phase 2, open-label, parallel-group, active-controlled trial (CT-004), comparing the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of three doses of once weekly ACP-001 to once daily Omnitrope in prepubertal pediatric subjects with GHD.

The Sponsor modified their rhGH product further. ACP-011 (lonapegsomatropin-tcgd) superseded ACP-001, as it contains a 40 kDa mPEG molecule, and is less viscous drug, allowing a more concentrated dosage formulation. The Agency considered ACP-011 as a new product and recommended to open a new IND for a new rhGH product.

On June 3, 2015, the Agency provided written responses to the Sponsor's pre-IND meeting package. The Agency agreed with the design of the proposed phase 1, single-dose clinical trial in healthy adult volunteers to establish the PK/PD comparability of ACP-001 and ACP-011.

On September 25, 2015, IND 126053 was opened for ACP-011 (lonapegsomatropin-tcgd). As an IND opening study, the Sponsor proposed a phase 1, randomized, open-label trial (CT-101) in healthy volunteers, investigating the safety and tolerability of a single dose of ACP-011 at three different dose levels and comparing the exposures of a single dose of ACP-011 to ACP-001 in a cross-over design. This trial was deemed safe to proceed from a clinical standpoint.

On July 27, 2016, an End of Phase 2 (EOP2) meeting was held between the Agency and the Sponsor. The Agency provided overall feedback on the proposed development program supporting a marketing application for lonapegsomatropin-tcgd. The Agency agreed with the proposed Phase 1, randomized, bioequivalence, crossover trial (CT-102) comparing PK exposure of hGH after a single dose of ACP-011 in vials, versus an auto-injector, and recommended that PD markers are also included in the phase 1 trial. The Sponsor also proposed to conduct a Phase 3 program consisting of a single pivotal Phase 3 clinical trial (CT-301), evaluating ACP-011 compared to Genotropin, in hGH treatment-naïve pediatric subjects with GHD, using a primary

endpoint of annual height velocity at 12 months, followed by a long-term extension trial. A non-inferiority margin of 2.0 cm/year was proposed by the Sponsor. The clinical safety and use of lonapegsomatropin-tcgd administered by auto-injector were to be evaluated in a minimum of 20 subjects dosed for at least 1 month in this trial. The Agency agreed that the proposed plan to support a Phase 3 clinical program with the data obtained from the completed ACP-001 clinical program and the completed Phase 1 clinical trial bridging ACP-001 and ACP-011 were overall acceptable, pending review of the results of the bridging study. The Agency also noted that the safety data from earlier clinical trials of longer duration with ACP-001 would not be applicable to ACP-011, which is a different drug. The Agency also raised concern that 12 months of treatment in pivotal trial may not be enough to evaluate the long-term safety and efficacy of lonapegsomatropin-tcgd and asked the Sponsor to provide information on how the short-term efficacy data (12 months) will be bridged with long-term improvement including final height. The Agency agreed with the primary efficacy endpoint of AHV at 12 months and recommended that changes in bone age vs. chronological age are also evaluated at the end of the trial. Lastly, the Agency asked to provide justification for the choice of the non-inferiority margin.

On September 13, 2016, the Sponsor submitted the protocol for the pivotal phase 3 trial, CT-301, along with a justification for the non-inferiority margin. According to the Sponsor, the non-inferiority margin of 2 cm/year presumed a large margin above placebo and a small margin for potential loss of efficacy with respect to Genotropin. The Agency agreed to the Sponsor's justification and recommended that for labeling claim(s) to be considered for more than one endpoint, a multiple testing method should be used that controls the overall one-sided Type 1 error rate at 0.025 or less.

On September 23, 2016, the Sponsor submitted an initial pediatric study plan (iPSP). The Agency denied (b) (4)

(b) (4)

The Agency also did not agree with the proposed plan

The Sponsor agreed and incorporated the Agency's comments in their iPSP. Subjects ≥6 months to ≤17 years were to be enrolled in the phase 3 trial CT-302. An agreed iPSP was issued by the Agency on March 24, 2017.

On October 2017, the Sponsor submitted the Statistical Analysis Plan (SAP) for the pivotal Phase 3 trial of lonapegsomatropin-tcgd. On January 30, 2019, the statistical reviewer Dr. Alexander Cambon provided recommendations regarding the SAP to the Sponsor. Dr. Cambon stated that "the adequacy of a single trial to support approval will be determined by its ability to support the efficacy claim based on the strength of the results. If only one clinical trial is conducted, then

internal consistency across study subsets, evidence of an effect on multiple endpoints, and statistically very persuasive efficacy results will be considered in the evaluation."

On July 9, 2019 the Sponsor submitted a fast track designation (FTD) request. The request was based on the fact that the product is for the treatment of serious disease and the preliminary data suggest improved efficacy over existing therapy. The Sponsor stated that the drug has the potential to fulfill an unmet medical need for a growth hormone replacement therapy that would not require daily injections, thus improving compliance and long-term outcomes. On September 3, 2019, the fast track designation was denied for the following reasons: 1) The Sponsor's development program was deemed not adequate to demonstrate an effect on a serious aspect of the condition (such as final adult height); 2) there are multiple FDA-approved immediate-release rhGH formulations for the treatment of GHD in children on US market; 3) there is no evidence that ACP-011 offers improved effect on annualized growth velocity and/or final adult height, or a better toxicity profile over existing therapy.

On December 4, 2019, a pre-BLA chemistry, manufacturing, and controls (CMC) meeting was held seeking the Agency's agreement on CMC topics such as drug substance specification, stability data and proposed shelf life date; essential performance requirements for GH auto-injector; and the structure of Module 3 at the time of BLA submission.

On December 10, 2019, a pre-BLA meeting was held to discuss the BLA content and format. The Agency agreed that the clinical development program, consisting of three Phase 3 clinical trials (CT-301, CT-302, CT-301EXT), one Phase 2 trial with the predecessor molecule ACP-001 (CT-004), and two Phase 1 trials (CT-101, CT-102) appears to be adequate, pending review of the results of interim analysis of the ongoing trial, CT-301EXT. The Agency disagreed with the Sponsor's proposal to pool the data from studies CT-301, CT-302 and CT-301EXT, given these studies had different design and randomization ratio, and were conducted in different patient population. The Agency agreed with the Sponsor's proposed plan to include efficacy results from each trial separately, i.e. results from trial CT-301 that provide pivotal efficacy data, as well as the Phase 3 trials CT-302 and CT-301EXT that provide supportive efficacy data and reiterated that assessment of efficacy will focus on the collective evidence from individual trials. The Agency agreed with the proposed 120-day safety update to include information starting with the data cut-off in May 2020, with the target submission in October 2020. The Agency agreed with the proposed duration of the exposure in study CT-301EXT of 291 subjects for ≥52 weeks.

On April 13, 2020, the Office of orphan products granted an orphan-drug designation to lonapegsomatropin-tcgd for the treatment of growth hormone deficiency.

On June 26, 2020, the Applicant submitted BLA for ACP-011 (b) (4)

The submission also included a request for priority review based on the fact that pediatric GHD

is a serious condition and the Applicant's data demonstrated significant improvement in the effectiveness over Genotropin for treatment of pediatric GHD. This request was denied for following reasons: 1) the Applicant's clinical program completed to date did not evaluate the effect of the drug on a serious aspect of the condition; 2) there was no evidence to suggest that treatment with lonapegsomatropin-tcgd offers significant, clinically meaningful improvement in effectiveness (annualized growth velocity), or a better toxicity profile over the existing therapy; 3) there was no evidence that lonapegsomatropin-tcgd offers an improved compliance/adherence as a potential benefit over existing therapies, given the study was not designed to compare the adherence between two products, and to demonstrate that improved adherence improves annualized growth velocity as well as final adult height.

3.3. Foreign Regulatory Actions and Marketing History

Lonapegsomatropin-tcgd is not currently approved or marketed in any foreign country.

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

4.1. Office of Scientific Investigations (OSI)

A clinical inspection summary was pending at the time of this review. Three clinical sites were selected for inspection. Site 741 was selected as this site enrolled large number (n=8) of subjects and it has never been inspected before. Site 731 was selected as several used cartridges disappeared at this site and it has never been inspected before. Site 748 was selected as this site enrolled subjects that did not meet inclusion/exclusion criteria. Additionally, 2 subjects in trial CT-301 and 1 subject in trial CT-302 inappropriately re-used lonapegsomatropin-tcgd vials at Site 748. However, due to the COVID-19 pandemic, the Office of Regulatory Affairs (ORA) was unable to conduct any of the inspections in time and all inspections were pending at the time of this review completion.

The protocol deviation at Site 748 is most concerning as 3 subjects inappropriately re-used lonapegsomatropin-tcgd vials. Given there is a lack of in-use stability data to support storage of reconstituted drug product beyond 4 hours, the purity and potency of the reconstituted solution at the time of use on Day 7 or later is not known. Thus, it cannot be determined if this protocol deviation resulted in diminished quality and/or efficacy of lonapegsomatropin-tcgd in these subjects. During the trial CT-301, there were 11 subjects included in a PK/PD sub-group, who underwent extensive blood sampling to assess PK/PD parameters of lonapegsomatropin-tcgd, hGH and mPEG. However, given none of the subjects at Site 748 were included in this PK/PD sub-group, the uncertainties raised by the protocol deviation at this site may not be significant with

respect to determination of the PK/PD profile of lonapegsomatropin-tcgd. Additionally, in order to mitigate the protocol deviation at site 748, efficacy analysis was conducted after removing all the subjects who were enrolled at this site. According to the analysis conducted by the statistical reviewer Dr. Alexander Cambon, removing the 3 subjects enrolled at site 748 lowered the AHV at Week 52 by 0.02 cm/year (0.8 to 0.78), and the confidence intervals were lowered from (0.13, 1.47) to (0.1, 1.46).

Given the difference in AHV after excluding subjects from Site 748 was not significant, and given none of the 3 subjects who were enrolled at Site 748 were included in the PK/PD subgroup, Site 748 was not excluded from the analysis. There were no protocol deviations or drug administration violations at Sites 741 and 731. Hence, all three sites were included in the analysis.

4.2. Product Quality

Office of Biotechnology Products (OBP) review was pending at the time of this review.

The drug substance used in the development program was the same as the 'to be marketed' product.

Drug Substance:
Generic name: lonapegsomatropin-tcgd

Chemical names:

(b) (4)

The hGH in lonapegsomatropin-tcgd is obtained from *Escherichia coli* using recombinant technology and has an amino acid sequence that is identical to that of the natural human growth hormone (GH), somatropin. Lonapegsomatropin-tcgd drug substance is produced by conjugation of rhGH to the mPEG-linker.

Drug product
Lonapegsomatropin-tcgd is supplied in a dual-chamber cartridge containing a lyophilized powder in one chamber and a diluent for reconstitution in second chamber. The reconstituted drug

product is a single-use, sterile solution for subcutaneous injection. The drug product is available in 9 strengths.

Office of Pharmaceutical Quality (OPQ) inspection of manufacturing sites was pending at the time of this review. It was delayed due to COVID pandemic.

4.3. Clinical Microbiology

Clinical microbiology review was pending at time of the is review completion. No issues with sterility and microbial control of drug product and drug substance were identified to date.

4.4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology/Toxicology review was pending at time of this review completion. However, no issues that preclude approvability of this drug were identified to date by Dr. Jeffrey Quinn.

Pharmacology
In vitro studies showed that lonapegsomatropin-tcgd pro-drug exhibits reduced binding to the hGH receptor and has minimal in vitro activity when compared to unconjugated hGH. However, the hGH released from lonapegsomatropin-tcgd is fully active and has a biopotency that is comparable to somatropin. In vivo studies conducted in hypophysectomized male Sprague Dawley rats and normal Cynomolgus monkeys demonstrated that once weekly lonapegsomatropin-tcgd resulted in sustained exposure to hGH. When compared to once daily somatropin, lonapegsomatropin-tcgd resulted in a larger increase in systemic IGF-1 levels in Cynomolgus monkeys and a greater body weight gain in male hypophysectomized rats. Similarly, repeat-dose toxicity studies demonstrated that lonapegsomatropin-tcgd increased IGF-1 levels, increased body/organ weights and/or altered metabolic parameters in female Sprague Dawley rats, female New Zealand white rabbits and/or Cynomolgus monkeys. Standard safety pharmacology studies did not demonstrate any effects on the central nervous, respiratory, or cardiovascular systems.

Immunogenicity
In the 26-week chronic toxicity study in Spring Dawley rats, majority of rats developed both binding and neutralizing anti-drug antibodies, that affected exposure to lonapegsomatropin-tcgd and impaired the IGF-1 levels. However, in the 52-week chronic toxicity study in monkeys, majority of the monkeys did not develop anti-drug antibodies after exposure to lonapegsomatropin-tcgd. The observed difference may be explained by a greater sequence identity between human and monkey GH.

General Toxicology

Toxicology studies consisted of 4- and 27-week studies in Sprague Dawley rats, and 4- (adult), 26- and 52-week (juvenile) studies in Cynomolgus monkeys. In the 27-week repeat dose studies in rats, no lonapegsomatropin-tcgd-related mortalities or adverse findings in clinical observations were observed, and the NOEL was determined to be 4.8 mg hGH/kg/week (highest dose studied). Similarly, in the 52-week repeat dose studies in monkey, no lonapegsomatropin-tcgd-related mortalities or adverse findings in clinical observations were observed and the NOEL was determined to be 4.8 mg hGH/kg/week (highest dose studied). The exposure margins between rats and monkeys at the NOEL (4.8 mg hGH/kg/week) and children with GHD at the recommended dose (0.24 mg hGH kg/week) are listed in Table 2.

Table 2: Exposure Margins between Rats and Monkeys at the NOAEL and Children with GHD at the recommended dose at Steady State

Analyte	Species	Week	$AUC_{0\text{-}168hr}$ (ng.hr/mL)	C_{max} (ng/mL)	MoE	
					AUC	C_{max}
hGH	Rat (Male)[a]	13	N/D	15.9	-	0.9
	Rat (Female)[a]	13	N/D	84.3	-	4.6
	Rat (Male)[a]	26	N/D	13.8	-	0.7
	Rat (Female)[a]	26	N/D	25.7	-	1.4
	Monkeys[bc]	1	26100	320	38	17
	GHD Children[d]	13	678[e]	18.5	-	-
mPEG	Rat (Male)[a]	26	6070000	48500	3.5	3.7
	Rat (Female)[a]	26	8840000	61000	5.1	4.7
	Monkeys[b]	26	54800000	391000	31	30
		52	58900000	425000	34	32
	GHD Children[d]		1740000	13100	-	-
Lonapegsomatropin-tcgd	Rat (Male)[a]	13	N/D	726	-	0.6
	Rat (Female)[a]	13	N/D	1340	-	1.1
	Rat (Male)[a]	26	N/D	251	-	0.2
	Rat (Female)[a]	26	N/D	686	-	0.6
	Monkeys[b]	26	3960000	42200	54	34
		52	3850000	37300	52	30
	GHD Children[d]	13	74000	1230	-	-

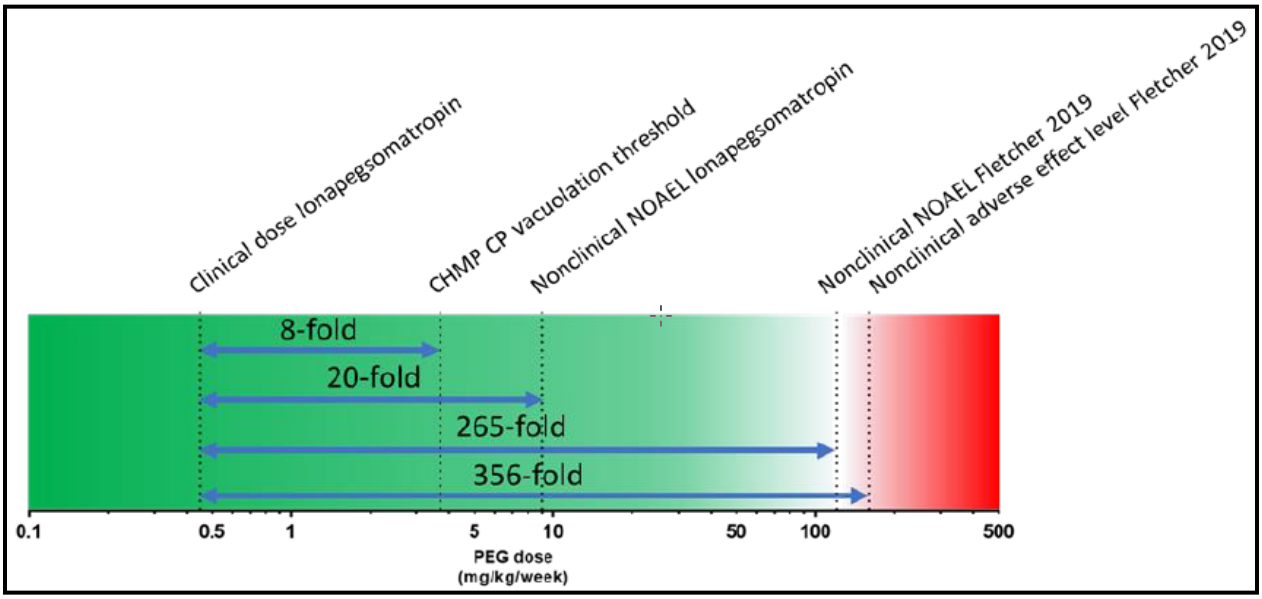
[a] Data from 27-week repeat-dose toxicity study (1704-037) in SD rats, C_{24h} are used for comparison to C_{max} due the incidence of anti-hGH antibodies impacting the accuracy of the TK parameters in the SD rat studies.
[b] Data from 52-week repeat-dose toxicity study (1704-035) in cynomolgus monkeys.
[c] Baseline corrected hGH used for cynomolgus monkey (corrected for baseline cynomolgus monkey GH).
[d] Data from the Phase 3 clinical trial CT-301 in GHD children. PK subset at Week 13
[e] $AUC_{0\text{-}t}$
Abbreviations: MoE: Multiple of Exposure, N/D: No Data, AUC area under curve, C_{max} Maximum observed concentration
Source: adapted from Dr. Jeffrey Quinn's pharmacology/toxicology review

mPEG Safety Assessment:
Safety of mPEG was assessed in 27-week study in adolescent/adult Sprague Dawley rats and 52-weeks study in juvenile cynomolgus monkeys. Immunohistochemical staining of mPEG and vacuolation were observed in the brain tissues of rats and monkeys in highly vascularized areas of the blood-brain barrier and blood-CSF barrier. Additionally, after the 27-week recovery period in rats, and 52-week recovery period in monkeys, there was a persistence of mPEG association with several cell types and vacuolation of the choroid plexus, indicating only a partial recovery upon withdrawal of lonapegsomatropin-tcgd. However, mPEG staining and vacuolation were not associated with a distortion of the cytoplasmic or nuclear compartments, degeneration, necrosis, or inflammation. Additionally, there was no evidence of signs of neurotoxicity such as tremors, convulsions, reactivity to handling or unusual behavior. In both rats and monkeys, the level of mPEG in cerebral spinal fluid did not exceed lower limit of quantification.

The NOEL for the mPEG vacuolation in brain of monkeys was 0.4 mg hGH/kg/week (low dose). The systemic mPEG exposure (3330 mcg.hr/mL) at this dose was 2-fold above the clinical mPEG exposure level (1740 mcg.hr/mL) at the proposed dose of 0.24 mg hGH/kg/week in children with GHD. Additionally, the total mPEG load administered to children with GHD was 8-fold below the theoretical threshold recommended by the Committee for Medicinal Products for Human Use for choroid plexus epithelial cells vacuolation, and 265-fold below the NOEL defined previously in other studies of cynomolgus monkeys administered a PEGylated compound for 3 months.[22] Refer to Figure 1.

Figure 1: Lonapegsomatropin-tcgd mPEG Dose Margins

[22] Fletcher AM, Tellier P, Douville J, et al. Adverse vacuolation in multiple tissues in cynomolgus monkeys following repeat-dose administration of a PEGylated protein. Toxicol Lett. 2019;317:120-129.



Source: adapted from Dr. Jeffrey Quinn's pharmacology/toxicology review

Based on this, the pharmacology/toxicology reviewer, Dr. Jeffrey Quinn concluded that at the proposed therapeutic dose of 0.24 mg hGH/kg/week, lonapegsomatropin-tcgd administration in pediatric subjects carries a low risk of adverse central nervous system effects secondary to mPEG induced vacuolation in the choroid plexus epithelial cells.

Genotoxicity
Based on the standard battery of in vitro and in vivo genotoxicity tests, there was minimal concern for genotoxic potential of lonapegsomatropin-tcgd or its products of autocleavage.

Carcinogenicity
Rodent carcinogenicity studies were not conducted with lonapegsomatropin-tcgd. The carcinogenicity assessment of lonapegsomatropin-tcgd was based on nonclinical and clinical data, as well as published nonclinical and clinical information. According to the Pharmacology/Toxicology reviewer Dr. Jeffrey Quinn, lonapegsomatropin-tcgd, hGH or the products of its autocleavage carry a minimal carcinogenic potential in children with GHD.

Reproductive and Development Toxicology
Based on the reproductive and developmental toxicity studies conducted in Sprague Dawley rats and rabbits, the Pharmacology/Toxicology reviewer Dr. Jeffrey Quinn concluded that there is minimal concern regarding the reproductive and development toxicity potential of lonapegsomatropin-tcgd, hGH or the products of its autocleavage in children with GHD.

4.5. Clinical Pharmacology

Clinical Pharmacology review was pending at time of this review completion. However, no issues

that preclude approvability of this drug were identified to date by Dr. Sang Chung. Lonapegsomatropin-tcgd was evaluated in six clinical pharmacology trials: two phase 1 trials in healthy adults (CT-101 and CT-102), one phase 2 trial (CT-004) in subjects with pediatric GHD and three phase 3 trials (CT-301, CT-302 and CT-301EXT) in subjects with pediatric GHD.

4.5.1. Mechanism of action

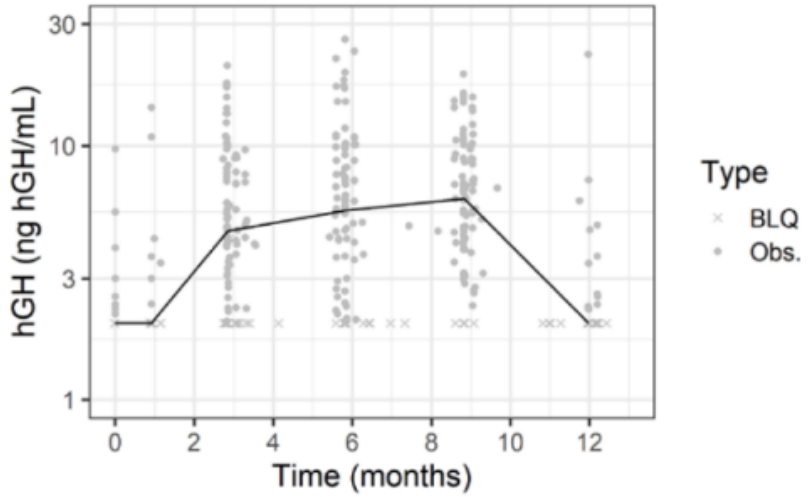
Lonapegsomatropin-tcgd is a hGH prodrug consisting of rhGH that is transiently conjugated to a mPEG carrier via a proprietary TransCon linker, that slowly releases the active molecule hGH via hydrolysis. hGH acts directly via stimulation of GH-receptor and indirectly via IGF-1 primarily produced in the liver. GH via its action on GH-receptors present on multiple tissues results in growth stimulation, change in body composition and stimulation of metabolic actions.

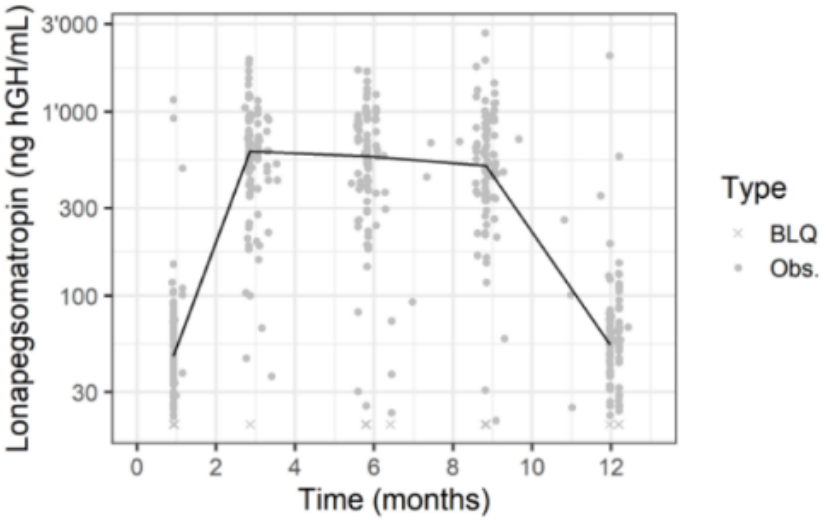
4.5.2. Pharmacokinetics

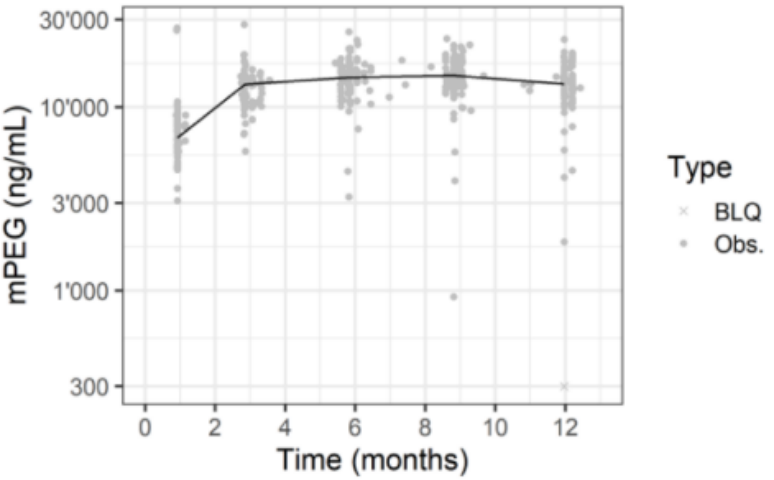
Absorption
The PK of single dose of lonapegsomatropin-tcgd was evaluated in healthy subjects in trial CT-101 at dose levels of 0.24, 0.30 or 0.42 mg hGH/kg. Following administration of the 0.24 mg hGH/kg dose, the median time to peak serum concentration (T_{max}) was 16-, 36- or 240-hours post-dose for hGH, lonapegsomatropin-tcgd or mPEG, respectively. However, the Area Under the Curve (AUC_{0-168}) and the maximum observed concentration (C_{max}) increased in greater than dose-proportional manner.

The steady state PK was evaluated in pediatric subjects with GHD following multiple doses of lonapegsomatropin-tcgd in trial CT-301 and following multiple doses of the predecessor molecule ACP-001 in trial CT-004. Time to reach steady-state for hGH, lonapegsomatropin-tcgd or mPEG was not well characterized, as these were assessed at Week 1 and 13 with trough concentrations (C_{trough}) from other visits in both trials. Apparent steady-state was reached in 13 weeks. There was no accumulation of hGH and lonapegsomatropin-tcgd. However, significant accumulation of mPEG was observed. Refer to Figure 2.

Figure 2: Individual and median hGH (top), lonapegsomatropin-tcgd (middle) and mPEG (bottom) concentrations during treatment of pediatric GHD (Trial CT-301)


hGH (ng hGH/mL)
30
10
3
1
0
2
4
6
8
10
12
Time (months)
Type
BLQ
Obs.


Lonapegsomatropin (ng hGH/mL)
3'000
1'000
300
100
30
0
2
4
6
8
10
12
Time (months)
Type
BLQ
Obs.


mPEG (ng/mL)
30'000
10'000
3'000
1'000
300
0
2
4
6
8
10
12
Time (months)
Type
BLQ
Obs.

Source: adapted from Dr. Sang Chung's clinical pharmacology review

In trial CT-301, the coefficient of variation (CV) of AUC_{0-168} was relatively high at 82.3%, 67%, 34% for hGH, lonapegsomatropin-tcgd and mPEG, respectively. There was an apparent cross-reactivity in bioanalytical method that measured hGH from lonapegsomatropin-tcgd, however this was not significant.

Distribution
The Applicant did not conduct any formal study for evaluating the distribution of lonapegsomatropin-tcgd or mPEG. The estimated mean volume of distribution for hGH, lonapegsomatropin-tcgd and mPEG in a pediatric subject with GHD weighing approximately 20 kg was 61.8, 1.3, 3.5 L, respectively. The mean volume of distribution of hGH was significantly higher from lonapegsomatropin-tcgd administration compared to the estimated volume of distribution from daily hGH and may be explained by the difference in bioavailability.

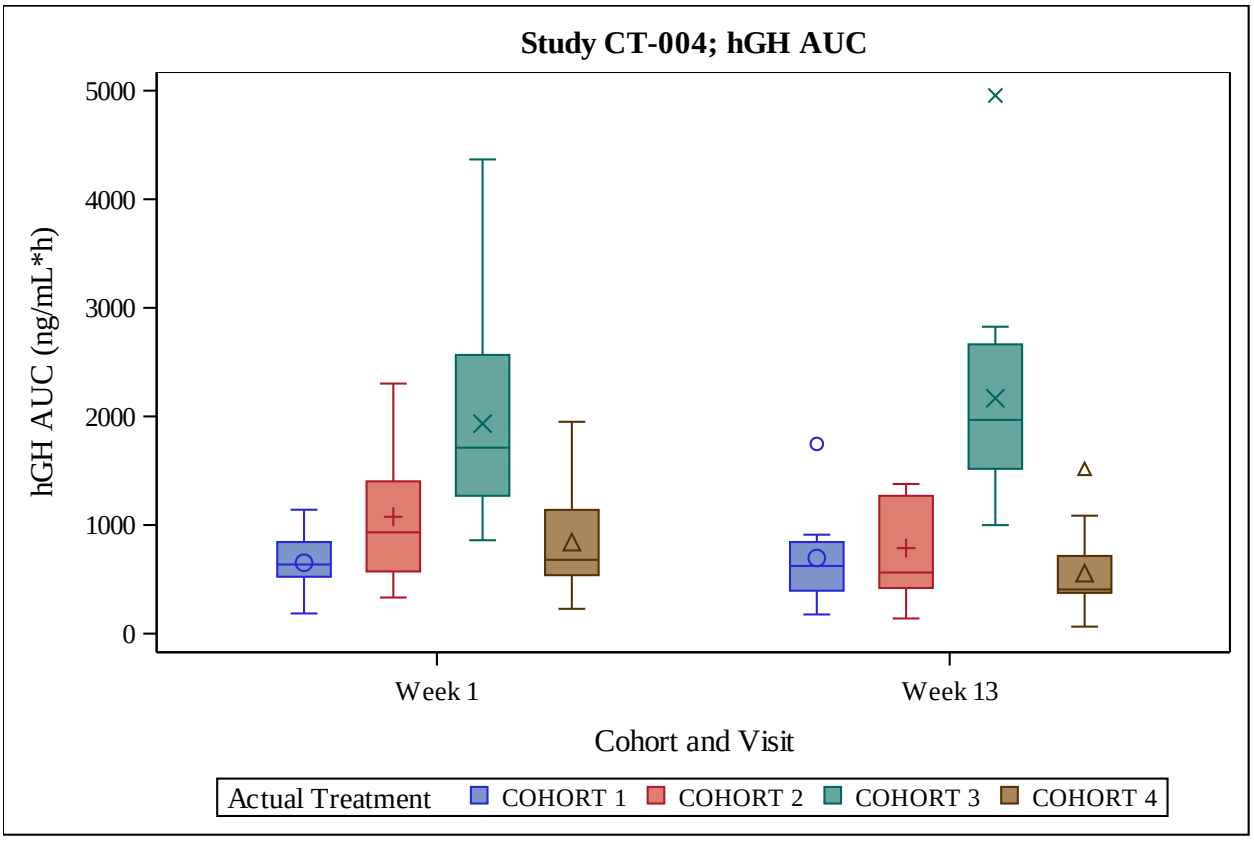
Metabolism and elimination
Following administration of 0.24 hGH/kg in adults, the terminal half-life was 25.4, 51.9, and 508 hours for hGH, lonapegsomatropin-tcgd, and mPEG, respectively. The mean clearance of hGH for a subject with pediatric GHD weight 19 kg was estimated as 125 L/day and was similar to the mean clearance of daily hGH in adult GHD.

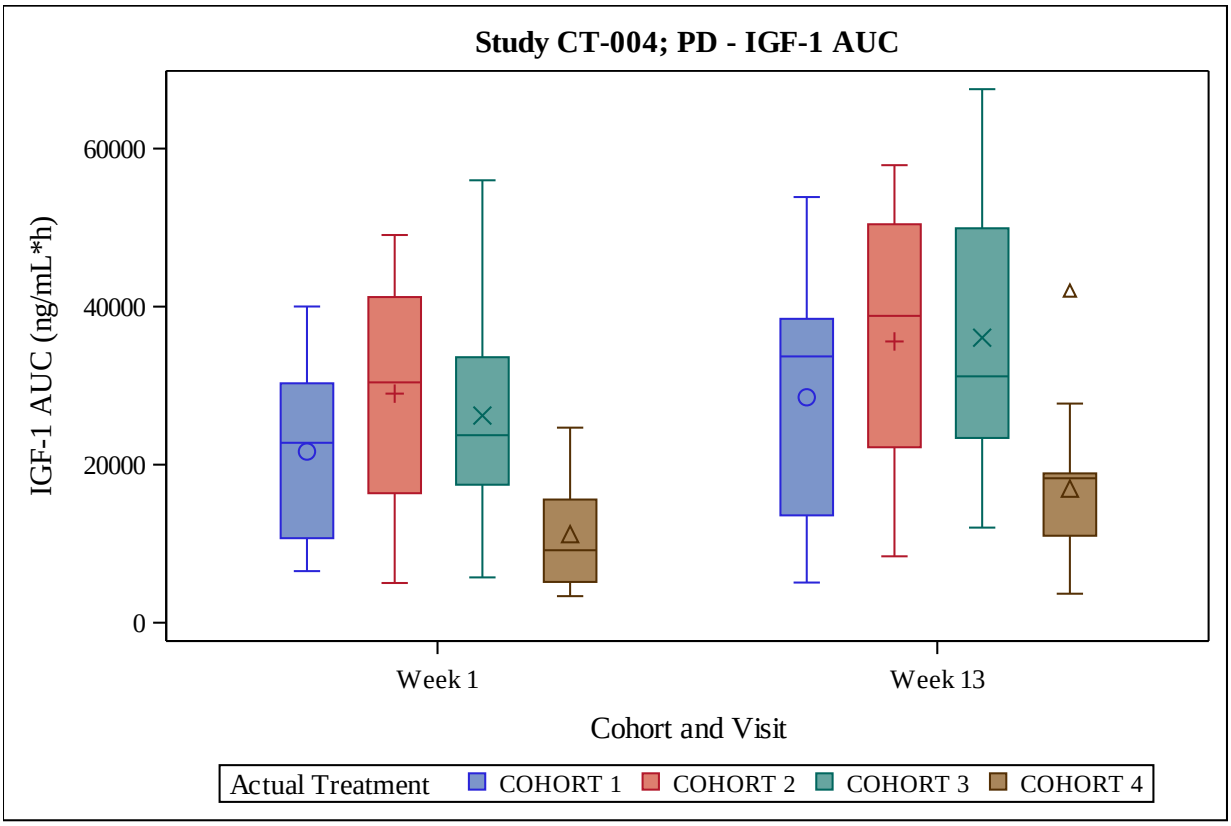
Drug-Drug interaction
There was no formal study with lonapegsomatropin-tcgd evaluating the potential for drug-drug interaction. According to the clinical pharmacology reviewer, given mPEG is primarily excreted into the urine through the glomerular filtration, and metabolism is a minor elimination pathway, there is no significant mechanistic potential for drug-drug interaction from lonapegsomatropin-tcgd or mPEG. However, given hGH can induce changes in CYP450 activity, concomitant treatment with CYP450 substrates will be addressed in the labeling.

4.5.3. Pharmacodynamics

IGF-1 Levels:
In the phase 2 trial (CT-004) of the predecessor molecule ACP-001, the efficacy of all doses of ACP-001 was higher compared to Genotropin. Additionally, the efficacy increased with increasing dose. Exposure of hGH was comparable between both treatment groups, however, IGF-1 levels were higher following 0.21 mg hGH/kg/week ACP-001 compared to Genotropin. The IGF-1 AUC was similar between 0.21 and 0.3 mg hGH/kg/week, indicating that 0.21 mg hGH/kg/week was the minimum effective dose.

Figure 3: Box plot of AUC (hGH; top, IGF-1; bottom) by cohort and visit; AUC_{0-168h} for cohorts 1-3, AUC_{0-24h} x7 for cohort 5 (Study 004)





Cohort 1; 0.14 mg hGH/kg/week, Cohort 2; 0.21 mg hGH/kg/week, Cohort 3; 0.30 mg hGH/kg/week
Cohort 4; 0.03 mg hGH/kg/day (Genotropin once daily)
Source: adapted from Dr. Sang Chung's clinical pharmacology review

Dosing and drug product:
For the pivotal trial CT-301 a dose of 0.24 mg hGH/kg/week was selected for both lonapegsomatropin-tcgd and Genotropin based on the results of trial CT-004. In the pivotal trial CT-301, no dose adjustments were allowed to improve efficacy. Thus, there is no data to support different starting dose or dose adjustment in the label.

According to the clinical pharmacology reviewer, based on the results of the clinical pharmacology trials and population PK analysis of the data from Phase 3 trials, dose adjustment based on gender, race, ethnicity, or renal function are not required.

Lastly, the drug product used in pivotal trial CT-301 was different from the to-be-marketed product. The Applicant conducted a phase 1 trial comparing lonapegsomatropin-tcgd administered via syringe and needle vs. auto-injection (CT-102) in order to bridge the proposed to-be-marketed product (auto-injector and dual chamber cartridge) to the clinical product (pre-filled syringe and needle with lyophilized powder in vial). According to the clinical pharmacology reviewer, trial CT-102 demonstrated comparability of hGH between the to-be-marketed product and the clinical product.

Effect on QT/QTc interval:
The Applicant did not conduct a dedicated QT/QTc trial with lonapegsomatropin-tcgd. Electrocardiogram (ECGs) were collected in phase 3 study CT-301 at baseline and Week 26 from all subjects. additionally, ECGs were collected extensively matching to PK sampling in a sub-set of 11 subjects. Refer to Section 8.4.9 for further details.

4.6. Devices and Companion Diagnostic Issues

Device
Final review by Center for Devices and Radiological Health (CDRH) was pending at the time of this review completion.

Lonapegsomatropin-tcgd is supplied in a dual-chamber cartridge containing a lyophilized powder in one chamber and a diluent for reconstitution (water) in the second chamber. The dual-chamber cartridge consists of (b) (4) Refer to Figure 4. The reconstituted drug product is a single-use, sterile solution for subcutaneous injection. The drug product is available in following 9 strengths: 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.

Figure 4: Drawing of the Dual Chamber Cartridge

Source: Description of Container Closure System provided by the Sponsor in Module 2

The lonapegsomatropin-tcgd auto-injector is specific to the lonapegsomatropin-tcgd drug product in a dual chamber cartridge. Refer to Figure 5. The auto-injector is a re-usable, electronic auto-injector that allows motorized delivery of full, single doses of lonapegsomatropin-tcgd drug product in the dual chamber cartridge. The dual chamber cartridge and the auto-injector are classified as cross-labeled combination product.

Figure 5: GH Auto-Injector shown with Dual Chamber Cartridge and Needle

Source: Description of Container Closure System provided by the Sponsor in Module 2

The mixing of the lyophilized drug product includes an automatic mixing step that is controlled by the auto-injector device, followed by a manual mixing step in which the user turns the device 5 or 10 times. The manual mixing step is monitored by the device and guided by light and sound signals. (b) (4) The injection needle needs to be manually inserted into the skin, however, the delivery of the auto-injector automatically provides a motorized delivery of the reconstituted drug product. The auto-injector has built in electronics and software that provides confirmation that the full dose is delivered.

The auto-injector is reusable. The drug product is enclosed within the dual-chamber cartridge and not in contact with the device.

The to-be-marketed device was not used in the pivotal clinical trial CT-301 and the supportive phase 3 trial CT-302. During the extension trial CT-301EXT, once the auto-injector was available, subjects were switched to the to-be-marketed device. The phase 1 trial CT-102 established the bioequivalence of a single subcutaneous (SC) injection of a 13.3 mg hGH dose of lonapegsomatropin-tcgd administered via syringe/needle and via an auto-injector.

Human Factors
According to the preliminary review by the Division of Medication Error Prevention and Analysis (DMEPA) reviewer Ebony Whaley, Pharm D, the human factors validation study submitted by the Applicant had multiple study methodology deficiencies that preclude assessment of whether the proposed combination product user interface supports safe and effective use by the intended users, for the product's intended uses and under the expected use conditions (refer to review in DARRTS dated 01/14/2021). DMEPA has thus recommended that the Applicant conducts another Human Factor validation study. At the time of this review, DMEPA is reviewing a protocol submitted the Applicant for their Human Factor validation study. Results of this study will determine the approvability of the proposed combination product, which includes a reusable autoinjector, and a single dose, dual-chamber glass cartridge containing lyophilized lonapegsomatropin-tcgd powder and the diluent.

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3. Listing of Clinical Trials Relevant to this BLA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
CT-101	Phase 1, randomized, open-label, crossover, bridging (ACP-011 vs ACP-001)	Group 1: ACP-001 0.24 mg hGH/kg, single SC injection Lonapegsomatropin-tcgd 0.24 mg hGH/kg, single SC injection Group 2: Lonapegsomatropin-tcgd 0.30 mg hGH/kg, single SC injection Lonapegsomatropin-tcgd 0.42 mg hGH/kg, single SC injection	Safety and tolerability of single dose of ACP-011 at 3 different dose levels	44 days	46 ACP-001: 28 Lonapegsomatropin-tcgd: 45	Healthy adult volunteers	Single-center (United States)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
CT-102	Phase 1, randomized, open-label, crossover, bioequivalence (Syringe/needle vs. GH Auto-Injector)	Lonapegsomatropin-tcgd 13.3 mg hGH, single SC injection via syringe/needle Lonapegsomatropin-tcgd 13.3 mg hGH, single SC injection via GH Auto-injector	hGH maximum concentration and area under the concentration -time curve	Two doses separated by a washout period of at least 14 days	28	Healthy adult male volunteers	Single-center (Australia)
CT-004	Phase 2, randomized, open-label, active control	ACP-001 0.14, 0.21, 0.30 mg hGH/kg/week, SC injections administered once weekly Genotropin 0.21 mg hGH/kg/week divided in daily doses, SC injections administered daily		26 weeks	53 ACP-001: 40 Genotropin: 13	Prepubertal pediatric subjects with GHD	20 sites (Belarus, Bulgaria, Egypt, Greece, Hungary, Poland, Romania, Russia, Turkey, Ukraine

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
CT-301	Phase 3, randomized, open-label, active control	Lonapegsomatropin-tcgd 0.24 mg hGH/kg/week, SC injection administered once weekly Genotropin 0.24 mg hGH/kg/week divided in daily doses, SC injections administered daily	AHV at Week 52	52 weeks	161 Lonapegsomatropin-tcgd: 105 Genotropin: 56	Prepubertal pediatric subjects with GHD	54 sites (Armenia, Australia, Belarus, Bulgaria, Georgia, Greece, Italy, New Zealand, Poland, Romania, Russia, Turkey, Ukraine, United States)
CT-302	Phase 3, open-label, uncontrolled	Lonapegsomatropin-tcgd 0.24 mg hGH/kg/week, SC injection administered once weekly		26 weeks	146	Pediatric subjects with GHD	24 sites (Australia, Canada, New Zealand, United States)

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
CT-301 EXT	Phase 3, long-term, open-label uncontrolled extension	Lonapegsomatropin-tcgd 0.24 mg hGH/kg/week, SC injection administered once weekly		Ongoing, long-term	296	Pediatric subjects with GHD	63 sites (Armenia, Australia, Belarus, Bulgaria, Canada, Georgia, Greece, Italy, New Zealand, Poland, Romania, Russia, Turkey, Ukraine, United States)

5.2. Review Strategy

Pivotal trial CT-301 that was a randomized, active-controlled trial of 12 months duration (core phase) in pediatric subjects with GHD is the primary focus of this efficacy review. This review includes the Applicant's analyses for efficacy with this medical reviewer's commentary. A separate analysis and review were performed by the FDA statistician, Dr. Alexander Cambon, who confirmed the Applicant's findings of efficacy. The supportive efficacy data was provided from trials CT-302 and CT-301EXT. Although the phase 2 trial CT-004 was conducted using the predecessor molecule ACP-001, it provided only limited data on efficacy of lonapegsomatropin-tcgd.

The safety data analyzed primarily included the pivotal phase 3 trial CT-301 and was supported by the two phase 3 trials CT-302 and CT-301 EXT. This review includes Applicant's analyses, as well as analyses generated by this medical reviewer using JMP clinical software. The safety data from earlier trials with ACP-001 were not used to evaluate the safety of lonapegsomatropin-tcgd, as agreed during the meeting between the Agency and the Sponsor on July 27, 2016.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. TransCon hGH CT-301, A multicenter, Phase 3, randomized, open-label, active-controlled, parallel-group trial investigating the safety, tolerability, and efficacy of lonapegsomatropin-tcgd administered once a week versus standard daily hGH replacement therapy over 52 weeks in prepubertal children with growth hormone deficiency.

6.1.1. Study Design

Overview and Objective

Trial CT-301 was designed to evaluate the safety, tolerability, and efficacy of once weekly dosing of lonapegsomatropin-tcgd in pediatric subjects with growth failure due to GHD.

The primary objective of this trial was to demonstrate the efficacy of once weekly lonapegsomatropin-tcgd compared to daily hGH formulation (Genotropin) on AHV in prepubertal children with growth failure due to GHD at 52 weeks.

The secondary objectives were to compare the safety of weekly lonapegsomatropin-tcgd and Genotropin at 52 weeks; to compare the effect of weekly lonapegsomatropin-tcgd and Genotropin on AHV and height SDS over 52 weeks; to compare the effect of weekly

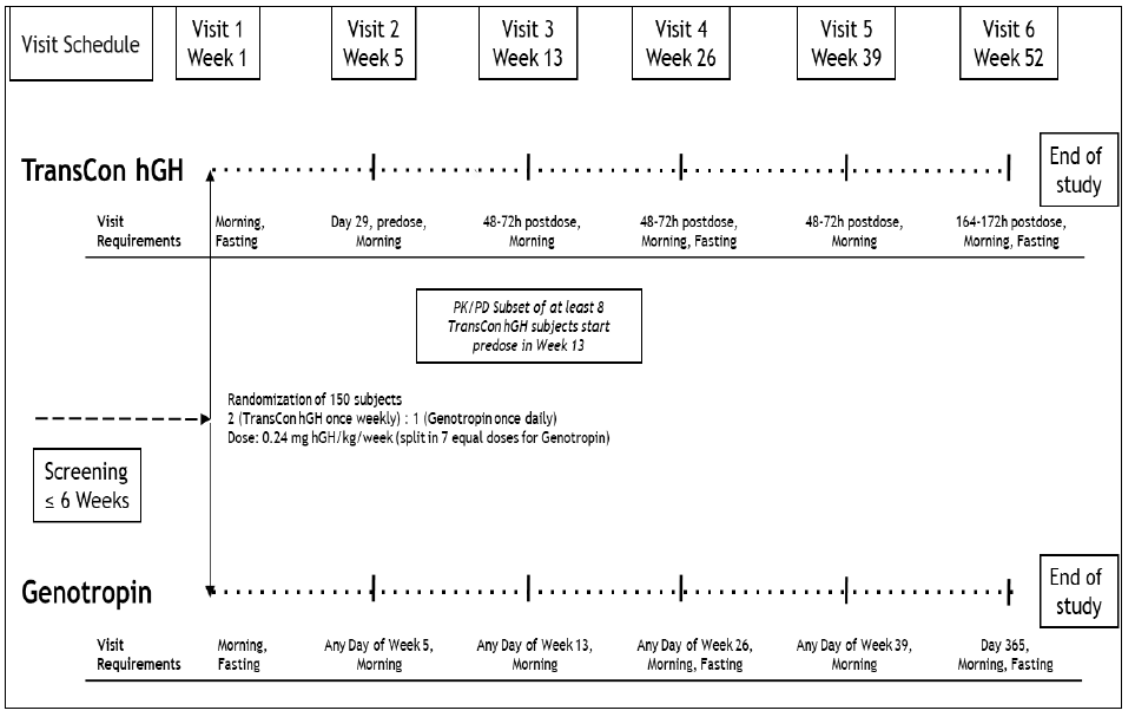
lonapegsomatropin-tcgd and Genotropin on serum IGF-1, IGFBP-3, IGF-1 SDS, IGFBP-3 SDS and normalization of IGF-1 SDS over 52 weeks; to describe PK/PD profile of lonapegsomatropin-tcgd weekly injection, measured as serum hGH, IGF-1, IGF-1 SDS, IGFBP-3, IGFBP-3 SDS and mPEG levels in a PK/PD subset of subjects in lonapegsomatropin-tcgd group; to compare the Cmax for hGH of lonapegsomatropin-tcgd to the anticipated Cmax of daily hGH; and to determine the incidence of anti-hGH antibodies for both treatments, and treatment-emergent anti-mPEG antibodies for lonapegsomatropin-tcgd over 52 weeks.

Trial Design

Trial CT-301 was a phase 3, randomized, open-label, parallel, active-controlled, multinational, multicenter trial comparing the efficacy and safety of once weekly lonapegsomatropin-tcgd to once daily Genotropin over 52 weeks in 161 pre-pubertal, treatment-naïve subjects with growth failure due to GHD, aged 3-11 years for females and 3-12 years for males.

The trial consisted of a screening period (up to 6 weeks plus up to 2 weeks between randomization and visit 1) and a treatment period (52 weeks of dosing with a total of 6 trial visits). All subjects who completed this trial, including subjects on Genotropin, were offered treatment with lonapegsomatropin-tcgd in the extension trial, CT-301EXT. Refer to Figure 6 below.

Figure 6: Schematic of Trial CT-301



Abbreviations: hGH = human growth hormone; kg = kilogram; mg = milligram; PD = pharmacodynamic; PK = pharmacokinetic

Source: Clinical Study Report for CT-301, page 28

Refer to Appendix 1 and 2 for details on the specific procedures that were carried out at each visit.

Initially 150 pre-pubertal, hGH-treatment naïve children with growth failure due to GHD were planned for enrollment, and ultimately 161 subjects received at least one dose of study drugs (lonapegsomatropin-tcgd or Genotropin). A total of 105 subjects received lonapegsomatropin-tcgd, and 56 subjects received Genotropin.

Key inclusion criteria (all criteria needed to be met):

- Prepubertal children with GHD in Tanner stage 1, who were naïve to GH therapy
- Boys aged 3-12 years, inclusive, and girls aged 3-11 years, inclusive
- Height SDS ≤ -2, standardized for chronological age and sex or if approved by the medical monitor, height SDS less than 1.5 below the mid-parental height
- Body Mass Index (BMI) within ±2 SD of mean BMI for chronological age and sex
- Diagnosis of GHD confirmed by 2 different GH stimulation tests. Peak GH level of ≤ 10 ng/mL was used.
- Bone age at least 6 months less than chronological age
- Baseline IGF-1 SDS ≤ -1, standardized for age and sex
- Normal fundoscopy at screening

Key exclusion criteria:

- Children with a body weight < 12kg
- Tanner stage >1
- Prior exposure to recombinant hGH or IGF-1 therapy
- Children with past or present intracranial tumor growth
- Children born small for gestational age, with idiopathic short stature, with psychosocial dwarfism, or with other causes of short stature
- Children with malnutrition (serum albumin < lower limit of normal or serum iron < lower limit of normal, or BMI ≤ -2 SD for age and sex)
- History or presence of malignant disease, any evidence of current tumor growth
- Any clinically significant abnormality likely to affect growth or the ability to evaluate growth
- Poorly controlled diabetes mellitus, defined as hemoglobin A1c ≥ 8% or diabetic complications
- Known chromosomal abnormalities and other medical syndromes known to impact growth
- Closed epiphyses
- Concomitant administration of other treatments that can affect growth (anabolic steroids except for hormone replacement therapy or requirement for glucocorticoid therapy at

doses >400 mcg/day inhaled budesonide or equivalents for >1 month during a calendar year)
- Major medical conditions and/or presence of contraindication to hGH treatment

The subjects were centrally randomized in a 2:1 ratio to receive either lonapegsomatropin-tcgd or Genotropin. Randomization was stratified using age (>3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender.

Lonapegsomatropin-tcgd was administered weekly at a dose of 0.24 mg hGH/kg/week by the trial staff or by the subject/parent/legal guardian. Genotropin was administered daily at a dose of 0.034 mg hGH/kg/day, and administration was at the trial site during the first visit in morning hours, and subsequently by the subject/parent/legal guardian at bedtime.

Genotropin was available as a lyophilized powder in a 2-chamber cartridge. Lonapegsomatropin-tcgd was available as lyophilized powder in single-use glass vials which were to be reconstituted with 1 mL sterile water for injection were used. Two vial presentations were available, which provided the final concentration of 11 mg hGH/mL and 22 mg hGH/mL when reconstituted. Refer to Table 4 for the weight-based dose volumes that were used in the trial.

Table 4: Drug concentration, dosing brackets and volumes of Lonapegsomatropin-tcgd administered in CT-301

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

Source: Clinical Study Report for CT-301, page 35

The proposed for marketing lonapegsomatropin-tcgd auto-injector was not available for use in study CT-301; it was used later in study 301EXT.

Treatment was discontinued if a subject withdrew consent, experienced serious adverse event, or severe adverse drug reaction, developed neutralizing antibodies, used a prohibited concomitant medication, was a loss to follow-up, had poor compliance or experienced serious

protocol deviation.

No dose titration for the efficacy was implemented. As per protocol, the doses could be decreased for the safety reasons at any time during the trial. In subjects with IGF-1 >+2 SD at any visit, confirmed with a second measurement, the hGH dose was decreased to the next lower dose bracket for subjects in lonapegsomatropin-tcgd group and by 20% for subjects in Genotropin group. IGF-1 levels were measured in the morning for the Genotropin group and 48-72 h post dose for lonapegsomatropin-tcgd group. Prior to dose adjustment, levels were rechecked to confirm an abnormal result. Repeat levels were measured on any day for the Genotropin group and 5-7 days post dose for the lonapegsomatropin-tcgd group. Additionally, glucose parameters (Hemoglobin A1c (HbA1c) >6.2%, fasting glucose level >100 mg/dL or 2-h post dose glucose level during oral glucose tolerance test ≥140 mg/dL) were also used for dose decrease and/or discontinuation. In subjects with baseline borderline glucose intolerance or diabetes, hyperglycemia could be treated without initial adjustment to the trial drug dose. In subjects with no baseline evidence of glucose intolerance, if fasting plasma glucose and HbA1c repeated 2-4 weeks were same or worse, either treatment drug dose could be decreased (lonapegsomatropin-tcgd to next lower dose bracket and Genotropin dose by 20%), or appropriate anti-glycemic therapy(ies) could be started. Doses were further adjusted in subjects with progressively worsening glucose intolerance. Dose modifications were also considered in subjects who developed severe GH-related adverse event (peripheral edema, headache, intracranial hypertension) or adverse drug reaction and/or abnormal laboratory values.

Treatment compliance was assessed based on accountability and review of the patient diary. Subjects were asked to return all used and unused trial drug as well as completed patient diary at each visit.

Permitted concomitant therapies included replacement therapy for other pituitary deficiencies, glucocorticoid therapy for indications other than adrenal replacement at a dose <400 mcg/day for a maximum of approximately 1 month during 1 calendar year, treatment for diabetes and over-the-counter vitamins, minerals, or other dietary supplements approved by the Investigator. Prohibited therapies included estrogen, anabolic steroids, systemic corticosteroids (except for adrenal replacement or at a dose equivalent to inhaled budesonide <400 mcg/day for a maximum of approximately 1 month during 1 calendar year) and weight-reducing drugs or appetite suppressants (other than for the treatment of attention deficit-hyperactivity disorder).

Compliance with trial procedures and regulatory requirements were monitored (b) (4) (b) (4) and the Applicant, by conducting periodic visits to the investigational site. Additionally, audits were conducted by the Applicant's contractor (b) (4) the Applicant, or (b) (4)

Medical reviewer's comments:
A randomized, active-controlled, multinational, multicenter trial with a 52 weeks treatment duration is an adequate trial design and in accordance with the regulatory requirements for adequate and well-controlled trials (FDA 21 Code of Federal Regulations (CFR) 314.126). A similar trial design has also been accepted by the Agency for the approval of other rhGH formulations for use in pediatric subjects with growth failure due to GHD.

Given holding GH in pediatric subjects with growth failure due to GHD would be unethical, an active-controlled trial in leu of a placebo-controlled trial was acceptable. Genotropin has been a standard therapy for treatment for pediatric GHD for over 20 years and was an appropriate choice for the active comparator. The subjects were centrally randomized, and the strata used for randomization (age, peak GH levels in stimulation tests and gender) were appropriate.

An open label design, chosen as Genotropin is administered once-daily whereas lonapegsomatropin-tcgd is a once a week formulation, had been accepted by the Agency in an end-of-phase 2 meeting prior to the start of the trial. In order to minimize bias, selected staff members (medical monitors, medical experts, and statisticians) were blinded to treatment. Auxologists were blinded to treatment allocation, if possible. Additionally, the primary endpoint (AHV) chosen was objective, which also minimizes bias in an open-label trial.

The inclusion and exclusion criteria were generally appropriate. Appropriate diagnostic criteria were used, including evaluation of bone age, height at baseline; subjects underwent testing with 2 different GH stimulation tests in order to confirm the diagnosis of GHD. The trial did not include subjects <3 years; the efficacy and safety of the drug in younger subjects was evaluated in supportive trial CT-302.

Fixed doses of rhGH were used and subjects were started at a dose of 0.24 mg hGH/kg/week in this trial. The chosen starting dose is consistent with the pediatric endocrine society guidelines that recommend an initial rhGH dose of 0.16-0.24 mg/kg/week[1]. Prior phase 2 trial (CT-004) with the predecessor molecule ACP-001 demonstrated that a dose of 0.21 mg hGH/kg/week of ACP-001 was comparable to a dose of 0.3 mg hGH/kg/day of Genotropin, in terms of PK (hGH), C_{max} exposure over one week, efficacy (AHV), and safety/tolerability. Additionally, the bridging trial (CT-101) demonstrated comparable PK (hGH) and PD (IGF-1) of lonapegsomatropin-tcgd and ACP-001. The starting dose of 0.24 mg hGH/kg/week was thus acceptable and was agreed upon with the Agency in the end of phase 2 meeting prior to start of the trial. Refer to Clinical Pharmacology review for details.

Autoinjector was not available during the core phase of the trial and SC injection was administered via syringe/needle. Given trial CT-102 established the bioequivalence of a single SC injection of a 13.3 mg hGH dose of lonapegsomatropin-tcgd administered via syringe/needle and via an auto-injector, the data obtained from this trial can be applied to the final to be marketed formation (auto-injector). However, according to the preliminary review conducted by DMEPA, the human factors validation study submitted by the Applicant had multiple study methodology deficiencies. CDRH has thus recommend that the Applicant conducts another human factor validation study, that is currently pending. Results of this study will determine the approvability of the proposed combination product.

Subjects were centrally randomized in a 2:1 ratio to either lonapegsomatropin-tcgd or Genotropin. Randomization stratification based on age (>3 to ≤6 and >6 years), peak GH levels in stimulation tests (≤5 ng/mL and >5 ng/mL), and gender was appropriate.

Study drug dose was decreased in subjects who experienced elevated IGF-1 levels or hyperglycemia. The criteria for dose modification are acceptable and consistent with the pediatric endocrine society guidelines for treatment of GHD.[1] Subjects who discontinued treatment were encouraged to attend all the remaining trial visits and were not discontinued from the trial. Also, appropriate efforts were taken to ensure and measure treatment compliance. Compliance was assessed by reviewing the returned doses as well as the patient diary.

Study Endpoints

Primary Efficacy Endpoint:

- AHV at 52 weeks for weekly lonapegsomatropin-tcgd and daily hGH treatment groups

Secondary Efficacy Endpoint:

- AHV for the lonapegsomatropin-tcgd and the daily hGH treatment groups over 52 weeks
- Change in height SDS over 52 weeks for the lonapegsomatropin-tcgd and the daily hGH treatment groups
- Serum IGF-1 levels, IGFBP-3 levels, IGF-1 SDS and IGFBP-3 SDS; and the normalization of IGF-1 SDS over 52 weeks for the lonapegsomatropin-tcgd and the daily hGH treatment groups

Safety Endpoints:

- Incidence of adverse events
- Local tolerability
- Incidence of anti-hGH antibodies including neutralizing antibodies as needed (in both treatment groups) and incidence of treatment-emergent anti-mPEG binding antibodies

(in lonapegsomatropin-tcgd group)
- IGF-1 levels and IGF-1 SDS
- Parameters of glucose metabolism (fasting glucose and insulin level, hemoglobin A1c and lipid parameters)
- Hormone levels: thyroid status and morning cortisol
- Hematology and biochemistry blood parameters
- Electrocardiogram (ECG)
- Physical examinations, vital sign measurements
- Bone age at 52 weeks

PK Endpoints (in a subset of at least 8 lonapegsomatropin-tcgd treated subjects after 13 weeks of treatment):
- PK profile of lonapegsomatropin-tcgd over 1 week
- PK profile of hGH over 1 week
- PK profile of mPEG over 1 week
- C_{max} for hGH of lonapegsomatropin-tcgd

PD Endpoints:
- IGF-1 and IGFBP-3 over 1 week
- IGF-1 SDS and IGFBP-3 SDS over 1 week

Medical reviewer's comments:
AHV is a surrogate endpoint and has previously been accepted by the Agency for the approval of several other rhGH products with native GH sequence for treatment of pediatric subjects with growth failure due to GHD (Refer to Table 1 above) given the rhGH-induced changes in annualized growth velocity ultimately translate into increased final adult height. This evidence is supported by a clear mechanistic rationale (replacement therapy in subjects with GHD) and clinical data from the trials with short acting GH formulations where some subjects had been treated to final adult height (Table 1) and demonstrated that improvement in annualized growth velocity was associated with improvement in final adult height.

Height velocity during the first year of treatment with rhGH is an important predictor of subsequent growth[23] and change in height SDS during the first year of treatment is an

[23] Ranke MB, et al. Prediction of response to growth hormone treatment in short children born small for gestational age: Analysis of Data from KIUGS (Pharmacia International Growth Database). *The Journal of Clinical Endocrinology and Metabolism.* 2003, 88:125-131

important predictor of final adult height achieved.[24] Studies conducted with initially approved rhGH products with native GH sequence also demonstrated an improvement in final adult height and height velocity. AHV or height SDS at 1 year have thus been accepted as primary efficacy endpoints by the Agency for approval of GH products in pediatric subjects with GHD.

Additionally, IGF-1 is a marker of GH activity and given GH is a replacement therapy, GH treatment should lead to improvement in IGF-1 levels. Prior in vitro studies demonstrated that hGH released from lonapegsomatropin-tcgd binds to human growth hormone receptor (hGHR) and treatment with lonapegsomatropin-tcgd leads to an increase in IGF-1 levels. AHV at 12 months was thus accepted by the Agency as an objective, primary endpoint for this open-label pivotal phase 3 trial during an EOP2 meeting.

The secondary endpoints as well as the safety endpoints were acceptable.

Statistical Analysis Plan

[24] De Ridder M, et al, Prediction of Adult Height in Growth-Hormone-Treated Children with Growth Hormone Deficiency. *The Journal of Clinical Endocrinology and Metabolism.* 2007, 92:925-931

The statistical analysis plan (SAP) as well as any updates were finalized by a medical and statistical team blinded to randomization before the database lock.

A sample size of 147 subjects was determined based on the phase 2 trial (CT-004) and using an SD of 3.5 cm/year, non-inferiority margin of 2 cm, power of 90%, 2:1 randomization and a 1-sided alpha level of 0.025. A sample size of 150 subjects was chosen to account for imbalances in randomization.

The safety analysis population as well as Intention to Treat (ITT) population included all randomized subjects who had received at least 1 dose of active treatment. Per-protocol (PP) population were the subjects in ITT who had relevant data evaluable for the primary efficacy endpoint of AHV at 52 weeks, and excluded subjects who met the exclusion criteria, took the wrong treatment in error, missed or overdosed on at least 5 doses of lonapegsomatropin-tcgd or 35 doses of Genotropin or failed to have a height measurement at Week 52 visit. PK/PD population included all subjects in the safety analysis population who had PK/PD assessments and was pre-identified.

Primary efficacy analysis was performed on the ITT and PP populations; however, the primary analysis population was the ITT population. The safety analyses were based on the safety analysis population.

Missing height velocity (HV) data were imputed using multiple imputation method which used 100 simulated datasets. Missing height values were imputed using the Markov Chain Monte Carlo method, which used variables such as gender, baseline age, peak log-transformed GH levels at stimulation test, baseline height SDS – average parental height SDS and all available post-baseline height values.

Primary efficacy endpoint of AHV at Week 52 was analyzed using an analysis of covariance (ANCOVA) model using baseline age, peak log-transformed GH levels at stimulation test, baseline height SDS – average SDS of parental height as covariates, and treatment and gender as factors. A 2-sided 95% confidence interval (CI) was calculated for the difference in least square (LS) means between the 2 treatment groups at Week 52. A non-inferiority margin of 2 cm/year was used. If the lower confidence bound was greater than -2 cm, non-inferiority was demonstrated and if the lower confidence bound was >0, superiority was established.

Secondary efficacy endpoints were analyzed using mixed models for repeated measurements (MMRM). MMRM model for HV included baseline age, peak log-transformed GH levels at stimulation test, baseline height SDS – average SDS of parental height as covariates, treatment, time point, treatment-by-time point interaction and gender as fixed factors, and subject as a random effect. Whereas, the MMRM model for the remaining secondary efficacy endpoints (change in height SDS, absolute and change from baseline in IGF-1, IGFBP-3, IGF-1 SDS and IGFBP-

3 SDS) included baseline age, peak log-transformed GH, baseline of the corresponding variable as covariates, treatment, time point, treatment-by-time point interaction and gender as fixed factors, and subject as a random effect.

Subgroups were based on age (<6 years and ≥6 years), gender, peak GH levels from stimulation test (≤5 ng/mL and >5 ng/mL), and etiology and extent of GHD. No interim analysis was planned, and final analyses was performed after completion of the trial.

There were no changes to the planned analyses. After the trial unblinding, following post-hoc analyses were conducted:

- By visit analysis of change from baseline in height SDS was conducted by ANCOVA analysis in order to account for difference in covariate effect.
- In order to adjust for baseline difference, ANCOVA analysis of change from baseline in QTcF at Week 26 was conducted by baseline QTcF subgroups
- Subgroup analysis was conducted by US vs. non-US
- In order to evaluate subjects with reduced growth response, logistic regression was used to analyze the ratio of subjects with AHV <8 cm/year at Week 52. In order to determine the potential causes of reduced treatment response in growth, change from baseline in average IGF-1 SDS was summarized for subjects with AHV <8 cm/year and ≥8 cm/year.
- Anti-lonapegsomatropin-tcgd antibodies were tested post database lock.

The SAP as well as its revisions were previously reviewed by Dr. Alexander Cambon (refer to review in DARRTS from March 25, 2019, under IND 126053). The SAP was found overall acceptable. For additional details regarding SAP, see Statistical Review by Dr. Alexander Cambon.

Protocol Amendments

Amendment #1 (dated September 12, 2017)

- Clarification that auxology could be performed by trial staff or the investigator who was not blinded to treatment arm
- Wording of the dose adjustment criteria was changed. This allowed the Investigator to determine if IGF-1 level of >+2 SD on routine screening is clinically significant and whether the level should be repeated. Additionally, hGH dose was to be decreased if the IGF-1 SDS was still >+2 and deemed to be of clinical concern by the Investigator.
- Glucose parameters were modified to be consistent with standard medical practice. The Investigator could initiate anti-glycemic therapy as clinically indicated.
- Clarification that MMRM models were to be used as efficacy endpoint methodology. Definition of superiority was added.
- Addition of neutralizing antibodies as a potential reason for early termination of a subject
- Addition of possibility for sequential testing of endpoints
- Modification of schedules of events for both treatment groups, in order to clarify the

assessments of post dose vital signs, injection site reaction and the bioanalytical samples

- Changes were made to reflect different practices relating to diagnosis of GHD and height measurement across different regions
-

Medical reviewer's comments:
The amendment allowed the Investigator to determine if an IGF-1 level of >+2 SD was of clinical significance and whether the hGH dose should be decreased. Given this was an open-label trial, this raises concern for introducing potential bias, if there were a greater number of subjects in lonapegsomatropin-tcgd group that did not undergo down titration of dose compared to subjects in Genotropin group.

Data Quality and Integrity

Data were collected using an internet-based, remote data entry system, which allowed to enter, modify, maintain, archive, retrieve and transmitted data. Changes in the data did not obscure the original information. The Applicant as well as a contract research organization (b) (4) conducted periodic visits to the investigational site to monitor compliance with trial procedures and regulatory requirements, and reviewed data periodically to ensure appropriate data collection and reporting. Additionally, independent site audits were conducted to verify the quality and compliance of trial conduct. The Applicant's contractor (b) (4) the Applicant, or (b) (4) were provided a direct access to source data while conducting these audits of various sites throughout the trial. Investigators' meetings were held at regular intervals. Laboratory tests were conducted in local and central laboratories.

Medical reviewer's comments:
The applicant's monitoring for data quality and integrity was acceptable.

6.1.2. Study Results

Compliance with Good Clinical Practices

The trial was conducted in compliance with the International Conference on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), the Declaration of Helsinki and its revisions, and national laws of the participating countries.

Financial Disclosure

The Applicant has adequately disclosed financial interests/arrangements with the clinical investigators as recommended in the guidance for industry.

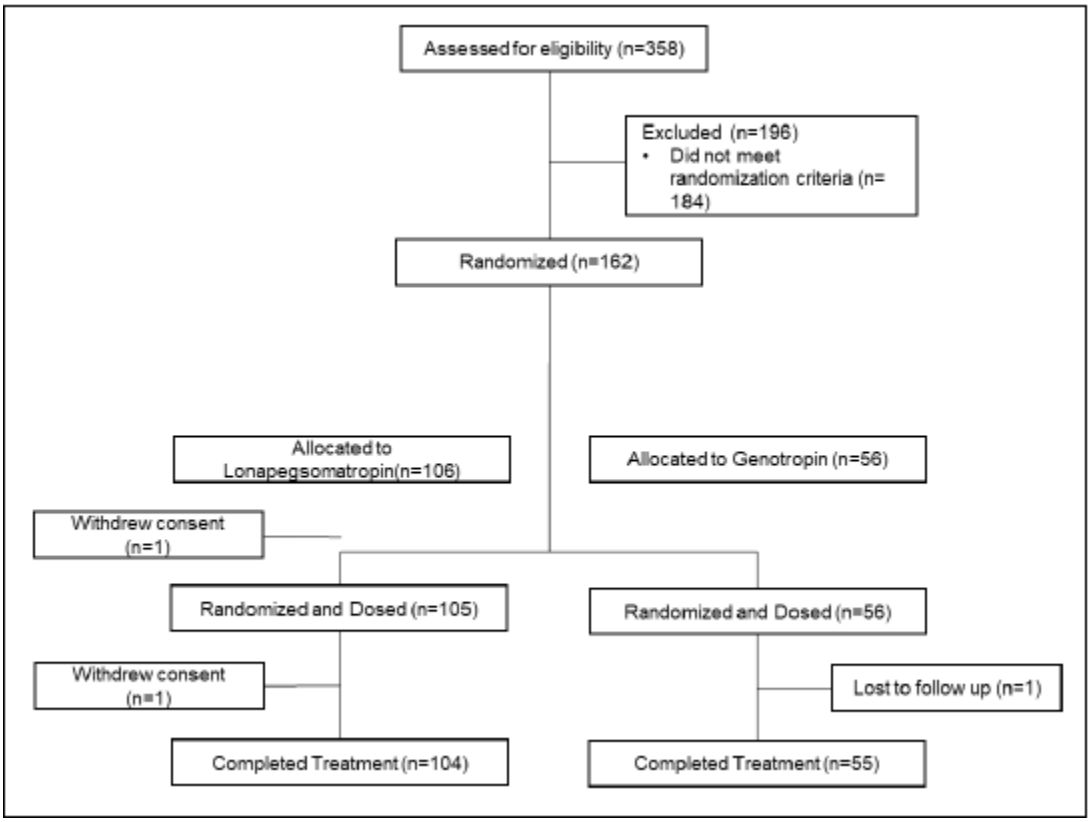
There was one investigator out of 710 investigators at 78 clinical sites who had disclosable financial interests. This investigator received payments from the Applicant for consultation in the area of pediatric endocrinology. The compensation was provided by the Applicant to this Investigator for travel and consultations, including participation and presentation to the Expert Advisory Board. The Applicant did not approve any grants to fund this Investigator's research and did not provide any compensation in the form of equipment. Out of the 307 subjects who were treated with either lonapegsomatropin-tcgd or placebo during the phase 3 clinical development program, this investigator enrolled a total of 12 subjects (4%).

Given the clinical trials of lonapegsomatropin-tcgd were randomized, and since the Investigator with financial interests/arrangements with the Applicant only enrolled 4% of subjects who received treatment during the phase 3 clinical development program of lonapegsomatropin-tcgd, the disclosed interests/arrangements do not raise any major concerns about the integrity of the data.

Patient Disposition

A total of 358 subjects were screened for this trial, 162 subjects were randomized, 161 subjects received treatment drug (105 subjects received lonapegsomatropin-tcgd and 56 subjects received Genotropin) and 159 subjects completed the trial (Figure 7).

Figure 7: Subject Disposition



Source: Clinical Study Report for CT-301, page 65

Two subjects discontinued the treatment drug, one subject on lonapegsomatropin-tcgd withdrew consent and one subject on Genotropin was a loss to follow up. There were no AEs that lead to discontinuation of study drug.

Protocol Violations/Deviations

There were a total of 18 subjects (11.2%) who experienced major protocol deviations. Major protocol deviations that occurred in Trail CT-301 are summarized in Table 5 and detailed below.

Table 5: Summary of Major Protocol Deviations (ITT Population)

Major Protocol Deviation Type	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Subjects with a major protocol deviation[a]	9 (8.6)	9 (16.1)	18 (11.2)
Enrollment of a subject who did not meet one or more of the inclusion criteria or who met one or more of the exclusion criteria according to the current protocol	1 (1.0)	4 (7.1)	5 (3.1)
Errors in injection timing or schedule	1 (1.0)	0	1 (0.6)
Significant alteration of schedule of the trial drug administration or a visit missed completely	1 (1.0)	0	1 (0.6)
Mishandling/ potential theft/ loss of medication at the site	3 (2.9)	3 (5.4)	6 (3.7)
Visit not done within Visit Window	2 (1.9)	0	2 (1.2)
Use of an invalid outdated consent form	1 (1.0)	1 (1.8)	2 (1.2)
Use of prohibited co-medication[b]	1 (1.0)	1 (1.8)	2 (1.2)
Subject overdoses/misuses or abuses trial drug	0	1 (1.8)[c]	1 (0.6)

Source: Clinical Study Report for CT-301, page 67

Inclusion/exclusion/randomization criteria

- Subjects (b) (6) did not meet the inclusion criteria as they did not have a second GH stimulation test completed
- Subject (b) (6) had a body weight of 11.1 kg and met the exclusion criteria of body weight below 12 kg
- Subject (b) (6) had a low baseline HV (5.35 cm/year), low baseline peak GH (4.5 ng/mL), low baseline IGF-1 (-1.78), and delayed bone age (2.8 years delayed). However, with a height SDS -1.1, this subject did not meet the inclusion criteria of height SDS ≤ -2. This subject had a delta average-parental height of -1.68 and the protocol was later amended to included delta average-parental height <-1.5 SD as an inclusion criterion
- Subject (b) (6) who had a GH stimulation test 6 months prior and congenital GHD did not meet the inclusion criteria as did not have a second GH stimulation test. Additionally, this subject also had a prior history of medulloblastoma, which was an exclusion criterion.

Informed Consent:

- Two subjects (subject (b) (6)) signed an older version of informed consent.

Use of prohibited medication:

- Two subjects (subject (b) (6)) took budesonide during the trial.

Incorrect visit window:

- Two subjects (subject (b) (6)) did not have visit 6 performed within 164-172 hours after last lonapegsomatropin-tcgd dose.

Mishandling/potential theft/loss of medication:

- Three subjects (b) (6) were reported to have loss of medication from the site. There were 6 used and returned cartridges missing from the site location.
- Three subjects (b) (6) were reported to have loss of medication from the site. There were 13 used and returned vials that were missing from the site location.

Alteration of schedule/errors in injection/misuse of medication:

- Subject (b) (6) who was lost to follow up took 19 additional doses of medication after being recorded as early termination
- Subject (b) (6) informed the site of withdrawal of consent 16 days after the last injection
- Subject (b) (6) missed a dose after forgetting the medication at home while on vacation in another city

Medical reviewer's comments:
Protocol deviations occurred in 11.2% of subjects, were minor, and were unlikely to have affected the integrity of the efficacy or safety results.

Demographic Characteristics

A total of 161 subjects were treated with either Lonapegsomatropin-tcgd (n = 105) or Genotropin (n= 56) and were included in the ITT population. There were more males than females (82% vs 18%). The age range was 3.2 to 13.1 years, with a mean (SD) age of 8.5 (2.7) years. Majority of subjects were white (94.4%). Most subjects were located in Europe (60.2%), followed by North America (26.1%). A total of 26.1% of subjects were from the US. Mean (SD) baseline height was 112.66 (14.48) cm, HV was 3.93 (1.91) cm/year and height SDS was -2.93 (0.87). The most common etiology of GHD was isolated idiopathic GHD (65.2%), followed by isolated organic and multiple pituitary hormone deficiencies (17.4%, each). The peak stimulated GH concentration was >5 ng/mL in 64% of subjects and ≤5 ng/mL in 36% of subjects (

Table 6, Table 7 and Table 8).

Table 6: Demographic characteristics of the ITT population:

Variable	Lonapegsomatropin (N = 105)	Genotropin (N = 56)	Total (N = 161)
Age (years), mean (SD)	8.5 (2.7)	8.5 (2.8)	8.5 (2.7)
Age (years), range	3.3-13.1	3.2-12.9	3.2-13.1
Age, n (%)			
<6 years	25 (23.8)	14 (25.0)	39 (24.2)
≥6 years	80 (76.2)	42 (75.0)	122 (75.8)
Male Sex – n (%)	86 (81.9)	46 (82.1)	132 (82.0)
Race, n (%)			
Asian	1 (1.0)	0	1 (0.6)
Black or African American	2 (1.9)	1 (1.8)	3 (1.9)
White	100 (95.2)	52 (92.9)	152 (94.4)
Other	2 (1.9)	3 (5.4)	5 (3.1)
Ethnicity, n (%)			
Hispanic or Latino	5 (4.8)	2 (3.6)	7 (4.3)
Not Hispanic or Latino	100 (95.2)	54 (96.4)	154 (95.7)
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)
Country, n (%)			
US	27 (25.7)	15 (26.8)	42 (26.1)
Non-US	78 (74.3)	41 (73.2)	119 (73.9)

Source: Clinical Study Report for CT-301, page 71

Table 7: Subject distribution by Age

Age (years)	Lonapegsomatropin-tcgd (N= 105)	Genotropin (N= 56)	Total (N= 161)
3	6 (5.7%)	3 (5.3%)	9 (5.6%)
4	7 (6.7%)	7 (12.5%)	14 (8.7%)
5	14 (13.3%)	4 (7.1%)	18 (11.2%)
6	7 (6.7%)	3 (5.5%)	10 (6.2%)
7	11 (10.5%)	5 (8.9%)	16 (9.9%)
8	12 (11.4%)	9 (16.1%)	21 (13%)
9	14 (13.3%)	6 (10.7%)	20 (12.4%)
10	14 (13.3%)	8 (14.3%)	22 (13.7%)
11	8 (7.6%)	6 (10.7%)	14 (8.7%)
12	10 (9.5%)	5 (8.9%)	15 (9.3%)
13	2 (1.9%)	0 (0%)	2 (1.2%)

Medical reviewer generated table

Table 8: Baseline Data of the ITT Population:

Variable	Lonapegsomatropin (N = 105)	Genotropin (N = 56)	Total (N = 161)
Height (cm), n	105	56	161
Mean (SD)	112.93 (14.09)	112.15 (15.29)	112.66 (14.48)
HV at baseline (Visit 1) (cm/year), n	94	54	148
Mean (SD)	3.93 (2.04)	3.93 (1.66)	3.93 (1.91)
Height SDS, n	105	56	161
Mean (SD)	-2.89 (0.85)	-3.00 (0.90)	-2.93 (0.87)
Weight (kg), n	105	56	161
Mean (SD)	21.01 (6.54)	21.20 (6.67)	21.08 (6.56)
BMI (kg/m^2), n	105	56	161
Mean (SD)	16.06 (1.78)	16.46 (2.17)	16.20 (1.93)
Range	13.2-22.2	13.7-24.7	13.2-24.7
BMI SDS, n	105	56	161
Mean (SD)	-0.32 (0.95)	-0.14 (1.07)	-0.25 (0.99)
Average-parental height SDS[a], n	103	56	159
Mean (SD)	-0.56 (0.77)	-0.44 (0.79)	-0.52 (0.78)
Delta average-parental height SDS[b], n	103	56	159
Mean (SD)	-2.32 (1.14)	-2.55 (1.27)	-2.40 (1.19)
Bone age (years), n	105	56	161
Mean (SD)	5.84 (2.60)	5.98 (2.68)	5.88 (2.62)
Delay in bone age (years), n	105	56	161
Mean (SD)	2.48 (1.30)	2.31 (1.10)	2.42 (1.23)
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-1 SDS at baseline (Visit 1), n	105	56	161
Mean (SD)	-2.08 (0.88)	-1.96 (0.98)	-2.04 (0.92)
Peak stimulated GH concentration (ng/mL)	105	56	161
Mean (SD)	5.89 (2.78)	5.48 (2.97)	5.75 (2.85)
Peak stimulated GH concentration, n (%)			
≤5 ng/mL	37 (35.2)	21 (37.5)	58 (36.0)
>5 ng/mL	68 (64.8)	35 (62.5)	103 (64.0)

Source: Clinical Study Report for CT-301, page 72

Medical reviewer's comments:
Overall, baseline demographic characteristics were similar between the two treatment groups.

There were more males (82%) than females (18%) in this trial. However, pivotal trials for other rhGH formulations such as Nutropin and Zomacton also included more males than females. There were 85.5% and 73% males in Nutropin and Zomacton pivotal trials, respectively. Lastly, GHD in general, is diagnosed more frequently in males compared to females. Overall, the demographic characteristics of studied population match the demographic characteristics of pediatric patients with GHD in general population.

Only 26.1% of subjects were from the US. However, the diagnostic criteria used in the trial were consistent with the criteria used in the US, and the treatment for GHD is the same throughout the world. Thus, given that there is no reason to suspect bioavailability of lonapegsomatropin-tcgd to be different between the US and other countries' populations and that this is a product that is dosed based on clinical response, this medical reviewer considers the foreign data to be adequate for the approval of the product in the US. Lastly, these baseline differences were included in subgroup analysis (by gender and region) refer to Section 7.1.3.

Baseline missing data were minimal. None of the subjects were missing baseline height data. Baseline HV data were missing for 13 (8%) subjects and average parental height SDS data were missing for 2 (1%) subjects. Given the primary efficacy endpoint was AHV induced by lonapegsomatropin-tcgd compared to the AHV induced by Genotropin, impact of these missing data on the primary efficacy analysis can be considered minimal.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Pituitary hormone deficiencies other than GHD that were known at screening were present in 24 (14.9%) subjects, were slightly more common in Genotropin group (16.1% compared to 14.3% in lonapegsomatropin-tcgd group), and included Thyroid Stimulating Hormone (TSH) deficiency (13%), Adrenocorticotropic Hormone (ACTH) deficiency (6.8%) and Anti-Diuretic Hormone (ADH) deficiency (2.5%). Baseline sellar magnetic resonance imaging (MRI) was normal in 68.3% of subjects (Table 9 and Table 10).

Table 9: Pituitary Hormone deficiencies other than GHD known at screening

Pituitary Hormone Deficiencies Other Than GHD[a] Known at Screening	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Overall	15 (14.3)	9 (16.1)	24 (14.9)
TSH deficiency	13 (12.4)	8 (14.3)	21 (13.0)
ACTH deficiency	7 (6.7)	4 (7.1)	11 (6.8)
ADH insufficiency	2 (1.9)	2 (3.6)	4 (2.5)
LH and/or FSH deficiency	0	0	0

Source: Clinical Study Report for CT-301, page 74

Table 10: Results of Baseline Sellar MRI

Sellar MRI Result Assessment	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Normal	71 (67.6)	39 (69.6)	110 (68.3)
Abnormal NCS	26 (24.8)	14 (25.0)	40 (24.8)
Abnormal CS	8 (7.6)	3 (5.4)	11 (6.8)

Source: Clinical Study Report for CT-301, page 75

After GHD, the most common medical condition was secondary hypothyroidism (14.3%) (Table 11).

Table 11: Medical Conditions at a frequency of **≥5%** in either treatment group

PT	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Growth hormone deficiency	105 (100.0)	56 (100.0)	161 (100.0)
Secondary hypothyroidism	14 (13.3)	9 (16.1)	23 (14.3)
Attention deficit/hyperactivity disorder	9 (8.6)	1 (1.8)	10 (6.2)
Eczema	8 (7.6)	1 (1.8)	9 (5.6)
Asthma	4 (3.8)	4 (7.1)	8 (5.0)
Secondary adrenocortical insufficiency	7 (6.7)	1 (1.8)	8 (5.0)
Seasonal allergy	4 (3.8)	3 (5.4)	7 (4.3)
Retinal vascular disorder	6 (5.7)	0	6 (3.7)
Adrenal insufficiency	0	3 (5.4)	3 (1.9)

Source: Clinical Study Report for CT-301, page 74

Medical reviewer's comments:
Even though pituitary hormone deficiencies other than GHD were more common in the Genotropin group, the difference was minimal. Additionally, the severity of GHD, as

demonstrated by peak stimulated GH levels, was comparable between the two groups. Hence, the slightly increased frequency of other pituitary hormone deficiencies in the Genotropin group is unlikely to have affected the efficacy analysis.

A difference in frequency of medical conditions such as attention deficit/hyperactivity disorder, eczema and asthma was noted between the two groups. However, these differences would not be expected to impact the pathophysiology of GHD or the efficacy and safety analysis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
Assessment of treatment compliance was based on drug accountability and review of patient diary and instructions for use. Overall, the trial demonstrated good compliance in both groups, with more subjects in lonapegsomatropin-tcgd group with a compliance rate between >95% and ≤100% (99% compared to 94.6% in Genotropin group). None of the subjects in the lonapegsomatropin-tcgd had a compliance rate of ≤80%, compared to 1 subject (1.8%) in the Genotropin group (Table 12).

Table 12: Summary of treatment compliance

Compliance	Lonapegsomatropin (N = 105)	Genotropin (N = 56)	Total (N = 161)
Compliance rate, n (%)			
≤80%	0	1 (1.8)	1 (0.6%)
>80% and ≤90%	0	0	0
>90% and ≤95%	1 (1.0)	2 (3.6)	3 (1.9)
>95% and ≤100%	104 (99.0)	53 (94.6)	157 (97.5)
>100%	0	0	0
Compliance, %			
Mean (SD)	99.6 (1.19)	98.6 (4.73)	99.2 (2.97)
Range	92.5-100.0	65.9-100.0	65.9-100.0

Source: Clinical Study Report for CT-301, page 77

Concomitant Medications:
There was no significant difference in the types of concomitant medications used between the two groups (Table 13).

Table 13: Concomitant medications reported for **≥10%** of either treatment group

Concomitant Medications	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Any concomitant medication	78 (74.3)	39 (69.6)	117 (72.7)
Analgesics	32 (30.5)	16 (28.6)	48 (29.8)
Antibacterials for systemic use	30 (28.6)	18 (32.1)	48 (29.8)
Antiinflammatory and antirheumatic products	25 (23.8)	15 (26.8)	40 (24.8)
Thyroid therapy *	22 (21.0)	13 (23.2)	35 (21.7)
Cough and cold preparations	23 (21.9)	11 (19.6)	34 (21.1)
Antihistamines for systemic use	22 (21.0)	11 (19.6)	33 (20.5)
Drugs for obstructive airway diseases	16 (15.2)	12 (21.4)	28 (17.4)
Nasal preparations	20 (19.0)	8 (14.3)	28 (17.4)
Throat preparations	13 (12.4)	8 (14.3)	21 (13.0)
Corticosteroids for systemic use	11 (10.5)	7 (12.5)	18 (11.2)
Vitamins	14 (13.3)	2 (3.6)	16 (9.9)
Vaccines	6 (5.7)	7 (12.5)	13 (8.1)

Source: Clinical Study Report for CT-301, page 76

Medical reviewer's comments:
Concomitant medications used in the trial were unlikely to have affected the efficacy of GH treatment.

Efficacy Results – Primary Endpoint

The trial met its primary efficacy endpoint of AHV at 52 weeks in the ITT population.

According to the Applicant's analysis, the difference in the LS mean (standard error (SE)) of AHV between lonapegsomatropin-tcgd and Genotropin groups was 0.86 (0.33) cm/year [95% CI 0.22, 1.5], which was above the prespecified non-inferiority margin of -2 cm/year. Additionally, given the lower confidence bound was above 0, the Applicant stated that superiority was established (Table 14).

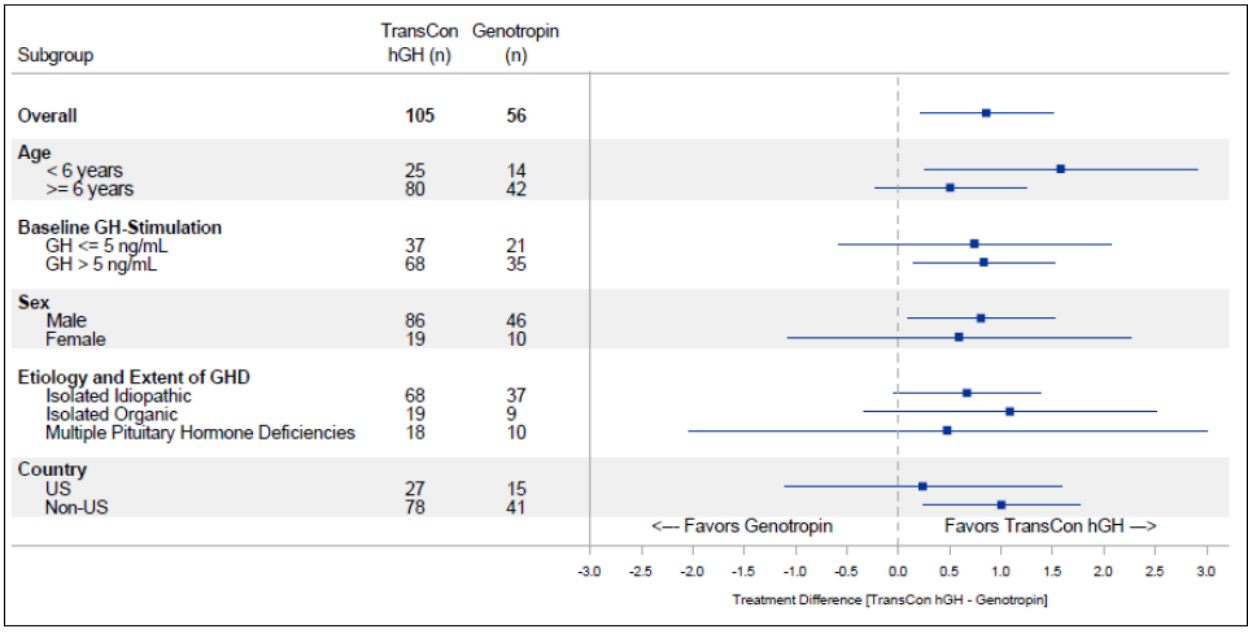
Table 14: Primary efficacy analysis - AHV at Week 52 (ITT)

Summary Statistic	Lonapegsomatropin (N=105)	Genotropin (N=56)	Estimate of Difference (lonapegsomatropin - Genotropin)	*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

Source: Clinical Study Report for CT-301, page 78

The Applicant also conducted analysis of AHV at Week 52 by subgroups: age, peak stimulated GH, gender, etiology of GHD, and country (Figure 8)

Figure 8: Forest Plot of subgroup analysis for AHV at Week 52



Source: Clinical Study Report for CT-301, page 82

The primary analysis results were also independently verified and confirmed by the FDA's statistician, Dr. Alexander Cambon, using the Applicant's analysis for primary endpoint (for details, see Statistical Review by Dr. Alex Cambon in DARRTS, dated February 19, 2021).

Dr. Cambon agreed with the Applicant's pre-specified estimand and the definition of ITT population. The preferred estimand was treatment policy estimand, that includes all data within the final 52-Week assessment window regardless of intercurrent events such as treatment discontinuation or initiation of alternative therapy.

There were two subjects with missing final assessments, one in each arm. Given the subject in Genotropin arm was still on treatment at Week 52, single imputation ANCOVA was used with missing at random (MAR) assumption, and the fitted value from the ANVOCA model was used to impute the missing assessment for this subject. Given the subject in lonapegsomatropin-tcgd arm had discontinued treatment at 34 weeks, single imputation ANCOVA was used with not MAR (NMAR) assumption, and the baseline value was used to impute the missing assessment for this subject.

The results of Dr. Cambon's analysis were very similar to the Applicant's analysis. Refer to Table 15.

Table 15: Primary Endpoint – AHV at 52 weeks (FDA Statistician's analysis)

Endpoint	Lonapegsomatropin-tcgd	Genotropin	Difference	Confidence Interval	P-Val
Annualized Height Velocity (cm/yr)	11.1	10.3	0.80	(0.13, 1.47)	0.02
ANCOVA, Unequal Var.**			0.55**	(-0.07, 1.17)	
Change in Height SDS			0.55		

.*All endpoints are assessed at Week 52 – No multiple testing procedure was used to control Type 1 error over primary and secondary endpoints; Abbreviations: cm/yr =centimeters per year; SDS-Standard Deviation Score; Exp.-Experimental Arm; Ctr.-Control Arm; Diff.-Treatment Difference; LCL-Lower Confidence Limit; UCL Upper Confidence Limit; P-Val-P-Value; Var.-Variance;;
**In this analysis, residuals are derived from ANCOVA model including all factors/covariates except treatment. Then Hodges-Lehmann method is conducted on residuals to ascertain treatment effect shown in table; 0.55 is also the confidence interval midpoint; 0.55 is the location shift (median difference).

In addition, Dr. Cambon also performed subgroup analysis of the primary endpoint by gender, age, region, and etiology. Race subgroup analyses could not be conducted due to sparsity of non-White race subgroups in the study. Refer to Table 16.

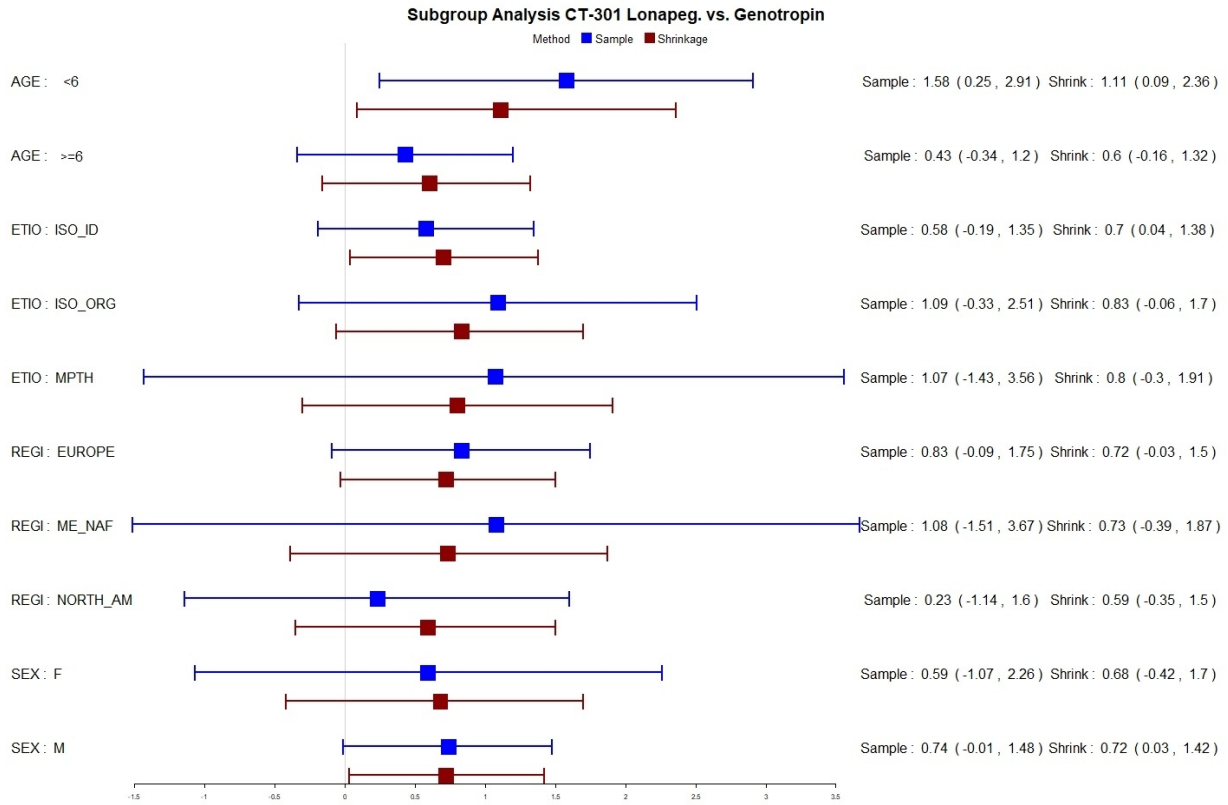
Table 16: Treatment difference in AHV at Week 52, by Subgroup (FDA Statistician's analysis)

Subgroup	Sample Size	Estimate (SE)	Lower 95%	Upper 95%
Overall	161	0.80 (0.34)	0.13	1.47
Female	29	0.59 (0.81)	-1.07	2.26
Male	132	0.74 (0.38)	-0.01	1.48
Age $\geq$ 6	122	0.43 (0.39)	-0.34	1.20
Age < 6	39	1.58 (0.65)	0.25	2.91
North America	27	0.23 (0.67)	-1.14	1.60
Europe	66	0.83 (0.46)	-0.09	1.75
Middle East/North Africa*	12	1.08 (1.15)	-1.51	3.67
Isolated Idiopathic	105	0.58 (0.39)	-0.19	1.35
Isolated Organic**	28	1.09 (0.67)	-0.33	2.51
Multiple Pituitary Hormone deficiency**	28	1.07 (1.21)	-1.43	3.56

Abbreviations: SE – Standard Error;
* all the subjects in this region are male;
** sex not included in model due to sparsity;
Source: adapted from Dr. Alexander Cambon's statistical review

Subgroup analysis was conducted using two different methods: frequentist subgroup analysis and Bayesian shrinkage analysis. Treatment effects were generally consistent across subgroups. However, statistical significance was not consistent across sensitivity analyses. Refer to Figure 9.

Figure 9: Forest Plot Comparing Frequentist Subgroup Analysis to Bayesian Shrinkage Analysis (FDA Statistician's analysis)



Abbreviations: ME_NAF-Middle East/North Africa region; Etio-etiology; II-Isolated Idiopathic; IO-Isolated Organic; MPHD-Multiple Pituitary Hormone Deficiencies
Source: adapted from Dr. Alexander Cambon's statistical review

Medical reviewer's comments:
The trial met the primary efficacy endpoint given the lower confidence bound of the difference in LS mean of AHV between the lonapegsomatropin-tcgd and Genotropin groups was above the prespecified non-inferiority margin of -2 cm/year. Additionally, given the lower bound of confidence interval was >0, statistical superiority was established. However, (b) (4) *one well controlled study, and the observed statistically significant difference of 0.86 cm/year in AHV at 12 months between the two treatment groups is small. This treatment difference is >50% smaller in magnitude than the non-inferiority margin, and of unknown clinical significance.*

It should also be noted that this difference in AHV at 52 weeks favoring lonapegsomatropin-tcgd was statistically significant in subjects <6 years of age, and a similar statistically significant difference was not observed in subjects ≥6 years of age. Additionally, female subjects did not show a significant difference similar to male subjects. Given 82% of subjects were male in this trial, the results may have been affected by the baseline demographics of the trial. Lastly, in 26% of the subjects in the trial who were from the US, lonapegsomatropin-tcgd was not found to be superior compared to Genotropin.

(b) (4)

[redacted]

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoints were not adjusted for multiplicity and were not hierarchy tested.

AHV over 52 weeks:
According to the Applicant's analysis, difference in AHV was statistically significant starting at Week 26, and maintained through Week 52 (Table 17)

Table 17: AHV by visit by ANCOVA model with multiple imputation (ITT)

Visit	Lonapegsomatropin LS Mean (SE) [95% CI] N=105	Genotropin LS Mean (SE) [95% CI] N=56	Estimate of Difference[a] in LS Means (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: Clinical Study Report for CT-301, page 85

Height SDS over 52 weeks:
According to the Applicant's analysis, change from baseline in the height SDS over 52 weeks was not statistically significant between the two groups using the MMRM analysis. However, this difference was statistically significant starting at Week 26, using the ANCOVA analysis (Table 18)

Table 18: Change from baseline in Height SDS by Visit: ANCOVA model

Visit	Lonapegsomatropin LS Mean (SE) [95% CI] N=105	Genotropin LS Mean (SE) [95% CI] N=56	Estimate of Difference[a] in LS Means (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: Clinical Study Report for CT-301, page 89

IGF-1:
GH is a replacement therapy, thus the marker of GH activity, IGF-1, should normalize with GH treatment. At baseline, the mean IGF-1 SDS values were -2.08 in the lonapegsomatropin-tcgd group and -1.96 in the Genotropin group. For the lonapegsomatropin-tcgd group, given the serum IGF-1 levels were measured at trough levels at Weeks 5 and 52 and at peak levels at Weeks 13, 26 and 39, the average IGF-1 SDS values were obtained from a nonlinear population PD model. In contrast, for the Genotropin group, given the serum IGF-1 levels were measured at any time during the specified study week, the average IGF-1 SDS values were represented by the observed values.

According to the Applicant's analysis, the IGF-1 SDS values improved from baseline and continued to increase in subsequent visits in both treatment groups. Additionally, the average IGF-1 SDS levels were higher in the lonapegsomatropin-tcgd group compared to Genotropin group (Table 19).

Table 19: Average IGF-1 SDS by visit by ANCOVA (ITT)

Visit	Lonapegsomatropin LS Mean (SE) [95% CI] N=105	Genotropin LS Mean (SE) [95% CI] N=56	Estimate of Difference[a] in LS Means (SE) [95% CI]	*P* Value
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]	<0.0001
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]	<0.0001
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]	<0.0001
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]	<0.0001

Source: Clinical Study Report for CT-301, page 91

Average IGF-1 SDS <-2 was more frequent in the Genotropin group, whereas time within the normal range and average IGF-1 SDS >+2 was more frequent in the lonapegsomatropin-tcgd group (Table 20 and Table 21).

Table 20: Proportion of subjects with normalization of average IGF-1 SDS by visit

Average IGF-1 SDS Category	Lonapegsomatropin (N=105) n (%)	Genotropin (N=56) n (%)	Difference in Normalization Rates (%)[a] [95% CI][b]
Week 13, N	105	56	-
<-2.0	1 (1.0)	6 (10.7)	-
-2.0 to 0	42 (40.0)	37 (66.1)	-
0 to +2.0	62 (59.0)	11 (19.6)	39.4 [25.4, 53.4]
>+2.0	0	2 (3.6)	-
Week 26, N	104	56	-
<-2.0	1 (1.0)	6 (10.7)	-
-2.0 to 0	30 (28.8)	31 (55.4)	-
0 to +2.0	71 (68.3)	18 (32.1)	36.1 [21.0, 51.3]

>+2.0	2 (1.9)	1 (1.8)	-
Week 39, N	103	56	-
<-2.0	1 (1.0)	2 (3.6)	-
-2.0 to 0	26 (25.2)	35 (62.5)	-
0 to +2.0	73 (70.9)	18 (32.1)	38.7 [23.7, 53.8]
>+2.0	3 (2.9)	1 (1.8)	-
Week 52, N	104	54	-
<-2.0	0	1 (1.9)	-
-2.0 to 0	24 (23.1)	21 (38.9)	-
0 to +2.0	72 (69.2)	31 (57.4)	11.8 [-4.1, 27.7]
>+2.0	8 (7.7)	1 (1.9)	-

Source: Clinical Study Report for CT-301, page 93

Table 21: Subjects with >50% time within IGF-1 normal range

	Lonapegsomatropin (N=105) n (%)	Genotropin (N=56) n (%)
Subjects with ≥50% time within IGF-1 normal range (SDS -2 to +2) overall	104 (99.0)	53 (94.6)

Source: Clinical Study Report for CT-301, page 96

IGFBP-3:

Concentration of IGFBP-3, a major IGF binding protein, increases in response to GH administration, making it an important marker to assess the response to GH therapy. Similar to IGF-1 levels, the serum IGFBP-3 levels were also measured at trough levels at Week 5 and 52, and at peak levels at Weeks 13, 26 and 39 in the lonapegsomatropin-tcgd group, and without any predefined time targets in the Genotropin group. However, unlike IGF-1, average IGFBP-3 SDS values were not derived using any PD model.

According to the Applicant's analysis, an improvement from baseline in the IGFBP-3 levels was observed at each visit in both groups. The IGFBP-3 SDS values were higher in the lonapegsomatropin-tcgd group in Weeks 13, 26, and 39, when IGF-1 was measured at peak levels, and lower in the lonapegsomatropin-tcgd group in Weeks 5 and 52, when IGF-1 was measured at trough levels (Table 22).

Table 22: IGFBP-3 SDS by visit by MMRM analysis

Visit	Lonapegsomatropin LS Mean (SE) [95% CI] N=105	Genotropin LS Mean (SE) [95% CI] N=56	Estimate of Difference in LS Means (SE) [95% CI]	*P* Value
Week 5	-0.62 (0.07) [-0.75, -0.49]	-0.36 (0.09) [-0.54, -0.19]	-0.25 (0.10) [-0.45, -0.05]	0.0134
Week 13	0.34 (0.08) [0.18, 0.49]	-0.38 (0.11) [-0.59, -0.17]	0.71 (0.13) [0.46, 0.96]	<0.0001
Week 26	0.28 (0.078) [0.13, 0.44]	-0.30 (0.10) [-0.50, -0.09]	0.58 (0.12) [0.34, 0.82]	<0.0001
Week 39	0.42 (0.07) [0.27, 0.56]	-0.18 (0.10) [-0.37, 0.01]	0.60 (0.11) [0.37, 0.82]	<0.0001
Week 52	-0.22 (0.074) [-0.37, -0.08]	0.01 (0.10) [-0.18, 0.21]	-0.24 (0.12) [-0.47, -0.01]	0.0454

Source: Clinical Study Report for CT-301, page 97

HV SDS:
According to the Applicant's analysis, mean (SD) HV SDS was 5.87 for the lonapegsomatropin-tcgd group and 5.27 for the Genotropin group. This corresponded to a mean change from baseline of 8.07 for the lonapegsomatropin-tcgd group and 7.41 for the Genotropin group (Table 23).

Table 23: HV SDS by Visit

	Lonapegsomatropin N=105		Genotropin N=56	
Visit	n	Mean (SD)	n	Mean (SD)
Baseline	94	-2.20 (2.22)	54	-2.14 (2.02)
Week 5	105	8.09 (9.81)	56	7.40 (10.57)
Week 13	105	7.92 (5.09)	56	7.14 (5.64)
Week 26	104	7.42 (3.71)	56	6.29 (4.05)
Week 39	104	6.53 (2.98)	56	5.82 (3.23)
Week 52	104	5.87 (2.76)	55	5.27 (3.01)

Source: Clinical Study Report for CT-301, page 101

BMI:
It is expected that improvement in biochemical markers of the disease will improve other signs and symptoms of the disease, e.g., weight, lipid abnormalities, etc. The baseline mean BMI SDS was -0.32 in lonapegsomatropin-tcgd group and -0.14 in Genotropin group. According to the Applicant's analysis, at Week 52, the mean BMI SDS was -0.03 in lonapegsomatropin-tcgd and -0.4 in Genotropin group, which resulted in a mean change in BMI SDS of 0.29 in lonapegsomatropin-tcgd and -0.26 in Genotropin group (Table 24).

Table 24: BMI SDS by visit

Visit	Lonapegsomatropin N=105		Genotropin N=56	
	n	Mean (SD)	n	Mean (SD)
Baseline	105	-0.32 (0.95)	56	-0.14 (1.07)
Week 5	105	-0.18 (0.90)	56	-0.08 (1.01)
Week 13	105	-0.07 (0.85)	56	-0.26 (1.06)
Week 26	104	-0.05 (0.87)	56	-0.46 (1.04)
Week 39	104	-0.01 (0.83)	56	-0.47 (1.06)
Week 52	104	-0.03 (0.84)	55	-0.40 (1.00)

Source: Clinical Study Report for CT-301, page 99

Bone Age:
Both lonapegsomatropin-tcgd and Genotropin groups had a similar change in bone/chronological age ratio from baseline to Week 52. The mean (SD) bone age/chronological age ratio was 0.7 (0.16) for the lonapegsomatropin-tcgd group and 0.7(0.14) for the Genotropin group at baseline, and 0.7 (0.15) for the lonapegsomatropin-tcgd group and 0.8(0.14) for the Genotropin group at Week 52.

Medical reviewer's comments:
Overall, the results of the secondary analyses are supportive of the primary analysis. However, given the secondary endpoints were not adjusted for multiplicity, caution is warranted while interpreting the results of the secondary endpoints.

As expected, replacement therapy with lonapegsomatropin-tcgd resulted in improved height SDS and bone age compared to baseline. In addition, IGF-1 normalized during the treatment indicating an adequate replacement with missing hormone. The average IGF-1 SDS over 52 weeks as well as the proportion of subjects with ≥50% time within IGF-1 normal range was greater in the lonapegsomatropin-tcgd group. The average IGFBP-3 SDS over 52 weeks improved from baseline in both groups. However, given the IGFBP-3 levels were measured at different times throughout the trial, the measurements in the lonapegsomatropin-tcgd group may not represent true average IGFBP-3 SDS values, and a conclusive comparison between the two groups cannot be made.

This medical reviewer agrees that height SDS provides important information to the prescribers and patients, and should be included in the label. However, height SDS should be included without any indication of statistical significance. This medical reviewer recommends not to include BMI SDS in the label, as BMI SDS changes are of unknown clinical significance in pediatric subjects. Also, BMI changes may be secondary to increase in weight due to GH therapy related fluid retention. (b) (4)

(b) (4)

Dose/Dose Response

Given only one dose was studied, dose response cannot be assessed based on this trial.

Durability of Response

Long-term response to lonapegsomatropin-tcgd was addressed in trial CT-301EXT, which enrolled subjects that had completed either trial CT-301 or CT-302. All subjects were switched to (subjects who were enrolled in the Genotropin group during trial CT-301) or continued treatment with lonapegsomatropin-tcgd during trial CT-301EXT.

A total of 102 subjects who were in the lonapegsomatropin-tcgd group during the trial CT-301 were enrolled in trial CT-301EXT. Of these, 100 subjects reached Week 26 of trial CT-301EXT, resulting in a total exposure to lonapegsomatropin-tcgd of 78 weeks in these subjects. For this subgroup, the mean AHV was 11.2 cm/year at Week 52 and 9.4 cm/year at Week 78 (Table 25). Similarly, the mean change in height SDS was 1.1 at Week 52 and 1.39 at Week 78 (

Table 26) and the mean (SD) IGF-1 levels were -0.680 (1) at Week 52 and 0.608 (1.336) at Week 78.

Table 25: Summary of AHV (cm/year) by Visit

Visit	CT-301 Lonapegsomatropin-tcgd -> CT-301EXT (N = 102) Mean (SD)	CT-301 Genotropin -> CT-301EXT (N = 54) Mean (SD)
Baseline	3.93 (2.04)	3.93 (1.66)
Week 13	13.28 (0.49)	12.22 (0.63)
Week 26	12.65 (0.33)	11.22 (0.42)
Week 39	11.89 (0.26)	10.91 (0.33)
Week 52	11.16 (0.23)	10.31 (0.3)
Week 65	10.12 (0.21)	9.50 (0.27)
Week 78	9.42 (0.21)	9.28 (0.26)

Source: Summary of Clinical Efficacy, page 34

Table 26: Change from Baseline in Height SDS by Visit

Visit	CT-301 Lonapegsomatropin-tcgd -> CT-301 EXT (N = 102) Mean (SD)	CT-301 Genotropin -> CT-301 EXT (N = 54) Mean (SD)
Baseline	-2.89 (0.85)	-3 (0.9)
Week 13	0.38 (0.02)	0.33 (0.03)
Week 26	0.68 (0.03)	0.58 (0.04)
Week 39	0.92 (0.03)	0.8 (0.04)
Week 52	1.10 (0.04)	0.96 (0.05)
Week 65	1.25 (0.05)	1.10 (0.06)
Week 78	1.39 (0.05)	1.24 (0.06)

Source: Summary of Clinical Efficacy, page 36

Medical reviewer's comments:
Extension trial CT-301EXT enrolled subjects that had completed trial CT-301 or CT-302 and assessed the durability of response. Overall, growth continued during the second year of treatment with the drug. A reduction in AHV from 11.2 cm/year at Week 52 to 9.4 cm/year at Week 78 of treatment with lonapegsomatropin-tcgd that was observed during the extension trial is expected and minor; similar trend is observed with treatment with approved rhGH products.

However, given trial CT-301EXT was a single-arm, open-label trial, and some subjects were exposed to Genotropin during the first 52-weeks of treatment, the results need to be interpreted with caution.

Persistence of Effect

The persistence of drug effect after treatment is stopped or withheld was not assessed during the clinical development program.

Additional Analyses Conducted on the Individual Trial

The Applicant conducted a *post hoc* analysis of subjects with AHV <8 cm/year. At Week 52, the incidence of AHV <8 cm/year was 3.8% in the lonapegsomatropin-tcgd group and 0.9% in the Genotropin group. As a part of this analysis, the Applicant obtained a ratio of average IGF-1 SDS

mean change from baseline in subjects with AHV <8 cm/year to average IGF-1 SDS mean change from baseline in subjects with AHV ≥8 cm/year in both treatment groups. Based on these data, subjects in the Genotropin group with reduced growth velocity were found to have lower IGF-1 SDS values compared to subjects with higher growth velocity. Similar lower IGF-1 response was not demonstrated in the subjects in lonapegsomatropin-tcgd group (Table 27).

Table 27: Mean change from baseline in average IGF-1 SDS for AHV <8 cm/year and **≥8** cm/year across 52 weeks

Visit	Lonapegsomatropin			Genotropin		
	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: Clinical Study Report for CT-301, page 101

Medical reviewer's comments:
Although the post-hoc analysis conducted by the Applicant are supportive of the efficacy of lonapegsomatropin-tcgd, these results are not reliable given the limitations of a post-hoc analysis. (b) (4)

6.2. TransCon hGH CT-302, A multicenter, Phase 3, Open-Label, 26-Week Trial Investigating the Safety, Tolerability and Efficacy of Lonapegsomatropin-tcgd Administered Once Weekly in Children with Growth Hormone Deficiency.

6.2.1. Study Design

Overview and Objective

The primary objective of this trial was to assess the safety and tolerability of once weekly lonapegsomatropin-tcgd in children with growth failure due to GHD from 6 months to 17 years old.

The secondary objectives were to assess AHV in children with GHD at 26 weeks; to assess the proportion of subjects with IGF-1 SDS in the normal range of 0 to +2 at 26 weeks; to evaluate the change in height SDS at 26 weeks; to determine the incidence of antibodies against lonapegsomatropin-tcgd (anti-hGH and anti-polyethylene glycol (anti-PEG)) over 26 weeks; to assess the expected C_{max} of lonapegsomatropin-tcgd in children with GHD ≥6 months to <3 years

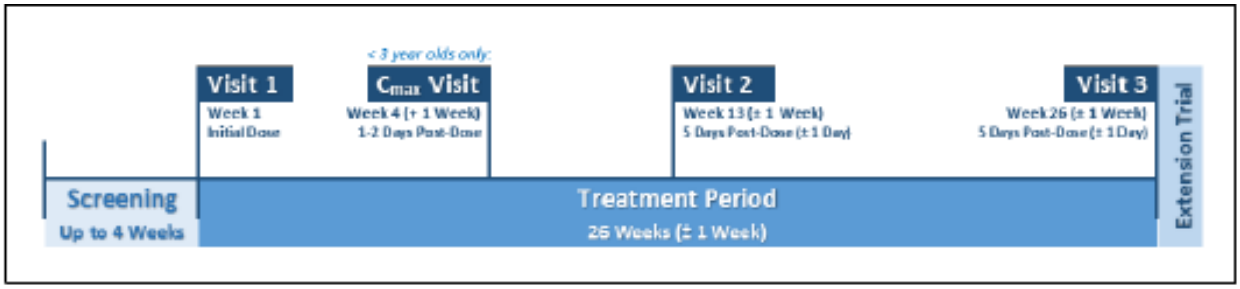
old; to assess the preference for weekly lonapegsomatropin-tcgd or commercially available daily hGH treatment; and to assess the treatment satisfaction of weekly lonapegsomatropin-tcgd

Trial Design

This was a multicenter, multinational, phase 3, open-label, single-arm, 26-week trial of weekly lonapegsomatropin-tcgd in children 6 months to 17 years old with open epiphysis, who were previously treated with daily hGH for ≥13 weeks but ≤130 weeks (children ≥6 months but <3 years old may have been hGH treatment-naïve). This trial was an open-label, single-arm trial as the primary objective was to assess the safety and tolerability of weekly lonapegsomatropin-tcgd in pediatric subjects with GHD previously treated with daily hGH therapy.

The trial consisted of a screening period of up to 4 weeks and a treatment period of up to 27 weeks (Figure 10).

Figure 10: Trial Design for Trial CT-302



Source: Clinical Study Report for CT-302, page 25

Refer to Appendix 3 for details on the specific procedures that were carried out at each visit.

The trial planned to enroll approximately 150 male and female children with GHD, who had open epiphyses and were in Tanner stage <5. GHD was determined by the Investigator with at least one of the following: 2 GH stimulation tests with peak GH levels ≤10 ng/mL; impaired height (≥2 SD below the mean height for chronologic age and sex or ≥1.5 SD below mid-parental height); IGF-1 levels ≥1 SD below the mean IGF-1 level standardized for age and sex; bone age x-ray ≥6 months less than chronologic age; diagnosis of at least 1 additional pituitary hormone deficiency; or congenital hypopituitarism due to congenital hypothalamic-pituitary defect. All subjects should have received at least 0.2 mg hGH/kg/week of daily hGH treatment for ≥13 weeks but ≤130 weeks, with the exception of subjects aged 6 months to <3 years who could either have been hGH treatment naïve or had been treated with ≥0.2 mg hGH/kg/week of daily hGH

treatment for ≤130 weeks.

Subjects with a weight of <5.5 kg or >80 kg, poorly controlled diabetes mellitus (HbA1c >8%), history of malignant disease or on concomitant medications that may affect growth such as anabolic steroids or glucocorticoid therapy (with the exception of hormone replacement therapies for hypopituitarism) were excluded from the trial.

All subjects, irrespective of their baseline daily hGH dose, were treated with weekly lonapegsomatropin-tcgd injections, at an average dose of 0.24 ±0.02 mg hGH/kg/week for 26 weeks. No washout period was required prior to the initiation of the treatment with lonapegsomatropin-tcgd. Dose adjustments were permitted at visit 2 (Week 13) based on weight or IGF-1 levels (
Table 28). IGF-1 levels were to be targeted between 0 and 2 SDS. In subjects with IGF-1 SDS <0 SDS, confirmed by a second measurement collected 5 days after dosing, the dose of lonapegsomatropin-tcgd may have been increased by approximately 20% to the next higher weight bracket (
Table 28).

Table 28: Lonapegsomatropin-tcgd bracketed weight table:

	DOSING		ALTERNATIVE DOSING[a]	
Weight (kg)	Drug Concentration (reconstituted)	Volume (mL)	Drug Concentration (reconstituted)	Volume (mL)
5.5–6.6	11.0 mg/mL	0.13	22.0 mg/mL	Contact MM
6.7–7.9	11.0 mg/mL	0.16	22.0 mg/mL	Contact MM
8.0–9.5	11.0 mg/mL	0.19	22.0 mg/mL	Contact MM
9.6–11.4	11.0 mg/mL	0.23	22.0 mg/mL	Contact MM
11.5–13.9	11.0 mg/mL	0.27	22.0 mg/mL	Contact MM
14.0–16.4	11.0 mg/mL	0.33	22.0 mg/mL	Contact MM
16.5–19.9	11.0 mg/mL	0.39	22.0 mg/mL	Contact MM
20.0–23.9	11.0 mg/mL	0.47	22.0 mg/mL	Contact MM
24.0–28.9	22.0 mg/mL	0.29	11.0 mg/mL	0.57
29.0–34.9	22.0 mg/mL	0.35	11.0 mg/mL	0.69
35.0–41.9	22.0 mg/mL	0.41	11.0 mg/mL	0.83
42.0–50.9	22.0 mg/mL	0.50	11.0 mg/mL	0.50 + 0.50
51.0–60.5	22.0 mg/mL	0.60	11.0 mg/mL	0.60 + 0.61
60.6–73.4	22.0 mg/mL	0.73	11.0 mg/mL	0.73 + 0.73
73.5–87.7	22.0 mg/mL	0.88	11.0 mg/mL	0.88 + 0.88

Abbreviation: MM = Medical Monitor.
a To be used only when drug availability required.

Source: Clinical Study Report for CT-302, page 30

Medical reviewer's comments:
Trial CT-302 was a single arm trial in children with GHD who were 6 months to 17 years old and was primarily designed to assess the safety of lonapegsomatropin-tcgd. The subjects were previously treated with rhGH and there was no washout period. Due to lack of a comparator arm and given the efficacy results obtained from this trial are confounded by the previous exposure to other GH formulations, efficacy assessment of trial CT-302 is complicated.

Additionally, the pediatric GHD guidelines do not recommend dose adjustment for the efficacy based on IGF-1 levels due to lack of evidence.[1] However, lonapegsomatropin-tcgd dose was increased in subjects with IGF-1 levels <0 SDS in this trial. The efficacy results obtained from trial CT-302 thus need to be interpreted cautiously.

Study Endpoints

Safety endpoints were measured throughout the trial and included incidence of AEs; local tolerability; incidence of antibodies against hGH; incidence of antibodies against PEG; incidence of IGF-1 SDS >2, >3 with confirmation; parameters of HbA1c and lipids; hormone levels, including thyroid status and morning cortisol; hematology and chemistry parameters; and vital sign measurements.

Efficacy endpoints were secondary endpoints measured at 26 weeks and included AHV; change in height SDS; proportion of subjects with IGF-1 SDS of 0 to 2, -2 to 2 and 1 to 2; IGF-1 SDS; and IGFBP-3 SDS.

Statistical Analysis Plan

SAP was finalized before the database lock.

Safety endpoints were measured throughout the 26 weeks.

Efficacy endpoints of AHV and height SDS were analyzed using an ANCOVA model, which included baseline age, peak GH levels (log transformed) at diagnosis, delta average-parental height SDS, prior GH dose level (log transformed) and prior GH dose (log transformed) duration as covariates and gender as a factor. Post baseline values and changes from baseline in IGF-1 SDS and IGFBP-2 SDS were analyzed using ANCOVA model. Baseline age, peak GH levels (log transformed) at diagnosis, baseline value, prior GH dose level (log transformed) and prior GH dose duration (log transformed) were used as covariates and gender was used as a factor.

Subgroup analysis was done by age (<3 years, ≥3 to <6 years, ≥6 to <11 years [girls] or ≥6 to <12

years [boys], and ≥11 years [girls] or ≥12 years [boys]), gender, baseline GH stimulation test results (≤5 ng/mL and >5 ng/mL) and prior exposure to hGH therapy.

Subgroup analysis based on Tanner stage; and subgroup analysis for AHV, IGF-1 SDS, and change in IGF-1 SDS based on prior daily hGH treatment duration at baseline (<0.5 years, ≥0.5 to <1 year, ≥1 to <1.5 years, ≥1.5 years) were conducted after finalization of SAP. Analysis of anti-lonapegsomatropin-tcgd antibodies was conducted after database lock.

6.2.2. Study Results

Compliance with Good Clinical Practices

This trial was conducted in accordance with ethical principles of GCP, the Declaration of Helsinki and regional regulations.

Patient Disposition

Out of 146 subjects who received at least 1 dose, 144 (98.6%) subjects completed the trial and 2 (1.4%) subjects withdrew consent (after 2 and 9 doses, respectively).

Protocol Violations/Deviations

Majority of deviations were minor. There were 5 (3.4%) subjects with a major protocol deviation. One subject did not provide assent at screening. One subject had been off daily GH for 39 days before starting lonapegsomatropin-tcgd. Three subjects had been on daily GH for >130 weeks (130 weeks + 5 days, 130 weeks + 3 days, and 180 weeks, respectively).

After the study report was finalized it was discovered that one subject had inappropriately administered reconstituted lonapegsomatropin-tcgd that was remaining after administration 7 days prior. There were 3 other subjects at the same site who may have also re-used lonapegsomatropin-tcgd vials.

Demographic Characteristics

Majority of subjects were male (75.3%), white (84.9%), from North America (95.2%) and in Tanner stage 1 (65.1%). Mean (SD) age was 10.6 (3.9) years. Majority of subjects (45.9%) were ≥11 years (girls) or ≥12 years (boys). Only 4 subjects (2.7%) were <3 years old. Mean (SD) height SDS was -1.4 (0.8) and mean (SD) IGF-1 SDS was 0.85 (1.29).

Only 3 subjects (2.1%), all <3 years old, were treatment naïve. Majority of subjects (97.9%) had been on GH treatment before enrollment, at a mean (SD) dose of 0.29 (0.05) mg/kg/week, for a mean (SD) duration of 1.1 (0.7) years

Peak GH concentration was ≤5 ng/mL for 35.6% of subjects and >5 ng/mL for 62.3% of subjects. Deficiencies of other pituitary axes were present in 12 (8.2%) subjects, and included thyroid axis deficiency (5.5%), adrenal axis deficiency (5.5%), gonadal axis deficiency (0.7%) and ADH insufficiency (0.7%).

Table 29: Demographics and Baseline Disease Characteristics

Variable	Total (N=146)
Sex, n (%)	
Male	110 (75.3)
Female	36 (24.7)
Age (years) at Baseline,[a] n	146
Mean (SD)	10.6 (3.9)
Min, Max	1.2, 17.4
Age category, n (%)	
<3 years	4 (2.7)
≥3 and <6 years	20 (13.7)
≥6 to <11 years (girls) or ≥6 to <12 years (boys)	55 (37.7)
≥11 years (girls) or ≥12 years (boys)	67 (45.9)
Race, n (%)	
Asian	6 (4.1)
Black or African American	3 (2.1)
Native Hawaiian or Other Pacific Islander	2 (1.4)
White	124 (84.9)
Multiple	2 (1.4)
Unknown	9 (6.2)
Ethnicity, n (%)	
Hispanic or Latino	10 (6.8)
Not Hispanic or Latino	124 (84.9)
Not reported	8 (5.5)
Unknown	4 (2.7)
Region, n (%)	
North America	139 (95.2)
Oceania	7 (4.8)
Height (cm), n	146
Mean (SD)	132.4 (22.5)
Min, Max	71.8, 171.0
Height SDS, n	146
Mean (SD)	-1.42 (0.84)
Min, Max	-4.71, 0.89

Variable	Total (N=146)
Weight (kg), n	146
Mean (SD)	32.3 (14.2)
Min, Max	8.0, 71.8
Body mass index (kg/m^2), n	146
Mean (SD)	17.5 (3.0)
Min, Max	12.7, 28.9
Tanner stage, n (%)	
1	95 (65.1)
2	14 (9.6)
3	30 (20.5)
4	7 (4.8)
5	0 (0)
Deficiencies of other pituitary axes, n (%)	
Thyroid axis deficiency	8 (5.5)
Gonadal axis deficiency	1 (0.7)
Adrenal axis deficiency	8 (5.5)
ADH insufficiency	1 (0.7)
Delta average-parental height SDS,[b] n	141
Mean (SD)	-1.14 (1.02)
Min, Max	-4.49, 2.03
IGF-1 SDS, n	146
Mean (SD)	0.85 (1.29)
Min, Max	-1.91, 3.98

Source: Clinical Study Report for CT-302, page 56

Medical reviewer Comments:
The pivotal trial CT-301 only included subjects >3 years old. In contrast, the trial CT-302 included subjects younger than 3 years of age and provides safety information in this age group. However, even though the trial CT-302 was designed to include subjects >6 months of age, the minimum age at baseline in this trial was 1.2 years. Thus, the drug should be indicated for pediatric subjects >1-year-old with GHD.

Dosing

Starting dose of lonapegsomatropin-tcgd was 0.24 mg hGH/kg/week. Last weekly dose was within the range of 0.15 to 0.28 mg hGH/kg/week, and the mean (SD) dose was 0.23 (0.03) mg hGH/kg/week.

In 29/144 (19.9%) subjects who underwent dose reduction, IGF-1 SDS values prior to dose adjustment were ≤2 in 1 (0.7%) subject, >2 to ≤3 in 19 (13%) subjects and >3 in 9 (6.2%) subjects. Two subjects (1.4%) underwent dose reduction due to mild AEs of headache (temporary reduction from 0.26 mg hGH/kg/week for one subject and permanent reduction from 0.24 mg hGH/kg/week for second subject).

Two subjects (1.4%) underwent an increase in the dose from 0.23 mg hGH/kg/week to 0.28 mg hGH/kg/week due to IGF-1 SDS values <1 at Week 13.

Treatment Compliance

Mean (SD) compliance was 98.4% (3.97%), and majority of subjects (89.7%) had compliance rate of >95% to 100%.

Efficacy Results

The LS mean for AHV was 9.16 cm/year (95% CI: 8.24, 9.2) at Week 13 and 8.72 cm/year (95% CI: 8.55, 9.77) at Week 26. Mean height SDS was -1.15 and the LS mean (SE) for change in height SDS was 0.25 (0.02) (95% CI: 0.21, 0.29) at Week 26.

The LS mean (SE) for IGF-1 SDS and change in IGF-1 SDS at Week 26 were 1.65 (0.11) and 0.74 (0.11), respectively. The LS mean (SE) for IGFBP-3 SDS and change in IGFBP-3 SDS at Week 26 0.96 (0.007) and 0.5 (0.07), respectively.

The safety results including IGF levels will be discussed in Section 8.4.6 – Laboratory Findings, below.

Subgroup analysis demonstrated that as expected, younger subjects, particularly subjects <3 years old, had a greater AHV response to lonapegsomatropin-tcgd. There was no significant difference in efficacy endpoints between the two genders. Subjects with peak GH levels after stimulation of ≤5 ng/mL and shorter duration of daily hGH treatment prior to start of the trial showed a better response (Table 30).

Table 30: Subgroup analysis at Week 26

Subgroup Category	AHV (cm/year)	Height SDS	ΔHSDS	IGF-1 SDS	ΔIGF-1 SDS
Age					
<3 years, n	4	4	4	4	4
Mean (SD)	16.24 (2.32)	-0.88 (1.08)	0.96 (0.43)	1.41 (1.75)	1.72 (1.26)
≥3 to <6 years, n	20	20	20	20	20
Mean (SD)	9.99 (1.96)	-0.87 (0.90)	0.41 (0.25)	1.59 (1.46)	0.93 (1.33)
≥6 to <11 years (girls), ≥6 to <12 years (boys), n	55	55	55	55	55
Mean (SD)	8.21 (2.21)	-1.17 (0.90)	0.26 (0.18)	1.22 (1.27)	0.39 (1.27)
≥11 years (girls), ≥12 years (boys), n	65	65	65	63	63
Mean (SD)	9.02 (2.60)	-1.25 (0.69)	0.23 (0.21)	1.98 (1.05)	0.97 (0.93)
Gender					
Male, n	109	109	109	107	107
Mean (SD)	9.04 (2.53)	-1.13 (0.75)	0.28 (0.22)	1.55 (1.25)	0.84 (1.16)
Female, n	35	35	35	35	35
Mean (SD)	9.05 (3.25)	-1.22 (1.02)	0.31 (0.31)	1.81 (1.26)	0.52 (1.19)
Baseline Peak GH Stimulation Strata Group[a]					
≤5 ng/mL, n	52	52	52	50	50
Mean (SD)	9.59 (2.85)	-1.08 (0.92)	0.34 (0.26)	1.87 (1.29)	0.95 (1.21)
>5 ng/mL, n	89	89	89	89	89
Mean (SD)	8.63 (2.50)	-1.20 (0.76)	0.24 (0.22)	1.50 (1.22)	0.63 (1.15)
Prior Exposure to hGH Therapy					
Yes, n	141	141	141	139	139
Mean (SD)	8.87 (2.45)	-1.15 (0.82)	0.27 (0.21)	1.64 (1.26)	0.73 (1.16)
No, n[b]	3	3	3	3	3
Mean (SD)	17.24 (1.44)	-1.39 (0.46)	1.15 (0.24)	0.56 (0.56)	2.30 (0.58)
Tanner Stage at Baseline					
Stage 1, n	95	95	95	95	95
Mean (SD)	8.91 (2.76)	-1.17 (0.88)	0.290 (0.27)	1.30 (1.25)	0.68 (1.25)
Stage 2, n	13	13	13	13	13
Mean (SD)	9.12 (3.19)	-1.36 (0.67)	0.25 (0.27)	1.77 (1.07)	0.94 (1.44)
Stage 3, n	30	30	30	28	28
Mean (SD)	9.64 (2.42)	-1.06 (0.70)	0.28 (0.19)	2.42 (0.94)	0.83 (0.77)
Stage 4, n	6	6	6	6	6
Mean (SD)	8.04 (2.14)	-0.85 (0.62)	0.30 (0.15)	2.57 (1.00)	1.28 (1.00)
Prior Daily hGH Treatment Duration at Baseline[c]					
<0.5 year, n	40	—	—	40	40
Mean (SD)	9.74 (2.11)	—	—	1.26 (1.05)	0.74 (1.01)
≥0.5 and <1 year, n	32	—	—	32	32
Mean (SD)	8.87 (2.34)	—	—	1.65 (1.24)	0.58 (1.03)
≥1 and <1.5 years, n	28	—	—	27	27
Mean (SD)	8.42 (3.13)	—	—	1.62 (1.28)	0.75 (1.26)
≥1.5 years, n	41	—	—	40	40
Mean (SD)	8.33 (2.13)	—	—	2.02 (1.36)	0.82 (1.36)

Source: Clinical Study Report for CT-302, page 70

Medical reviewer's comments:
Given trial CT-302 was a single arm trial in subjects with GHD who were previously treated with daily rhGH therapy, efficacy analysis based on this trial is limited. The effect of the drug on annual growth velocity is also unclear, since these patients have exaggerated response

to GH treatment during the first 6 months. However, given the AHV was 8.72 cm/year *and change from baseline in height SDS was 0.25 at Week 26, there was evidence supporting persistent growth in subjects who were switched to lonapegsomatropin-tcgd from a daily rhGH formulation.*

6.3. TransCon hGH CT-301EXT, A multicenter, Phase 3, Long-Term, Open-Label Trial Investigating Safety and Efficacy of Lonapegsomatropin-tcgd Administered Once-Weekly in Children with Growth Hormone Deficiency Who Have Completed a Prior Lonapegsomatropin-tcgd Clinical Trial.

6.3.1. Study Design

Overview and Objective

Trial CT-301EXT was designed to evaluate the long-term safety and efficacy of once weekly dosing of lonapegsomatropin-tcgd in pediatric subjects with growth failure due to GHD who had completed either trial CT-301 or CT-302.

The primary objective of this trial was to assess the long-term safety of weekly lonapegsomatropin-tcgd in children with GHD previously treated in a phase 3 lonapegsomatropin-tcgd trial.

The secondary objectives were to assess AHV with long-term dosing of weekly lonapegsomatropin-tcgd treatment; to assess the proportion of subjects with IGF-1 SDS in the normal range of 0 to +2 with long term lonapegsomatropin-tcgd treatment; to evaluate the change in height SDS with long-term dosing of weekly lonapegsomatropin-tcgd treatment; to determine the incidence of antibodies against lonapegsomatropin-tcgd (anti-hGH and anti-PEG; to assess the preference for weekly lonapegsomatropin-tcgd or daily Genotropin; to assess the treatment satisfaction of weekly lonapegsomatropin-tcgd; and to assess comfort, ease-of-use, and safety in a subset of subjects using the GH auto-injector.

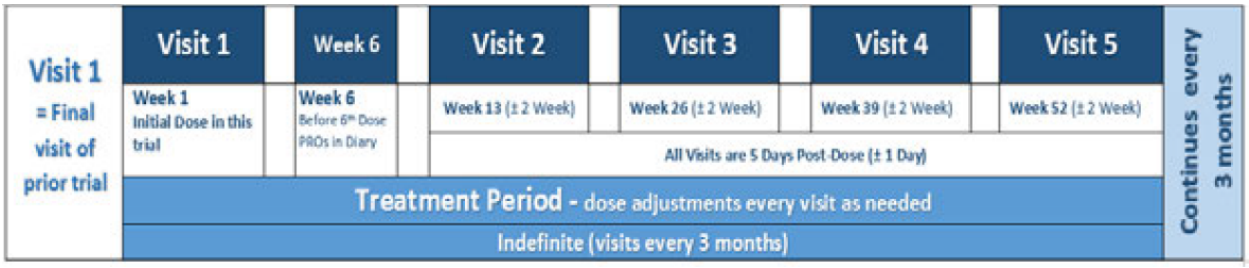
Trial Design

This was a multicenter, phase 3, long-term, open-label extension trial of weekly lonapegsomatropin-tcgd in children with GHD who previously participated in either trial CT-301 or CT-302. This trial was ongoing at the time of this application, and treatment under this trial was intended to continue until either the drug is approved, alternative arrangements were made for continued hGH treatment, or treatment for pediatric GHD was no longer considered appropriate. The trial planned to enroll up to 300 subjects.

Subjects either continued on or were switched to lonapegsomatropin-tcgd at the end of the parent trial. The starting dose was same as the last dose in the parent trial. The dose adjustment was based on IGF-1 values. IGF-1 SDS goal was between 0 and +2, and dose could be increased by approximately 20% in subjects with IGF-1 SDS values <0. Additionally, the dose could also be increased after consultation with the medical monitor in subjects with suboptimal HV. The "suboptimal" HV was not defined in the protocol.

Refer to Figure 11 for trial design and Appendix 4 for details on the specific procedures that were carried out at each visit.

Figure 11: Trial Design for trial CT-301EXT



Source: Clinical Study Report for CT-301EXT, page 23

Study Endpoints

Safety endpoints included incidence of AEs, incidence of antibodies against hGH and PEG, incidence of IGF-1 SDS >2 and >3 with confirmation, parameters of HbA1c and lipids, hormone levels including thyroid and morning cortisol, hematology and chemistry parameters, and vital sign measurements.

Efficacy endpoints included AHV, change in height SDS, proportion of subjects with IGF-1 SDS of 0 to +2, IGF-1 SDS and IGFBP-3 SDS.

6.3.2. Study Results

Compliance with Good Clinical Practices

This trial was conducted in accordance with ethical principles of GCP, the Declaration of Helsinki and regional regulations.

Patient Disposition

As of the data cut-off date of September 30, 2019, a total of 296 subjects were enrolled in the trial. Of these, 102 subjects were from CT-301 lonapegsomatropin-tcgd group, 54 subjects were from CT-301 Genotropin group, and 140 subjects were from the CT-302 lonapegsomatropin-tcgd

group. A total of 10 (3.4%) subjects withdrew prematurely, 7 (2.4%) due to withdrawn consent, 2 (0.7%) due to "other" reasons, and 1 (0.3%) due to protocol violation. There were no deaths or withdrawals due to adverse events.

Protocol Violations/Deviations

Majority of deviations were minor. There were 12 (4.1%) subjects with a major protocol deviation: 9 related to trial drug administration, 2 related to missed dose, 1 related to repeat IGF-1 being collected day 1 post-injection instead of day 5,

Demographic Characteristics

Majority of subjects were male (78.7%), white (90.5%), from North America (59.1%) and in Tanner stage 1 (71.6%). Mean (SD) age was 10.28 (3.43) years and mean bone age was 8.37 years. Majority of subjects (48.3%) were ≥6 to ≤11 years (girls) or ≥6 to ≤12 years (boys). Peak GH concentration was >5 ng/mL for 63.2% of subjects.

Table 31: Demographics and Baseline disease characteristics

Variable	CT-301		CT-302	Total (N=296)
	Lonapeg-somatropin (N=102)	Genotropin (N=54)	Lonapeg-somatropin (N=140)	
Sex, n (%)				
Male	83 (81.4)	44 (81.5)	106 (75.7)	233 (78.7)
Female	19 (18.6)	10 (18.5)	34 (24.3)	63 (21.3)
Age (years)[a]				
Mean (SD)	9.54 (2.686)	9.56 (2.808)	11.11 (3.923)	10.28 (3.428)
Min, max	4.4, 14.1	4.2, 13.9	1.7, 17.8	1.7, 17.8
Age, n (%)				
<3 years	0	0	4 (2.9)	4 (1.4)
≥3 and <6 years	10 (9.8)	9 (16.7)	17 (12.1)	36 (12.2)
≥6 to <11 years (girls), ≥6 to <12 years (boys)	65 (63.7)	29 (53.7)	49 (35.0)	143 (48.3)
≥11 years (girls), ≥12 years (boys)	27 (26.5)	16 (29.6)	70 (50.0)	113 (38.2)

Variable	CT-301		CT-302	Total (N=296)
	Lonapeg-somatropin (N=102)	Genotropin (N=54)	Lonapeg-somatropin (N=140)	
Race, n (%)				
Asian	1 (1.0)	0	5 (3.6)	6 (2.0)
Black or African American	2 (2.0)	0	3 (2.1)	5 (1.7)
Native Hawaiian or other Pacific Islander	0	0	2 (1.4)	2 (0.7)
White	97 (95.1)	51 (94.4)	120 (85.7)	268 (90.5)
Multiple	0	1 (1.9)	2 (1.4)	3 (1.0)
Other	2 (2.0)	2 (3.7)	0	4 (1.4)
Unknown	0	0	8 (5.7)	8 (2.7)
Ethnicity, n (%)				
Hispanic or Latino	5 (4.9)	2 (3.7)	8 (5.7)	15 (5.1)
Not Hispanic or Latino	97 (95.1)	52 (96.3)	121 (86.4)	270 (91.2)
Not reported	0	0	8 (5.7)	8 (2.7)
Unknown	0	0	3 (2.1)	3 (1.0)
Country, n (%)				
US	27 (26.5)	14 (25.9)	133 (95.0)	174 (58.8)
Non-US	75 (73.5)	40 (74.1)	7 (5.0)	122 (41.2)
Region, n (%)				
North America	27 (26.5)	14 (25.9)	134 (95.7)	175 (59.1)
Europe	64 (62.7)	30 (55.6)	0	94 (31.8)
Oceania	6 (5.9)	2 (3.7)	6 (4.3)	14 (4.7)
Middle East and North Africa	5 (4.9)	8 (14.8)	0	13 (4.4)
Height (cm), n	102	54	140	296
Mean (SD)	123.97 (13.109)	122.81 (15.087)	136.97 (22.268)	129.91 (19.454)
Height SDS, n	102	54	140	296
Mean (SD)	-1.864 (0.722)	-2.071 (0.810)	-1.148 (0.821)	-1.563 (0.880)
Weight (kg), n	102	54	140	296
Mean (SD)	26.68 (7.881)	25.45 (7.993)	36.39 (15.277)	31.05 (12.984)
Body mass index (kg/m^2), n	102	54	140	296
Mean (SD)	16.937 (2.024)	16.422 (2.288)	18.424 (3.012)	17.546 (2.710)

Variable	CT-301		CT-302	Total (N=296)
	Lonapeg-somatropin (N=102)	Genotropin (N=54)	Lonapeg-somatropin (N=140)	
Tanner Stage, n (%)				
1	91 (89.2)	44 (81.5)	77 (55.0)	212 (71.6)
2	11 (10.8)	8 (14.8)	21 (15.0)	40 (13.5)
3	0	2 (3.7)	22 (15.7)	24 (8.1)
4	0	0	17 (12.1)	17 (5.7)
5	0	0	3 (2.1)	3 (1.0)
Average parental height SDS, n	100	54	135	289
Mean (SD)	-0.535 (0.740)	-0.460 (0.801)	-0.248 (0.767)	-0.387 (0.773)
Delta average parental height SDS[d], n	100	54	135	289
Mean (SD)	-2.350 (1.132)	-2.520 (1.232)	-1.171 (0.955)	-1.831 (1.237)
IGF-1 SDS, n	101	53	138	292
Mean (SD)	-0.680 (1.000)[b]	-0.023 (1.164)	1.631 (1.258)[c]	0.532 (1.572)
Bone age (years), n	102	54	140	296
Mean (SD)	7.189 (2.732)	7.389 (2.949)	9.614 (3.691)	8.372 (3.454)
Delay in bone age (years), n	102	54	140	296
Mean (SD)	2.33 (1.436)	2.15 (1.059)	1.30 (1.087)	1.81 (1.306)
Peak stimulated GH prior to hGH therapy (ng/mL), n	102	54	137	293
Mean (SD)	5.870 (2.804)	5.461 (3.016)	5.948 (2.526)	5.831 (2.715)
Peak stimulated GH prior to hGH therapy, n (%)				
≤5 ng/mL	36 (35.3)	20 (37.0)	50 (35.7)	106 (35.8)
>5 ng/mL	66 (64.7)	34 (63.0)	87 (62.1)	187 (63.2)
Missing	0	0	3 (2.1)	3 (1.0)

Source: Clinical Study Report for CT-301EXT, page 54

Treatment Compliance

Mean (SD) compliance was 98.7%, and 90.5% of subjects reported compliance rates >95%.

Efficacy Results

Mean AHV (SD) was 8.81 (2.2) cm/year and mean (SD) change in height SDS from baseline was 0.27 (0.19) at Week 26.

Mean (SD) IGF-1 SDS was 0.532 (1.572) at baseline and 1.121 (1.336) at Week 26. At any given time during the trial, 144 (48.6%) subjects had IGF-1 SDS >2 and 58 (19.6%) subjects had IGF-1 SDS >3.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

7.1.1. Primary Endpoints

Pivotal trial CT-301 was the only trial which evaluated efficacy as a primary endpoint, by comparing the AHV at 52 weeks for weekly lonapegsomatropin-tcgd and daily rhGH treatment groups. The estimated difference in the LS mean (SE) of AHV between lonapegsomatropin-tcgd and Genotropin groups was 0.86 (0.33) cm/year [95% CI 0.22, 1.5], which was above the prespecified non-inferiority margin of -2 cm/year. Additionally, given the lower confidence bound was above 0, the Applicant stated that superiority was established.

However, (b) (4) a single study and the observed difference of 0.86 cm/year in AHV at 12 months between the two treatment groups is small and of unknown clinical significance. Secondly, statistical significance was not established across all subgroups. In 26% of the subjects in the trial who were from the US, lonapegsomatropin-tcgd was not found to be superior compared to Genotropin. Similarly, in subjects ≥6 years of age and in female subjects, lonapegsomatropin-tcgd was not found to be superior compared to Genotropin. Lastly, statistical significance was not consistent across two different sensitivity analyses (Frequentist subgroup analysis and Bayesian shrinkage analysis). (b) (4) Refer to Section 6.1.2 for further details.

7.1.2. Secondary and Other Endpoints

Pivotal trial CT-301 included secondary endpoints such as AHV over 52 weeks, height SDS, average IGF-1 SDS, average IGFBP-3 SDS and BMI SDS. However, given the secondary efficacy endpoints were not adjusted for multiplicity, secondary endpoints should be reported in the label without indicating the statistical significance. Refer to Section 6.1.2 for further details.

At Week 52, the change in mean height SDS from baseline was 1.10 in the lonapegsomatropin-tcgd group and 0.96 in the Genotropin group. (b) (4)

However, height SDS, a clinically meaningful endpoint, should be included in the label (b) (4)

(b) (4)

At Week 52, LS mean (SE) of IGF-1 SDS was 0.72 (0.09) in the lonapegsomatropin-tcgd group and -0.02 (0.12) in the Genotropin group. The average IGFBP-3 SDS over 52 weeks improved from baseline in both groups. However, given the IGFBP-3 levels were measured at different times throughout the trial, the measurements in the lonapegsomatropin-tcgd group may not represent true average IGFBP-3 SDS values, and a conclusive comparison between the two groups cannot be made. Refer to Section 6.1.2

Final adult height was not included as a secondary endpoint. As of the 120-day safety update, two subjects who had initially be enrolled in trial CT-302 had reached final adult height (defined as HV <2 cm over at least 9 months, or bone age >14 years for females or >16 years for males). Both subjects were treated with a different GH therapy prior to enrollment in trial CT-302 and continued on to the extension trial CT-301EXT. Given only two subjects reached final adult height during the whole clinical development program, and both subjects had previously been treated with a different growth hormone therapy, conclusions regarding the effect of lonapegsomatropin-tcgd on final adult height cannot be reached at this time. Subject (b) (6) was treated with a different GH therapy for 1.2 years prior to starting trial CT-302 and received treatment with lonapegsomatropin-tcgd for a total of 364 days. This subject had an improvement in height SDS from -2.02 to -1.79 on lonapegsomatropin-tcgd, and the last AHV was 3.7 cm/year. This subject's final height was 149.9 cm, and the mid-parental height was 150.95 cm, indicating that the subject was able to achieve final height that was close to their target height. Subject (b) (6) was treated with a different GH therapy for 1.3 years prior to starting trial CT-302 and received treatment with lonapegsomatropin-tcgd for a total of 553 days. This subject had an improvement in height SDS from -1.91 to -0.94 on lonapegsomatropin-tcgd, and the last AHV was 3.45 cm/year. This subject's final height was 168.8 cm; however, mid-parental height was not

available, and it is unclear if this subject reached target height.

Given none of the subjects reached final adult height during the pivotal phase 3 trial, the Applicant used a previously published prediction model to estimate the near adult height of subjects in trial CT-301. Based on this model, the mean (SD) of predicted near adult height SDS was -0.28 (0.81) for subjects in lonapegsomatropin-tcgd group and -0.63 (0.75) for subjects in Genotropin group. It should be noted that this predictive model has not been validated by Agency to date. However, AHV has previously been accepted by the Agency as a surrogate endpoint for the approval of several other rhGH products for pediatric GHD indications (refer to the discussion in Section 2.2).

7.1.3. Subpopulations

The Applicant also conducted analysis on the primary endpoint of AHV at Week 52 by following subgroups: age, peak stimulated GH, gender, etiology of GHD and country (Refer to the discussion of primary endpoint in Section 6.1.2).

Age:
The Applicant performed subgroup analysis for age groups <6 years and ≥6 years. In the lonapegsomatropin-tcgd group, the AHV at Week 52 was 12.41 cm/year in subjects <6 years old and 10.72 cm/year in subjects ≥6 years old. The difference in AHV at 52 weeks favoring lonapegsomatropin-tcgd was 1.59 and statistically significant in subjects <6 years of age. However, this difference was 0.51 and not statistically significant in subjects ≥6 years of age.

Peak Stimulated GH:
The Applicant performed subgroup analysis for subjects with peak stimulated GH response of ≤5 ng/mL and >5 ng/mL. In the lonapegsomatropin-tcgd group, the AHV at 52 weeks was 11.98 cm/year in the subjects with peak stimulated GH response of ≤5 ng/mL and 10.56 cm/year in the subjects with peak stimulated GH response of >5 ng/mL. Statistical superiority of lonapegsomatropin-tcgd over Genotropin was only established in the subjects with peak stimulated GH response of >5 ng/mL, with a difference in AHV at 52 weeks between lonapegsomatropin-tcgd and Genotropin groups of 0.84 cm/year in this subgroup. This difference in AHV at 52 weeks between lonapegsomatropin-tcgd and Genotropin groups was 0.75 cm/year and not statistically significant in subjects with peak stimulated GH response of ≤5 ng/mL. Of note, greater number of subjects (n = 103) in the trial were enrolled in the peak stimulated GH >5 ng/mL subgroup and it is unclear if this affected the primary efficacy endpoint results in the trial.

Gender:
AHV at 52 weeks was 10.74 cm/year in male subjects and 11.79 cm/year in female subjects. Statistical superiority of lonapegsomatropin-tcgd over Genotropin was only established in male

subjects. The difference in AHV at 52 weeks between the lonapegsomatropin-tcgd and Genotropin groups was 0.81 cm/year in male subjects and 0.59 cm/year in female subjects.

Etiology of GHD:
The Applicant's subgroup analysis based on etiology of GHD demonstrated AHV at 52 weeks as follows: 10.4 cm/year in subjects with isolated idiopathic GHD, 11.57 cm/year in subjects with isolated organic GHD and 12.68 cm/year in subjects with multiple pituitary hormone deficiency. The difference in AHV at 52 weeks between the lonapegsomatropin-tcgd and Genotropin groups in each of the subgroups based on etiology of GHD was not statistically significant.

Country:
In the pivotal trial CT-301, 26% of subjects were from the US. The AHV at 52 weeks in subjects from US was 9.5 cm/year in the lonapegsomatropin-tcgd group and 9.26 cm/year in the Genotropin group, with a difference of 0.24 cm/year between the two groups that was not statistically significant. In comparison, in subjects from non-US countries, the AHV at 52 weeks was 11.65 cm/year in the lonapegsomatropin-tcgd group and 10.64 cm/year in the Genotropin group, with a difference of 1.04 cm/year that was statistically significant.

Medical reviewer's comments:
The Applicant evaluated AHV at 52 weeks in following pre-defined subgroups: age, peak-stimulated GH, gender, etiology of GHD and country. Treatment effects were generally consistent across subgroups.

The subgroup analysis of AHV at 52 weeks confirmed the known better response to GH in pediatric subjects of younger age or with severe GHD. Subjects who were <6 years old had a slightly greater AHV at 52 weeks compared to subjects who were ≥ 6 years old (12.41 cm/year vs 10.72 cm/year); subjects with peak stimulated GH response of ≤5 ng/mL had a slightly greater AHV at 52 weeks compared to subjects with peak stimulated GH response of >5 ng/mL (11.98 cm/year vs. 10.56 cm/year); and subjects with multiple pituitary hormone deficiency had a greater AHV at 52 weeks compared to subjects with isolated idiopathic GHD (12.68 cm/year vs. 10.4 cm/year)

It is not clear why female subjects had a slightly greater AHV at 52 weeks compared to male subjects (11.79 cm/year vs. 10.74 cm/year). Response to GH therapy is typically not gender specific in prepubertal children. A lower number of female subjects in the trial (18%) may have played a role.

Subjects from the US had a lower AHV at 52 weeks compared to subjects from non-US countries (9.5 cm/year vs. 11.65 cm/year). This difference may be as the study included fewer subjects from the US (n=42, 26%).

Statistical significance was not consistent across subgroup analysis conducted by the FDA's statistician Dr. Alexander Cambon using two different methods (frequentist subgroup analysis and Bayesian shrinkage analysis). (b) (4)

7.1.4. Dose and Dose-Response

For a detailed evaluation of the dose and dose-response relation evaluation please refer to Clinical Pharmacology review.

The Applicant selected a starting dose of 0.24 mg hGH/kg/week for the phase 3 trials for following reasons: 1) prior phase 2 trial (CT-004) with the predecessor molecule ACP-001 demonstrated that a dose of 0.21 mg hGH/kg/week of ACP-001 was comparable to a dose of 0.3 mg hGH/kg/day of Genotropin in terms of PK (hGH), C_{max} exposure over one week, efficacy (AHV), and safety/tolerability; 2) the bridging trial (CT-101) demonstrated comparable PK (hGH) and PD (IGF-1) of lonapegsomatropin-tcgd and ACP-001; and 3) a dose of 0.24 mg hGH/kg/week is consistent with global somatropin dosing practices. This starting dose was agreed upon with the Agency in the end of phase 2 meeting prior to start of the phase 3 trials.

In pivotal trial CT-301, all subjects were started on a dose of 0.24 mg hGH/kg/week irrespective of the etiology of GHD, individual treatment goals, or expected sensitivity to therapy. Additionally, subjects were treated with a fixed dose of rhGH throughout the trial. The doses could only be decreased for safety reasons, and titration targeting improved efficacy was not permitted.

The body weight bracketing that was required with the limited number of cartridge strengths resulted in a deviation of -11% to 9% in the dosing from the proposed dosing of 0.24 mg hGH/kg/week. According to the clinical pharmacology reviewer, this deviation in the dosing did not result in any unusual levels of hGH, lonapegsomatropin-tcgd or mPEG, and there was a lack of apparent trend by dosing. Thus, the minor differences in the dosing due to the subject's weight and the proposed body weight bracketing in the label are acceptable.

Medical reviewer's comments:
During the pivotal trial CT-301 all subjects were started at a dose of 0.24 mg hGH/kg/week and fixed doses of rhGH were used. Hence, the starting dose in the label should be 0.24 mg hGH/kg/week, and individualization of starting dose based on etiology of GHD, treatment goals or expected sensitivity to therapy cannot be recommended at this time.

Given titration was not permitted for efficacy and the doses could only be decreased for safety reasons, the maximum labeled dose of lonapegsomatropin-tcgd should be 0.24 mg hGH/kg/week.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Onset of Efficacy Effects:
In general, efficacy effect of GH treatment, measured as an improvement in either HV or Height SDS, is not expected until after 6 months of treatment, and is more definite after the first year of treatment. Pediatric subjects with GH deficiency often exhibit an initial 'catch-up' growth, which results in an increase in HV. This 'catch-up' growth phase is expected to last until the subject reaches the height percentile that is consistent with the midparental height. It is expected that subsequently, the HV would decrease, making the HV at 12 months a better predictor of the response to GH therapy.

Duration of Efficacy Effects:
Duration of response to lonapegsomatropin-tcgd was addressed in trial CT-301EXT, which enrolled subjects that had completed either trial CT-301 or CT-302. All subjects enrolled in trial CT-301EXT were treated with lonapegsomatropin-tcgd, including subjects who were enrolled in the Genotropin group during trial CT-301.

A total of 102 subjects who were in the lonapegsomatropin-tcgd group during the trial CT-301 were enrolled in trial CT-301EXT. Of these, 100 subjects reached Week 26 of trial CT-301EXT, resulting in a total exposure to lonapegsomatropin-tcgd of 78 weeks in these 100 subjects. For this subgroup, the mean AHV was 11.2 cm/year at Week 52 and 9.4 cm/year at Week 78. Similarly, the mean change in height SDS was 1.1 at Week 52 and 1.39 at Week 78 and the mean (SD) IGF-1 levels were -0.680 (1) at Week 52 and 0.608 (1.336) at Week 78.

The Applicant also conducted analysis in 2 subject pools in order to demonstrate the durability of efficacy results. However, these analyses may have been affected by prior treatment with other rhGH therapies and were not reviewed by this medical reviewer. Efficacy Pool I combined data from CT-301 and CT-301 EXT in order to provide long term (>52 weeks) efficacy data. Efficacy Pool I included all subjects who received either lonapegsomatropin-tcgd or Genotropin in trial CT-301, and who were either continued on or were switched to lonapegsomatropin-tcgd in trial CT-301EXT. However, given baseline was defined as the first dose date of either lonapegsomatropin-tcgd or Genotropin, the AHV data obtained from this pool may have been affected by prior Genotropin treatment. Efficacy Pool II combined data from CT-302 and CT-301EXT and included subjects from the Genotropin arm in CT-301 and all treatment experienced subjects from trial CT-302 who were either continued on or were switched to lonapegsomatropin-tcgd in trial CT-301EXT. However, given Efficacy Pool II included subjects who were not treatment-naïve, the AHV data obtained from this pool may have been affected by prior treatment.

Medical reviewer's comments:
The duration of response to lonapegsomatropin-tcgd was assessed in the extension trial CT-301EXT that enrolled subjects who had completed trial CT-301 or CT-302. Overall, growth continued during the second year of treatment with the drug. A reduction in AHV from 11.2 cm/year at Week 52 to 9.4 cm/year at Week 78 of treatment with lonapegsomatropin-tcgd that was observed during the extension trial was minor and was also observed with other approved GH therapies. For example, in the pivotal phase 3 trial of Humatrope, the mean HV increased from 3.6 ±1.9 cm/year at baseline to 8.8 ±2.3 cm/year at 12 months. In a small subset of subjects (n =12) who were followed for 8 years, the mean HV was 6.3 ± 2.5 cm/year at Year 8 of treatment.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Post market Setting

None

7.2.2. Other Relevant Benefits

Poor adherence is one of the major limitations of the currently approved therapies for pediatric GHD. Given lonapegsomatropin-tcgd is administered via once a week injection, it may improve adherence to therapy. Patient preference was assessed in trials CT-302 and CT-301EXT. Subjects and parents showed a preference for once-weekly lonapegsomatropin-tcgd administered via vial with syringe/needle over daily somatropin therapy, with frequency of injections as the most commonly cited reason. However, the study was not properly designed or analyzed to compare directly the adherence between two products and to demonstrate that improved adherence improves annualized growth velocity and, ultimately final adult height. Thus, these data do not suggest that the drug offers an improved compliance/adherence as one of the potential benefits of this product over existing therapies.

7.3. Integrated Assessment of Effectiveness

Pivotal Trial CT-301 was the primary source of efficacy of lonapegsomatropin-tcgd in pediatric subjects. This trial was a randomized, open-label trial in treatment-naïve pediatric subjects. All subjects were treated with either lonapegsomatropin-tcgd or Genotropin, at a fixed dose of 0.24 mg hGH/kg/week. Titration targeting improved efficacy was not permitted and doses could only be decreased during this trial for safety reasons. Trials CT-302 and CT-301 EXT were single-arm, open-label trials that were primarily designed to assess the safety of lonapegsomatropin-tcgd, and only provided supportive evidence of efficacy.

Trial CT-301 met its primary endpoint of AHV at 52 weeks. Non-inferiority was established as the estimated difference in LS mean (SE) of AHV between lonapegsomatropin-tcgd and Genotropin

groups was 0.86 (0.33) cm/year, which was above the prespecified non-inferiority margin of -2 cm/year. Additionally, given the lower confidence bound was above 0, statistical superiority of lonapegsomatropin-tcgd over Genotropin was also established. However, the observed difference of 0.86 cm/year in AHV at 52 weeks between the two groups is of little clinical significance and was more than 50% smaller in magnitude than the non-inferiority margin. Additionally, there was only one well controlled study (b) (4)

The results of the secondary analyses were supportive of the primary analysis. However, given the secondary endpoints were not adjusted for multiplicity, caution is warranted while interpreting the results of the secondary endpoint (b) (4) Replacement therapy with lonapegsomatropin-tcgd resulted in improved height SDS compared to baseline. The change in mean height SDS from baseline to Week 52 was 1.1 in the lonapegsomatropin-tcgd group and 0.96 in the Genotropin group. Lonapegsomatropin-tcgd treatment resulted in normalization of IGF-1 levels indicating an adequate replacement with missing hormone, and improved bone age compared to baseline.

None of the subjects reached final adult height (defined as HV <2 cm over at least 9 months, or bone age >14 years for females and >16 years for males) during the pivotal phase 3 trial. The Applicant used a previously published prediction model to estimate the near adult height of subjects in trial CT-301. Based on this model, the mean (SD) of predicted near adult height SDS was -0.28 (0.81) for subjects in lonapegsomatropin-tcgd group and -0.63 (0.75) for subjects in Genotropin group. As of the 120-day safety update, two subjects who had initially be enrolled in trial CT-302 had reached final adult height. Both subjects were treated with a different GH therapy prior to enrollment in the CT-302 trial and continued on to the extension trial CT-301EXT. One of these subjects was able to achieve final adult height that was close to mid-parental height, whereas the mid-parental height was not available for the second subject. Given only two subjects reached final adult height during the whole clinical development program, both subjects had previously been treated with a different growth hormone therapy, and the mid-parental height is only available for one of these subjects, conclusions regarding the effect of lonapegsomatropin-tcgd on final adult height cannot be reached at this time.

The efficacy of lonapegsomatropin-tcgd was confirmed in all subgroups analyzed. Additionally, the subgroup analysis confirmed the known better response to GH therapy in pediatric subjects of younger age or with severe GHD. Subjects who were <6 years old had a slightly greater AHV at 52 weeks compared to subjects who were ≥ 6 years old (12.41 cm/year vs 10.72 cm/year); subjects with peak stimulated GH response of ≤5 ng/mL had a slightly greater AHV at 52 weeks compared to subjects with peak stimulated GH response of >5 ng/mL (11.98 cm/year vs. 10.56 cm/year); and subjects with multiple pituitary hormone deficiency had a greater AHV at 52 weeks compared to subjects with isolated idiopathic GHD (12.68 cm/year vs. 10.4 cm/year). It is not

clear why female subjects had a slightly greater AHV at 52 weeks compared to male subjects (11.79 cm/year vs. 10.74 cm/year), as response to GH therapy is typically not gender specific in prepubertal children. A lower number of female subjects enrolled in the trial (18%) may have played a role. Lastly, subjects from the US had a lower AHV at 52 weeks compared to subjects from non-US countries (9.5 cm/year vs. 11.65 cm/year). Similar difference was also seen in Genotropin group, with AHV at 52 weeks of 9.26 cm/year in subjects from the US and 10.64 cm/year in subjects from non-US countries. Lower AHV at 52 weeks in subjects from the US may be as fewer subjects from the US (n=42, 26%) were included in the study.

Duration of response to lonapegsomatropin-tcgd was addressed in trial CT-301EXT, which enrolled subjects that had completed either trial CT-301 or CT-302. Longest exposure to lonapegsomatropin-tcgd was observed in 100 subjects from the lonapegsomatropin-tcgd group in trial CT-301, who were enrolled in trial CT-301EXT, with a resulting total exposure to lonapegsomatropin-tcgd of 78 weeks. Analysis of this subgroup with the longest exposure to lonapegsomatropin-tcgd in the phase 3 development showed that growth continued during the second year of treatment with lonapegsomatropin-tcgd. A reduction in AHV from 11.2 cm/year at Week 52 to 9.4 cm/year at Week 78 of treatment with lonapegsomatropin-tcgd was minor and is expected with any GH therapy.

It should also be noted that given the pivotal trial CT-301 only included subjects >3 years old, efficacy data is not available for subjects <3 years old based on the pivotal trial. In contrast, the supportive trial CT-302 included subjects >1-year-old. However, trial CT-302 was a single-arm trial and was primarily designed to assess the safety of lonapegsomatropin-tcgd. All subjects were previously treated with hGH, except 3/4 subjects <3 years old who were naïve to GH therapy. Due to lack of a comparator arm and given the efficacy results obtained from this trial are confounded by the previous exposure to other GH formulations, efficacy assessment of trial CT-302 is complicated. Additionally, subjects were allowed to undergo dose titration based on IGF-1 SDS levels. Hence, even though trial CT-302 provides safety information in subjects <3 years old, efficacy data is limited in this age group. That said, there was supportive evidence of efficacy in this age group as subjects aged <3 years had a mean AHV of 16.24 cm/year in trial CT-302. Higher AHV observed in this age group may be because 3/4 subjects <3 years old were treatment naïve, and an exaggerated AHV response can be observed due to catchup growth during first 6 months.

Lastly, the phase 2 trial CT-004 was conducted using the predecessor molecule ACP-001 that is different from lonapegsomatropin-tcgd. However, given the bridging trial (CT-101) demonstrated comparable PK (hGH) and PD (IGF-1) of lonapegsomatropin-tcgd and ACP-001, the efficacy data from trial CT-004 provide additional evidence on the efficacy of the drug. CT-004 was an open-label, active-controlled trial comparing 3 different dose levels of ACP-001 (0.14, 0.21 and 0.3 mg hGH/kg/wk) administered once weekly, with Genotropin 0.03 mg hGH/kg/day (0.21 mg hGH/kg/wk) administered daily over a period of 26 weeks in 53 pre-pubertal pediatric subjects

with growth failure due to GHD, aged 3 to 11 years for girls and 3-12 years for boys. A dose of 0.21 mg hGH/kg/week of ACP-001 was comparable to a dose of 0.3 mg hGH/kg/day of Genotropin, in terms of PK (hGH), C_{max} exposure over one week, efficacy (AHV), and safety/tolerability. Mean AHV was 12.89 cm/year for the ACP-001 0.21 mg hGH/kg/wk cohort, and 11.64 cm/year for the Genotropin 0.21 mg hGH/kg/wk cohort. However, trial CT-004 was of 26-weeks duration, and given pediatric subjects often present with exaggerated response to GH treatment due to catch up growth during first 6 months of treatment, the effect of the drug on AHV is unclear and the data obtained from trial CT-004 need to be interpreted cautiously.

In conclusion, based on the evidence from the phase 3 program, lonapegsomatropin-tcgd was found to be non-inferior to Genotropin, and can be considered as an alternative rhGH therapy for pediatric subjects with GHD. Given the observed difference of 0.86 cm/year in AHV at 52 weeks between lonapegsomatropin-tcgd and Genotropin is of unknown clinical significance, and given there was only one well controlled study to support statistical superiority (b) (4) Height SDS is an important clinical outcome that provides crucial information to the prescribers and patients. However, the secondary endpoints were not adjusted for multiplicity. An improvement in height SDS of 1.1 from baseline to Week 52 should be included in the label without indicating the statistical significance. Lastly, given the clinical development program did not include subjects <1-year-old, the indication should only include pediatric subjects >1-year-old with growth failure due to GHD.

8. Review of Safety

8.1. Safety Review Approach

The safety data was derived from the 2 completed and 1 ongoing phase 3 trials (trials CT-301, CT-302 and CT-302EXT) and 2 clinical pharmacology trials (trial CT-101 and CT-102). Trial CT-004 was not included in the safety review as it was conducted with the predecessor molecule, ACP-001. The safety analysis population included all randomized subjects who had received at least 1 dose of study drug.

The Applicant presented safety data by individual trial as well as by pooled analysis, which included pooled data from two phase 2 trials in healthy adults (Safety Pool I) and pooled data from three phase 3 trials in children with GHD (Safety Pool II). Given trials CT-302 and CT-301 EXT were single-arm trials, the safety population used in the pooled analysis included only subjects who had received at least 1 dose of lonapegsomatropin-tcgd. Hence, for subjects who had received Genotropin in trial CT-301, only the data collected while the subject received lonapegsomatropin-tcgd in trial CT-301EXT was included. Adverse events were coded using

Medical Dictionary for Regulatory Activities (MedDra) version 19 for all three phase 3 trials that were included in Safety Pool II.

The safety profile of lonapegsomatropin-tcgd in pediatric patients with GHD was primarily obtained from the pivotal active-controlled phase 3 trial (CT-301). This medical reviewer used the safety data originating from trial CT-301 as the primary source of safety assessment, as this was the only trial which was active-controlled. Supportive evidence was obtained from the single-arm trial CT-302, and the single-arm extension trial CT-301EXT. All subjects who were treated with lonapegsomatropin-tcgd during the three phase 3 trials were included in a pooled data. However, there was a lack of a comparator arm in the pooled analysis, and hence, the data obtained from the safety pool can be considered supportive. This medical reviewer did not use the data from 'Safety Pool I' for safety evaluation, given this pool included different patient population, i.e. healthy adult volunteers. Where appropriate, trial specific safety findings were described as well.

This review includes Applicant's analyses, as well as analyses generated by this medical reviewer using the JMP software. Preferred terms were grouped using FDA Medical Queries (FMQ).

This safety review also focused on class-specific adverse events seen with currently approved growth hormone therapies, namely severe hypersensitivity, neoplasms, glucose intolerance, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses, progression of pre-existing scoliosis, pancreatitis, and lipoatrophy. Additionally, a risk of mPEG accumulation in choroid plexus was also identified in nonclinical studies and was thus reviewed as a potential safety concern.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

Table 32: Number of Subjects in the Safety Population by Clinical Study

Study	Population	Subjects exposed to lonapegsomatropin-tcgd	Subjects exposed to Genotropin	Study duration
Total single dose		*73*	*0*	
CT-101	healthy volunteers	45	0	single dose
CT-102	healthy volunteers	28	0	single dose
Total repeat doses[a]		*305*	*56*	
CT-301	Treatment naïve	105	56	52 weeks

Study	Population	Subjects exposed to lonapegsomatropin-tcgd	Subjects exposed to Genotropin	Study duration
	pediatric subjects with GHD			
CT-302	Pediatric subjects with GHD	146	0	52 weeks
CT-301EXT [b]	Pediatric subjects with GHD who had completed CT-301 or CT-302	296	0	ongoing

[a] Subjects exposed to lonapegsomatropin-tcgd in parent trial CT-301/CT-302 and extension trial CT-301EXT were only counted once.
[b] Includes subjects who previously received lonapegsomatropin-tcgd or Genotropin in trial CT-301 and lonapegsomatropin-tcgd in trial CT-302. 54 subjects exposed to Genotropin in trial CT-301 were exposed to lonapegsomatropin-tcgd in 301EXT.

Throughout the lonapegsomatropin-tcgd phase 3 clinical development program, 305 pediatric subjects with GHD were exposed to at least 1 dose of lonapegsomatropin-tcgd, with 301 (98.7%) subjects for >6 months, 252 (82.6%) subjects for >12 months, and 129 (42.3%) subjects for >18 months (Table 33). In the pivotal trial CT-301, 104 subjects were exposed to lonapegsomatropin-tcgd for 12 months.

Table 33: Duration of Exposure to Lonapegsomatropin-tcgd

Exposure Duration[a] (weeks)	CT-301 Lonapegsomatropin/ CT-301EXT	CT-301 Genotropin/ CT-301EXT	CT-302/ CT-301EXT	Total
Number of subjects, n				
≥26	105	53	143	301
≥52	104	21	127	252
≥78	98	3	28	129
≥104	44	0	0	44
≥130	3	0	0	3
≥156	0	0	0	0
Summary statistics				
Mean (SD)	95.0 (17.6)	44.8 (15.2)	61.7 (16.5)	70.2 (25.2)
Minimum, maximum	34, 142	13, 91	2, 96	2, 142

[a] A lower window of 2 weeks was applied to calculate exposure to lonapegsomatropin-tcgd, e.g., if a subject had ≥ (26×7) 14=168 days exposure, the subject was counted in the ≥26 weeks category.
Source: Summary of Clinical Safety, page 24

Medical reviewer's comments:
The level of exposure to lonapegsomatropin-tcgd during the clinical development program is consistent with the ICH E1 guidelines for chronically administered medications for safety assessment, which requires exposure data for 300-600 subjects at 6 months and 100 subjects at 1 year.

8.2.2. Relevant characteristics of the safety population:

The demographic characteristics, medical histories, and concomitant medications of trial CT-301 were described in Section 6.1.2 and were in general well balanced between the lonapegsomatropin-tcgd and Genotropin groups.

The demographics of subjects enrolled were similar between the trials CT-301 and CT-302, with a few exceptions. Trial CT-301 only enrolled treatment naïve subjects aged 3-12 (boys) or 3-11 (girls), whereas trial CT-302 enrolled subjects aged 6 months to 17 years who had previously been treated with daily rhGH.

Table 34: Baseline demographics and disease characteristics in trials CT-301 and CT-302

Variable Statistic	Trial CT-301			Trial CT-302 (N= 146)	Safety Pool II[a] (N = 305)
	Lonapegsomatropin-tcgd (N=105)	Genotropin (N=56)	Total (N=161)		
Gender, n (%)					
Male	86 (81.9%)	46 (82.1%)	132 (82%)	110 (75.3%)	240 (78.7%)
Female	19 (18.1%)	10 (17.9%)	29 (18%)	36 (24.7%)	65 (21.3%)
Age					
<3 years	0	0	0	4 (2.7%)	4 (1.3%)
≥3 and <6 years	25 (23.8%)	14 (25%)	39 (24.2%)	20 (13.7%)	54 (17.7%)
≥6 to <11 years (girls) or ≥6 to <12 years (boys)	80 (76.2%)	42 (75%)	122 (75.8%)	55 (37.7%)	149 (48.9%)
≥11 years (girls) or ≥12 years (boys)	0	0	0	67 (45.9%)	98 (32.1%)
Race, n (%)					
Asian	1 (1%)	0	1 (0.6%)	6 (4.1%)	7 (2.3%)
Black or African American	2 (1.9%)	1 (1.8%)	3 (1.9%)	3 (2.1%)	5 (1.6%)

Variable Statistic	Trial CT-301			Trial CT-	Safety Pool II[a]
Native Hawaiian or Other Pacific Islander	0	0	0	2 (1.4%)	2 (0.7%)
White	100 (95.2%)	52 (92.9%)	152 (94.4%)	124 (84.9%)	275 (90.2%)
Other/ multiple/ unknown	2 (1.9%)	3 (5.4%)	5 (3.1%)	11 (7.6%)	13 (4.3%)
Region, n (%)					
North America	27 (25.7%)	15 (26.8%)	42 (26.1%)	139 (95.2%)	180 (59%)
Europe	66 (62.9%)	31 (55.4%)	97 (60.2%)	0	96 (31.5%)
Middle East and North Africa	6 (5.7%)	8 (14.3%)	14 (8.7%)	0	14 (4.6%)
Oceania	6 (5.7%)	2 (3.6%)	8 (5%)	7 (4.8%)	15 (4.9%)
Country, n (%)					
US	27 (25.7%)	15 (26.8%)	42 (26.1%)	138 (94.5%)	179 (58.7%)
Non-US	78 (74.3%)	41 (73.2%)	119 (73.9%)	8 (5.5%)	126 (41.3%)
HV at baseline (cm/year)[b]					
Mean (SD)	3.93 (2.042)	3.93 (1.662)	3.93 (1.906)	-	-
Minimum, maximum	0.2, 12.9	-0.9, 6.2	-0.9, 12.9	-	-
Height SDS					
Mean (SD)	-2.89 (0.847)	-3 (0.903)	-2.93 (0.865)	-1.418 (0.839)	-2.04 (1.063)
Minimum, maximum	-6.8, -1.4	-5.6, -1.1	-6.8, -1.1	-4.71, 0.89	-6.81, 0.89
IGF-1 SDS at baseline					
Mean (SD)	-2.08 (0.883)	-1.96 (0.976)	-2.04 (0.915)	0.854 (1.294)	-0.313 (1.749)
Minimum, maximum	-4.2, -0.5	-3.7, -0.3	-4.2, -0.3	-1.91, 3.98	-4.17, 3.98
Peak stimulated GH concentration, n (%)					
≤5 ng/mL	37 (35.2%)	21 (37.5%)	58 (36%)	52 (35.6%)	109 (35.7%)
>5 ng/mL	68 (64.8%)	35 (62.5%)	103 (64%)	91(62.3)	193 (63.3%)
Deficiencies of other pituitary axes					
Thyroid axis deficiency	13 (12.4%)	8 (14.3%)	21 (13%)	8 (5.5%)	29 (9.5%)
Gonadal axis deficiency	0	0	0	1 (0.7%)	1 (0.3%)
Adrenal axis deficiency	7 (6.7%)	4 (7.1%)	11 (6.8%)	8 (5.5%)	19 (6.2%)

Variable Statistic	Trial CT-301			Trial CT-	Safety Pool II[a]
ADH insufficiency	2 (1.9%)	2 (3.6%)	4 (2.5%)	1 (0.7%)	5 (1.6%)

[a] safety pool II includes subjects who were exposed to lonapegsomatropin-tcgd during one of three phase 3 trials (Trial CT-301, CT-302 or CT-301EXT)
[b] data only available for trial CT-301
Source: combined from various tables in Summary of Clinical Safety on pages 34, 35, 36, 38, 39, 41, 43, 44 and 45.

Medical reviewer's comments:
Majority of subjects in the clinical program were males (78.7%). A diagnosis of GHD is more common in males than in females and may explain this difference. In one study, 64% of subjects diagnosed with GHD were males[2]. Additionally, similar differences in proportion of male and female subjects were also present in the pivotal trials for other rhGH formulations such as Nutropin (85.5% males) and Zomacton (73% males).

Trial CT-301 only included 26.1% of subjects from the United States. However, given trial CT-302 was predominantly conducted in the United States, approximately 59% of subjects in the safety pool II were from the United States.

8.2.3. Adequacy of the safety database:

The safety database was adequate for the proposed indication.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall data integrity and submission quality were adequate to perform an effective safety review.

8.3.2. Categorization of Adverse Events

- Safety population included all subjects who received at least one dose of study drug.
- The Applicant's definitions of adverse events (AE), serious adverse events (SAEs) and treatment emergent adverse events (TEAEs) in the protocol were accurate.
- AEs were defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, irrespective of a causal relationship.
- SAEs were defined as an AE that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability/incapacity or was a congenital anomaly/birth defect.

- TEAEs were defined as any AE that first occurred or worsened after the first dose of the trial drug.

- The Medical Dictionary for Regulatory Activities (MedDRA) version 19 was used for all phase 3 trials.

- AEs were not solicited and were collected in response to a general question about the subject's well-being, without any directed questioning for specific AE.

- All AEs, including SAEs and TEAEs were recorded from the time of the first study drug administration through the end of the trial visit. For the pivotal trial CT-301, the end of trial visit, was 1 week after the last dose.

- AEs were followed until they had either resolved, returned to baseline status, or were deemed stable or commensurate with ongoing disease processes.

- Severity categorization (mild, moderate, severe, or life-threatening) of AEs by the Applicant was appropriate.

- Verbatim terms were included in the data files and were appropriately translated to dictionary-derived term (AEDECOD) in the data file. Additionally, there appeared to be no lumping or splitting of terms except for a few cases where terms were lumped. For example, four cases of 'infection with fever' and three cases of 'infection with vomiting' were categorized as infection alone. These terms were recategorized by this medical reviewer prior to analysis.

- In order to further limit underestimation due to splitting, the adverse events were grouped by this medical reviewer using FDA medical queries (FMQ)

- The Applicant appropriately reported adverse events by cohort, as number of subjects and frequency per total number of subjects in the cohort.

- The Applicant primarily summarized TEAEs by Preferred Term (PT) and System Organ Class (SOC) and reported data for SOCs and PTs occurring in at least 5% of total subjects. This medical reviewer analyzed the safety data from the pivotal trial CT-301 using JMP clinical and reported TEAEs occurring more frequently in the lonapegsomatropin-tcgd group. Only TEAEs with a delta risk of ≥1.9% were reported.

- Medical events of special interest only included injections site reactions, whereas other events of interest included adverse reactions seen with other rhGH therapies such as increased risk of neoplasms, glucose intolerance, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses,

progression of pre-existing scoliosis, pancreatitis, and lipoatrophy. These AEs were ascertained throughout the trial via 1) physical examinations which included fundoscopic exams; 2) laboratory assessments which included parameters of glucose metabolism, thyroid hormone levels and morning cortisol levels; and 3) assessments of local tolerability and subjects' general well-being.

8.3.3. Routine Clinical Tests

Appropriate safety assessments were conducted throughout the clinical development of lonapegsomatropin-tcgd. Refer to Appendix 1 through 4 for schedule of events during the three phase 3 trials.

Clinical laboratory evaluation included hematology, blood chemistry, lipid, and glucose metabolism (fasting glucose, insulin, HbA1c, and oral glucose tolerance test (oGTT)), hormonal profile (TSH, free triiodothyronine (fT3), free thyroxine (fT4), and morning cortisol), bioanalytical samples (hGH, mPEG, IGF-1 and IGFBP-3). Physical examinations included fundoscopic exams and assessments of vital signs (heart rate, blood pressure, respiratory rate, body temperature, height, and weight measurements). ECG were obtained during trial CT-301.

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported during the clinical development program of lonapegsomatropin-tcgd.

8.4.2. Serious Adverse Events

Safety Pool II
Out of the 305 subjects who were treated with lonapegsomatropin-tcgd during the three phase 3 trials, a total of 7 (2.3%) subjects experienced a SAE. None of the SAEs were observed in more than one subject.

Table 35: Serious adverse events occurring in subjects treated with lonapegsomatropin-tcgd during CT-301, CT-302, or CT-301EXT

	CT-301 (N = 105)	CT-302 (N = 146)	CT-301 EXT (N = 296)	TOTAL (N = 305) *
SOC/PT	Count (%)	Count (%)	Count (%)	Count (%)
Any SAE	1 (0.95%)	1 (0.7%)	5 (1.7%)	7 (2.3%)

	CT-301 (N = 105)	CT-302 (N = 146)	CT-301 EXT (N = 296)	TOTAL (N = 305) *
SOC/PT	Count (%)	Count (%)	Count (%)	Count (%)
Infections and infestations	1 (0.95%)	0	1 (0.3%)	2 (0.7%)
Appendicitis	1 (0.95%)	0	0	1 (0.3%)
Gastrointestinal viral infection	0	0	1 (0.3%)	1 (0.3%)
Cardiac disorders	0	1 (0.7%)	0	1 (0.3%)
Atrioventricular block	0	1 (0.7%)	0	1 (0.3%)
General disorders and administration site conditions	0	1 (0.7%)	1 (0.3%)	2 (0.7%)
Chest pain	0	1 (0.7%)	0	1 (0.3%)
Pyrexia (Acute febrile illness)	0	0	1 (0.3%)	1 (0.3%)
Nervous system disorders	0	0	1 (0.3%)	1 (0.3%)
Generalized tonic-clonic seizure	0	0	1 (0.3%)	1 (0.3%)
Epilepsy	0	0	1 (0.3%)	1 (0.3%)
Gastrointestinal disorders	0	0	1 (0.3%)	1 (0.3%)
Vomiting	0	0	1 (0.3%)	1 (0.3%)
Respiratory, thoracic, and mediastinal disorders	0	0	1 (0.3%)	1 (0.3%)
Adenoidal hypertrophy	0	0	1 (0.3%)	1 (0.3%)
Skin and subcutaneous tissue disorders	0	0	1 (0.3%)	1 (0.3%)
Rash	0	0	1 (0.3%)	1 (0.3%)

N: subjects exposed; %: percentage of exposed subjects having the event;
* Subjects exposed to lonapegsomatropin-tcgd in parent trial CT-301/CT-302 and extension trial CT-301EXT were only counted once.
MedDRA version 19
Source: JMP clinical, medical reviewer generated report

Trial CT-301

Overall, the incidence of SAEs in this trial was low in both groups. A total of 2 SAEs occurred in 2 (1.2%) subjects, one in each treatment group. All SAE were unrelated to the drug.

Table 36: Serious Adverse Events (SAEs) by System Organ Class (SOC), preferred term (PT) and treatment group in Trial CT-301

	Lonapegsomatropin-tcgd (N = 105)	Genotropin (N = 56)	Total (N = 161)
SOC/PT	Count (%)	Count (%)	Count (%)
Any SAEs	1 (1.0%)	1 (1.8%)	2 (1.2%)
Infections and infestations	1 (1.0%)	0	1(0.6%)
Appendicitis	1 (1.0%)	0	1 (0.6%)
Injury, poisoning and procedural complications	0	1 (1.8%)	1 (0.6%)
Concussion	0	1 (1.8%)	1 (0.6%)

N: subjects exposed; %: percentage of exposed subjects having the event;
MedDRA version 19
Source: JMP Clinical, medical reviewer generated report

Individual SAEs were reviewed using the Applicant's narrative summaries in the Clinical Study Report (CSR) for Trial CT-301, and are summarized below:

Subject (b) (6) (SAE: Appendicitis) was a 10-year-old male with a medical history of GHD who was treated with lonapegsomatropin-tcgd 0.24mg/kg/week. On Day 191, the subject experienced appendicitis which required hospitalization. He had not been on any concomitant medications at the time of onset of appendicitis. He underwent appendectomy and was treated with ceftriaxone, ketorolac, lactated ringer's intravenous solution and sodium chloride intravenous solution. The subject recovered on Day 213. However, he subsequently terminated the trial after withdrawing consent, reportedly due to "medical fatigue" from hospitalization.

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAE is unlikely due to the temporal relationship with the study drug and an inherent increased rate of appendicitis in children.*

Subject (b) (6) (SAE: Concussion) was a 7-year-old male with a medical history of GHD, adrenal insufficiency, secondary hypothyroidism, ectopic posterior pituitary gland, pituitary hypoplasia, hypercholesterolemia who was treated with Genotropin. On Day 327, the subject experienced a fall off a slide which resulted in a concussion requiring hospitalization. Concomitant medications included hydrocortisone and levothyroxine. The subject did not require any treatment for the concussion and the subject was discharged on Day 328.

> *Medical reviewer's comments: The causal relationship between Genotropin and the reported SAE is unlikely due to the temporal relationship with the study drug and given it resolved without any changes to the Genotropin dose. Additionally, the concussion was preceded by a trauma.*

Trial CT-302

A total of 2 SAEs occurred in 1 (0.7%) subject during this trial; both SAE were not related to the study drug.

Subject (b) (6) (SAEs: atrioventricular block and chest pain) was a 13-year old male with a medical history of GHD, ectopic posterior pituitary gland, secondary adrenal insufficiency, congenital perimembranous ventricular septal defect and asthma. The Subject had undergone a repair of ventricular septal defect at 1 month of age, which was complicated by postoperative complete heart block and atrial tachycardia. Persistent sequelae included chronic left bundle branch block, ventricular septum regional scarring and dyskinesia, dilated left ventricular cardiomyopathy with chronic systolic heart failure, rare premature atrial contractions, and rare premature ventricular contractions. At the time of onset of SAEs, concomitant medications included atenolol, guanfacine, hydrocortisone, isradipine, lisinopril, methylphenidate hydrochloride and salbutamol (albuterol).

Prior to starting lonapegsomatropin-tcgd, the subject had been treated with rhGH (Humatrope) for 2.4 years. On Day 13, the subject presented to the emergency department with fever, cough, and palpitations, and experienced a life-threatening SAE of atrioventricular block (heart rate in 30s and 2 runs of ventricular tachycardia) that required hospitalization. He underwent biventricular pacemaker placement and was treated with atenolol. The subject also experienced upper respiratory tract infection and asthma exacerbation, which were treated with albuterol and high-dose prednisone. Subsequently, the subject experienced hypertensive episodes (blood pressure near 170/100) and required treatment with nicardipine, upward titration of lisinopril and addition of isradipine to be used as needed. On Day 21, the subject was discharged.

On Day 87, the subject experienced a second SAE of chest pain. The subject presented to the emergency department after a chest injury near the pacemaker site during an altercation 2 days earlier and required hospitalization for 2 days for a thorough evaluation.

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAEs is unlikely. The SAE of atrioventricular block is most likely attributed to the subject's underlying cardiac condition. The episode of asthma exacerbation is most likely attributed to upper respiratory tract infection, and the episode of hypertension was most likely due to the use of the high dose of steroids. The SAE of chest pain was likely secondary to trauma, and unlikely to be related to lonapegsomatropin-tcgd.*

Trial CT-301EXT

A total of 7 SAEs occurred in 5 (1.7%) subjects during this trial.

Subject (b) (6) (SAE: adenoid hypertrophy) was a 12-year-old male with a medical history of GHD, who had been treated with Genotropin in the parent trial CT-301 and was switched to

lonapegsomatropin-tcgd 0.24 mg/kg/week upon entering trial CT-301EXT. The subject experienced 2 to 3 months of difficulty with nasal breathing and underwent elective tonsillectomy for the SAE of adenoid hypertrophy on Day 201. Lonapegsomatropin-tcgd dose was not changed, and the subject recovered.

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAE is unlikely due to a lack of temporal relationship. Additionally, this subject had been treated with Genotropin in parent trial CT-301, which limits the interpretation of causality of the reported SAE.*

> *Throughout the phase 3 program, serious or nonserious AEs of adenoidal or tonsillar hypertrophy were reported by 3 subjects. Two of these subjects (Subjects (b) (6) and (b) (6)) had a history of prior treatment with another rhGH therapy whereas one subject (Subject (b) (6)) had no prior treatment. Hence, a causal relationship between lonapegsomatropin-tcgd therapy and incidence of adenotonsillar hypertrophy, in lieu of a GH therapy class effect, cannot be established at this time.*

Subject (b) (6) (SAE: gastrointestinal viral infection and vomiting) was a 9-year-old male with a medical history of GHD, medulloblastoma of the fourth ventricle status post-surgical debulking, chemotherapy and cranial irradiation, complicated by hydrocephalus status post ventribuloperitoneal shunt and panhypopituitarism including secondary adrenal insufficiency, secondary hypothyroidism, and diabetes insipidus. The subject had been treated with lonapegsomatropin-tcgd for 52 weeks in the parent trial CT-301 prior to his enrollment in the extension trial CT-301EXT. On Day 632, the subject presented after multiple episodes of vomiting which required hospitalization for 1 day, administration of stress dose steroids and intravenous fluids. The subject was diagnosed with a viral gastrointestinal infection and no changes were made to the trial drug. On Day 644, the subject experienced another SAE of vomiting which required hospitalization for 1 day, administration of stress dose steroids and intravenous fluids. Eventually, the subject was diagnosed with cyclic vomiting syndrome

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAEs is unlikely due to a lack of temporal relationship, and given the subject was eventually diagnosed with cyclic vomiting syndrome which could explain his symptoms. Additionally, his symptoms improved even though no changes were made to the lonapegsomatropin-tcgd dosing.*

Subject (b) (6) (SAE: pyrexia) was a 2.5-year-old female with a medical history of GHD, septo-optic dysplasia, secondary hypothyroidism, secondary adrenal insufficiency, jaundice, seizure, and developmental hip dysplasia who had been treated with lonapegsomatropin-tcgd for 26 weeks in the parent trial CT-302 prior to enrollment in trial CT-301EXT. Concomitant medications included hydrocortisone and levothyroxine. On Day 44, the subject presented to the emergency

department after experiencing lethargy and a fever of 39.3°C and was admitted overnight. No changes were made to the lonapegsomatropin-tcgd dosing.

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAE is unlikely due to a lack of temporal relationship, and given the symptoms improved even though no changes were made to the lonapegsomatropin-tcgd dosing. The etiology of pyrexia is not clear, however given the subject's age, an infectious etiology is the most likely explanation for the fever.*

Subject (b) (6) (SAE: generalized tonic-clonic seizure and epilepsy) was a 10-year-old male with a medical history of GHD, orchidopexy, asthma, functional cardiac murmur, and probable absence seizures, who had been treated with lonapegsomatropin-tcgd for 52 weeks during the parent trial CT-301 prior to enrollment in trial CT-301EXT. On Day 930, the subject experienced a generalized tonic-clonic seizure and was observed in the emergency room for several hours prior to discharge the same day. The subject underwent an electroencephalogram as an outpatient which revealed multifocal, bilateral, epileptic foci and a possibility of a generalized epileptic disorder. On Day 973, the subject presented to the emergency room for a second tonic-clinic seizure, was started on antiepileptics, and discharged home on the same day. No changes were made to the lonapegsomatropin-tcgd dosing.

> *Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAE is unlikely and is most likely due to the underlying seizure disorder. This subject had a probable history of absence seizures. There is a lack of temporal relationship, and symptoms improved even though no changes were made to the lonapegsomatropin-tcgd dosing.*

Subject (b) (6) (SAE: rash) was a 3-year-old male with a medical history of GDH, cleft lip and palate status post repair, dysmorphism, gastroesophageal reflux disease, Eustachian tube dysfunction, dysphagia and craniosynostosis, who had been treated with lonapegsomatropin-tcgd for 26 weeks in the parent trial CT-302 prior to enrollment in trial CT-301EXT. On Day 454, the subject was diagnosed with streptococcal pharyngitis and was treated with amoxicillin until Day 465, when he developed a pruritic rash. On Day 456, the subject also developed right knee pain and fever, and was admitted for further evaluation and treatment. Laboratory evaluation revealed elevated white blood cell count of 22.7 x 10^9/L (normal range 4.5 – 13.5 x 10^9/L) and elevated c-reactive protein of 3.1 mg/dL (normal range 0 – 0.5 mg/dL). He was treated with intravenous methylprednisolone and diphenhydramine, which resulted in an improvement in his rash, polyarthritis, and fever. No changes were made to the lonapegsomatropin-tcgd dosing. Additionally, this subject had negative anti-drug antibody titers throughout the trial.

Medical reviewer's comments: The causal relationship between lonapegsomatropin-tcgd and the reported SAE is unlikely, and the event is most likely due to the treatment with amoxicillin.

Medical reviewer's comments: Overall, the incidence of SAEs in the clinical development of lonapegsomatropin-tcgd was low, with 10 events reported in 7 (2.3%) subjects treated with lonapegsomatropin-tcgd. None of the events were experienced by more than 1 subject. Upon detailed review of the case narratives, this MO agrees that none of the events were likely related to the study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

There were no discontinuations due to adverse events during the three phase 3 trials of lonapegsomatropin-tcgd.

8.4.4. Significant Adverse Events

Severe Adverse Events

Adverse events were characterized as mild, moderate, severe, or life-threatening. Severe adverse events were defined as events which resulted in the subject being incapacitated and unable to work or participate in many or all usual activities; were of definite concern to the subject and/or possess substantial risk to the subject's health or well-being; and were likely to require medical intervention and/or close follow-up.

During the pivotal trial CT-301, majority of subjects experienced either mild or moderate TEAEs (Table 37). None of the subjects experienced life-threatening adverse events and 1 subject experienced severe TEAE. This subject was on lonapegsomatropin-tcgd, experienced 1 severe TEAE of appendicitis that required surgery, and was likely not related to the study drug. Refer to the description of serious adverse event experienced by subject (b) (6) in Section 8.4.2 above for further details.

Table 37: Number of subjects with any Adverse Event by Severity in Trial CT-301

	Lonapegsomatropin-tcgd (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) N (%)
No AEs	24 (22.9%)	17 (30.4%)	41 (25.5%)
At least 1 AE	81 (77.1%)	39 (69.6%)	120 (74.5%)
Mild	75 (71.4%)	34 (60.7%)	109 (67.7%)
Moderate	27 (25.7%)	19 (33.9%)	46 (28.6%)
Severe	1 (0.9%)	0	1 (0.6%)

	Lonapegsomatropin-tcgd (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) N (%)
Life-Threatening	0	0	0

N = total number of subjects in each treatment group. n = number of subjects experiencing adverse event, (%) = proportion of subjects experiencing the event.
Subjects with more than 1 AE of same severity were only counted once but subject who experienced AEs of more than 1 severity were counted more than once.
Source: JMP, medical reviewer generated report

A review of adverse events with the same preferred term and the same level of severity in each subject identified mostly mild and moderate severity in both treatment groups (Table 38)

Table 38: Number of Subjects with Adverse Events by Preferred Term and Severity in Trial CT-301

	Total AE preferred terms	Mild	Moderate	Severe	Life-threatening	Missing
All subjects	461	366	93	1	0	1
Lonapegsomatropin-tcgd	307	244	62	1	0	0
Genotropin	154	122	31	0	0	1

Subjects with a specific preferred term with the same level of severity were only counted once.
Source: JMP clinical, medical reviewer generated report.

During the trial CT-302, 1 (0.7%) subject experienced 1 severe TEAE of atrioventricular block which was likely not related to the study drug. Refer to the description of serious adverse event experienced by subject (b) (6) in Section 8.4.2 above for further details.

During CT-301EXT, 2 (0.7%) subjects experienced 1 severe TEAE each. Both TEAEs were likely not related to the study drug. Refer to the description of serious adverse event experienced by subject (b) (6) (vomiting) and subject (b) (6) (epilepsy) in Section 8.4.2 above for further details.

> *Medical reviewer's comments:*
> *Majority of adverse events were either mild or moderate. Out of the 305 subjects who were treated with lonapegsomatropin-tcgd during the phase 3 clinical development, 4 (1.3%) subjects experienced 1 severe adverse event each, and all were likely not related to the study drug. None of the subjects experienced a life-threatening event.*

Events leading to dose modification

During the pivotal trial CT-301, 3 (1.8%) subjects experienced a TEAE that lead to dose

modification: 2 (1.9%) subjects in the lonapegsomatropin-tcgd group underwent dose reduction due to elevated IGF-1 levels (asymptomatic) and 1 (1.8%) subject in Genotropin group underwent dose reduction due to facial edema.

During the trial CT-302, 29 (19.9%) subjects underwent dose reduction due to an elevated IGF-1 level. However, these subjects had been on rhGH therapy prior to enrollment, and 32(21.9%) of subjects had elevated IGF-1 of >2 SD at baseline. All subjects were asymptomatic. A total of 2 (1.4%) subjects experienced a TEAE other than elevated IGF-1 level that lead to dose reduction: one subject underwent a temporary dose reduction due to headache and second subject underwent a permanent dose reduction due to headache. Of note, headache is known AE associated with GH, however, it also commonly occurs in this age group.

During CT-301EXT, 2 (0.7%) subjects underwent dose reduction due to elevated IGF-1 levels. Three subjects experienced dose interruptions: one subject had 1 dose held due to arthritis, one subject had 2 doses held due to abdominal pain and one subject had a dose delayed due to gastroenteritis.

Medical reviewer's comments:
During the pivotal phase 3 trial, dose reductions were similar in the lonapegsomatropin-tcgd and Genotropin groups. Most cases of dose reduction were due to asymptomatic elevation of IGF-1 levels. Out of the 305 subjects who were treated with lonapegsomatropin-tcgd during the phase 3 clinical development, 2 (0.7%) subjects required dose reduction for reasons other than elevated IGF-1 (both were due to headache), and 3 (0.9%) subjects required dose interruptions (due to arthritis, abdominal pain, and gastroenteritis). All AEs resolved with dose reduction.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Given trial CT-301 was the only trial with an active comparator, data obtained from this trial was used as the primary source to review the treatment emergent adverse events (TEAEs) associated with lonapegsomatropin-tcgd.

The Applicant conducted analysis of adverse events coded using MedDRA version 19 and reported TEAEs occurring in ≥5% of total subjects. TEAEs were defined as AEs that first occurred or worsened after starting treatment. Each subject was counted only once within each preferred term.

TEAEs were reported by system organ class and preferred term. Refer to Table 39. Throughout the trial, a total of 120 (74.5%) subjects experienced at least 1 TEAE. The rate of TEAE was slightly higher in lonapegsomatropin-tcgd group, with at least one TEAE experienced by 81 (77.1%) subjects in lonapegsomatropin-tcgd group and 39 (69.6%) subjects in Genotropin group. The

TEAEs were most commonly reported in the system order class of Infections and infestations (54.7%), respiratory, thoracic, and mediastinal disorders (21.7%), Gastrointestinal disorders (19.9%), General disorders and administration site conditions (16.8%), Nervous system disorders (14.3%), and Injury, poisoning and procedural complications (12.4%).

Table 39: TEAEs by System Organ Class and Preferred Term in **≥5%** of Total Subjects

SOC PT	Lonapegsomatropin (N = 105) n (%)	Genotropin (N = 56) n (%)	Total (N = 161) n (%)
Any TEAE	81 (77.1)	39 (69.6)	120 (74.5)
Infections and infestations	56 (53.3)	32 (57.1)	88 (54.7)
Nasopharyngitis	12 (11.4)	8 (14.3)	20 (12.4)
Pharyngitis	10 (9.5)	10 (17.9)	20 (12.4)
Upper respiratory tract infection	6 (5.7)	5 (8.9)	11 (6.8)
Respiratory tract infection	7 (6.7)	3 (5.4)	10 (6.2)
Respiratory, thoracic, and mediastinal disorders	27 (25.7)	8 (14.3)	35 (21.7)
Cough	10 (9.5)	4 (7.1)	14 (8.7)
Gastrointestinal disorders	24 (22.9)	8 (14.3)	32 (19.9)
Vomiting	9 (8.6)	3 (5.4)	12 (7.5)
Diarrhea	6 (5.7)	3 (5.4)	9 (5.6)
General disorders and administration site conditions	18 (17.1)	9 (16.1)	27 (16.8)
Pyrexia	16 (15.2)	5 (8.9)	21 (13.0)
Nervous system disorders	14 (13.3)	9 (16.1)	23 (14.3)
Headache	13 (12.4)	7 (12.5)	20 (12.4)
Endocrine disorders	9 (8.6)	6 (10.7)	15 (9.3)
Secondary hypothyroidism	7 (6.7)	3 (5.4)	10 (6.2)

Source: Clinical Study Report for CT-301, page 119

FDA Medical Queries (FMQ) analysis using JMP Clinical was performed by this medical reviewer. Treatment emergent AEs that occurred in ≥5% of subjects in either lonapegsomatropin-tcgd or Genotropin groups are listed in Table 40, in the order of frequency of occurrence in the total study population. TEAEs that occurred at <5% frequency but are a known class effect of GH therapy included administration site reactions, that were present in 2 (1.9%) subjects in lonapegsomatropin-tcgd group and 2 (3.6%) subjects in Genotropin group.

Table 40: TEAEs with **≥5%** incidence in either lonapegsomatropin-tcgd or Genotropin groups during trial CT-301, arranged by incidence in total study population

Treatment Emergent Adverse Event	Lonapegsomatropin-tcgd	Genotropin (N = 56)	TOTAL (N= 161)

	(N = 105) n (%)	n (%)	n (%)
Any TEAE	81 (77.1%)	39 (69.6%)	120 (74.5%)
Infection, all	56 (53.3%)	32 (57.1%)	88 (54.7%)
Upper respiratory tract infection, combined term[a]	41 (39%)	24 (42.9%)	65 (40.4%)
Pyrexia	16 (15.2%)	5 (8.9%)	21 (13%)
Headache	13 (12.4%)	8 (14.3%)	21 (13%)
Diarrhea, infectious enteritis, and gastroenteritis	12 (11.4%)	7 (12.5%)	19 (11.8%)
Cough	11 (10.5%)	4 (7.1%)	15 (9.3%)
Nausea, vomiting	11 (10.5%)	4 (7.1%)	15 (9.3%)
Hypothyroidism	8 (7.6%)	5 (8.9%)	13 (8.1%)
Allergic reaction, combined term[b]	6 (5.7%)	4 (7.1%)	10 (6.2%)
Diarrhoea	6 (5.7%)	3 (5.4%)	9 (5.6%)
Haemorrhage	7 (6.7%)	1 (1.8%)	8 (5%)
Abdominal pain	6 (5.7%)	2 (3.6%)	8 (5%)
Rash	5 (4.8%)	3 (5.4%)	8 (5%)
Arthralgia and arthritis	6 (5.7%)	1 (1.8%)	7 (4.3%)

N = total number of subjects in each treatment group. n = number of subjects experiencing the event, (%) = proportion of subjects experiencing the event.
TEAEs that are in Bold are known class effects
[a]Upper respiratory tract infection combined term includes upper respiratory infection, influenza like illness, laryngitis, nasopharyngitis, pharyngitis, pharyngotonsillitis, rhinitis, sinusitis, and tonsillitis.
[b]Allergic reactions combined term includes allergic conjunctivitis, allergic dermatitis, facial edema, hypersensitivity, injection site atrophy, laryngospasm, lip swelling and urticaria.
Source: FMQ analysis conducted using JMP clinical, medical reviewer generated report.

Same JMP clinical analysis was used to sort the TEAEs by delta risk (i.e. incidence in lonapegsomatropin-tcgd group – incidence in Genotropin group). TEAEs that occurred in ≥5% of subjects and more frequently in the lonapegsomatropin-tcgd group, when compared to Genotropin included: pyrexia (15.2% vs. 8.9%), hemorrhage (6.7% vs. 1.8%), viral infection (15.2% vs. 10.7%), arthralgia and arthritis (5.7% vs. 1.8%), cough (10.5% vs. 7.1%), nausea and vomiting (10.5% vs. 7.1%) abdominal pain (5.7% vs 3.6%), and diarrhea (5.7% vs. 5.4%). Refer to Table 41. Of these, arthralgia is associated with GH treatment, and remaining TEAEs are discussed further below.

Table 41: TEAEs by Preferred Term occurring in at least 5% of subjects, and occurring more frequently in lonapegsomatropin-tcgd group compared to Genotropin group during trial CT-301, sorted by delta risk

	Lonapegsomatropin-tcgd (N = 105) n (%)	Genotropin (N =56) n (%)	D risk (%)	**RR; 95% CI**
Any AE	81 (77.1%)	39 (69.6%)	7.5	1.1 (0.9, 1.4)
Pyrexia	16 (15.2%)	5 (8.9%)	6.3	1.7 (0.7, 4.4)
Hemorrhage	7 (6.7%)	1 (1.8%)	4.9	3.7 (0.5, 29.6)
Infection, viral	16 (15.2%)	6 (10.7%)	4.5	1.4 (0.6, 3.4)
Arthralgia and arthritis	6 (5.7%)	1 (1.8%)	3.9	3.2 (0.4, 25.9)
Cough	11 (10.5%)	4 (7.1%)	3.3	1.5 (0.5, 4.4)
Nausea and vomiting	11 (10.5%)	4 (7.1%)	3.3	1.5 (0.5, 4.4)
Abdominal pain	6 (5.7%)	2 (3.6%)	2.1	1.6 (0.3, 7.7)
Diarrhoea	6 (5.7%)	3 (5.4%)	0.4	1.1 (0.3, 4.1)

N = total number of subjects in each treatment group. n = number of subjects experiencing the event, (%) = proportion of subjects experiencing the event.
In bold are AEs that are known to be associated with GH drug class
[a]Gastrointestinal events combined term includes abdominal pain, constipation, diarrhea, dyspepsia, nausea, and vomiting
Source: JMP clinical, medical reviewer generated report.

Medical reviewer's comments:
The AEs by preferred terms that were more frequent in the lonapegsomatropin-tcgd group when compared to Genotropin group, and are not a known class effect of GH therapy are discussed below:

- *Gastrointestinal events: according to the FMQ analysis conducted by this medical reviewer, gastrointestinal adverse events including abdominal pain, constipation, diarrhea, dyspepsia, nausea, and vomiting were present in 26 (24.8%) subjects in lonapegsomatropin-tcgd group compared to 10 (17.9%) subjects in Genotropin group. Additionally, each of the individual adverse events was more frequent in the lonapegsomatropin-tcgd group compared to Genotropin group as follows: abdominal pain 5.7% vs. 3.6%, constipation 2.9% vs. 0%, diarrhea 5.7% vs. 5.4%, dyspepsia, nausea and vomiting 12.4% vs. 7.1%. All of these events were mild and lasted for 1 to 7 days, except for one subject who had symptoms that started on day 16, were ongoing at the end of the trial, and were thought to be possibly related to treatment drug by the Investigator. Overall, the higher rate of GI AEs associated with treatment with lonapegsomatropin-tcgd is not clear. But more importantly, these all adverse events were mild, resolved with or without treatment adjustment and can be monitored and treated as needed.*

- *Pyrexia: Pyrexia was reported by 16 (15.2%) subjects in lonapegsomatropin-tcgd group and 5 (8.9%) subjects in Genotropin group. Overall, the etiology of pyrexia is unclear. A*

total of 3 (60%) subjects in Genotropin group and 10 (62.5%) subjects in the lonapegsomatropin-tcgd group experienced pyrexia without any concomitant infection. Out of the 10 subjects in lonapegsomatropin-tcgd group who had pyrexia without any concomitant infection, the onset of pyrexia was within 3 to 104 days of starting treatment for 7 subjects. Additionally, 2 subjects who experienced pyrexia at day 259 and 260 of treatment, respectively, were positive for anti-lonapegsomatropin-tcgd antibodies. All events were mild and resolved. In general, pyrexia is commonly seen in this age group. However, a relationship between lonapegsomatropin-tcgd and pyrexia cannot be completely ruled out.

- *Hemorrhage: Hemorrhage was reported by 7 (6.7%) subjects in lonapegsomatropin-tcgd group and 1 (1.8%) subject in Genotropin group. In the Genotropin group, the etiology was epistaxis, whereas in the lonapegsomatropin-tcgd group, the etiologies of hemorrhage were epistaxis (3), contusion (2), petechiae (1) and eye hemorrhage (1). Additionally, in 3 subjects, hemorrhage was related to either a fall (1 subject with contusion) or concurrent infection (2 subjects with epistaxis), where as in 4 (3.8%) subjects, hemorrhage was unexplained. None of these subjects had abnormal platelets (coagulation markers were not tested during this trial). These events were of either mild (5) or moderate (2) severity, did not require any changes to the study drug dose, and based on the etiology, were unlikely to be related to the study drug.*

- *Infection, viral: Rate of viral infections was greater in the lonapegsomatropin-tcgd group (16 [15.2%] subjects vs 6 [10.7%] subjects). However, infections may be more common in pediatric subjects in general, and concomitant leukopenia was only present in 4 (25%) of these subjects. The observed imbalance between the groups can also be due to the fact that more subjects were treated with lonapegsomatropin-tcgd compared to Genotropin.*

- *Cough: Cough was reported in 11(10.5%) of subjects in the lonapegsomatropin-tcgd group, compared to 4 (7.1%) of subjects in Genotropin group. All events were mild and resolved without additional treatment. The reason for the observed imbalance in the frequency in this AE is unclear.*

8.4.6. Laboratory Findings

Given trial CT-301 was the only trial with an active comparator, data obtained from this trial were used to review the laboratory findings associated with lonapegsomatropin-tcgd. Data from CT-302 and CT-301EXT were used as supportive data when indicated. Data were analyzed by this reviewer using the tables provided by the Applicant, and also by performing own analysis using JMP Clinical when indicated.

Glycemic control

Decreased insulin sensitivity and glucose metabolism due to GH related insulin antagonistic effects in liver and other tissues is a known class effect of rhGH formulations. Glucose, insulin, and hemoglobin A1c levels were thus monitored at regular intervals during the trials.

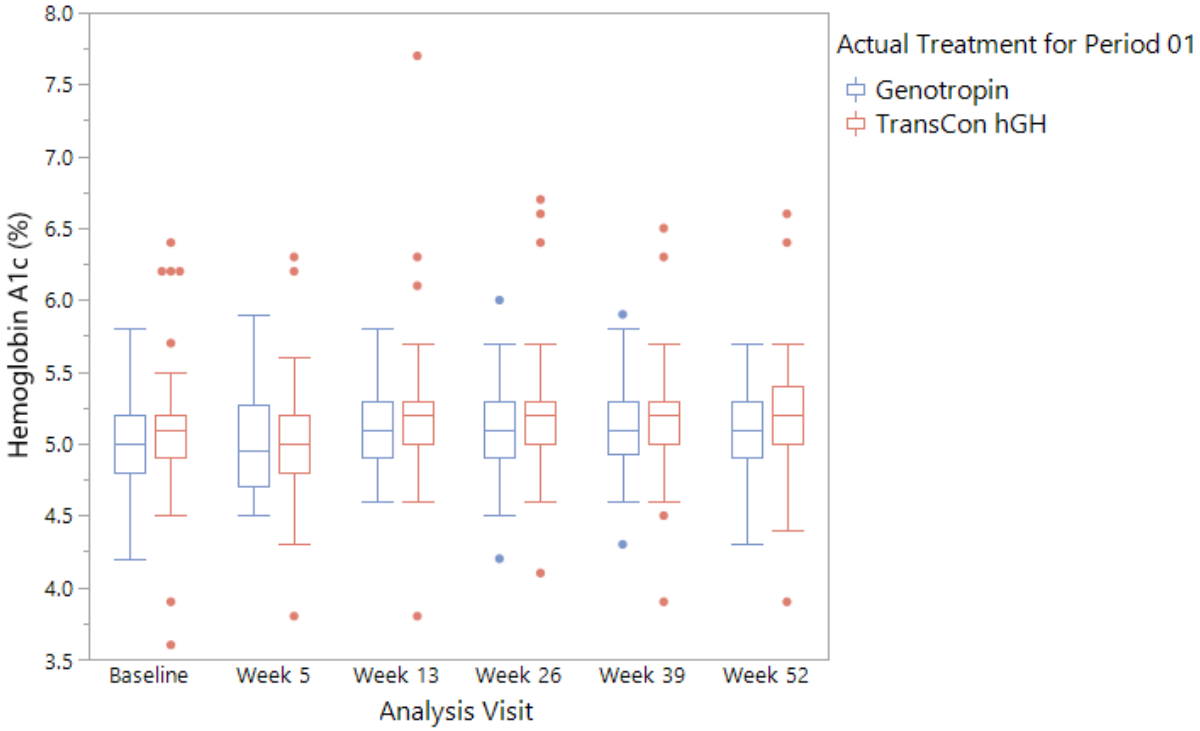
During trial CT-301, the mean glucose, insulin and hemoglobin A1c values remained stable from baseline in both lonapegsomatropin-tcgd and Genotropin treatment groups (Table 42 and Figure 12). Similarly, the number of subjects who shifted from normal to high glucose levels were similar in both groups at Week 52 (Table 43). Even though a greater number of subjects in lonapegsomatropin-tcgd group shifted from normal to high insulin levels at Week 39 (14.7% vs. 3.7%), a similar rate of shift from normal to high glucose levels was not observed at Week 39 (6.9% vs 3.6%). Additionally, this difference in shift from normal to high insulin levels was smaller at Week 52 (3.9% vs. 0%) and may thus be a transient effect.

Table 42: Glycemic status during trial CT-301

Variable Visit	Lonapegsomatropin (N=105)		Genotropin (N=56)	
	Absolute Value	Change from Baseline	Absolute Value	Change from Baseline
Hemoglobin A1c (%)				
Baseline, n	105	—	56	—
Mean (SD)	5.05 (0.32)	—	5.00 (0.33)	—
Week 13, n	104	104	55	55
Mean (SD)	5.18 (0.40)	0.13 (0.35)	5.12 (0.29)	0.12 (0.28)
Week 26, n	104	104	56	56
Mean (SD)	5.20 (0.32)	0.14 (0.24)	5.11 (0.32)	0.11 (0.27)
Week 52, n	104	104	54	54
Mean (SD)	5.19 (0.34)	0.13 (0.26)	5.11 (0.28)	0.11 (0.25)
Glucose (mg/dL)				
Baseline, n	104	—	56	—
Mean (SD)	87.1 (9.7)	—	88.9 (9.2)	—
Week 13, n	103	103	55	55
Mean (SD)	94.3 (9.6)	7.2 (10.9)	91.1 (15.9)	1.9 (15.8)
Week 26, n	103	103	56	56
Mean (SD)	92.7 (9.3)	5.8 (10.0)	89.4 (8.3)	0.5 (9.6)
Week 52, n	103	103	54	54
Mean (SD)	87.9 (8.2)	1.0 (9.9)	91.0 (9.1)	2.1 (10.4)
Insulin (mIU/L)				
Baseline, n	105	—	56	—
Mean (SD)	3.60 (3.64)	—	3.80 (2.26)	—
Week 13, n	102	102	55	55
Mean (SD)	9.75 (10.71)	6.16 (11.12)	8.94 (12.00)	5.10 (12.02)
Week 26, n	102	102	56	56
Mean (SD)	8.02 (5.75)	4.68 (5.49)	5.54 (3.31)	1.74 (3.00)
Week 52, n	103	103	53	53
Mean (SD)	5.54 (6.13)	2.23 (6.11)	5.97 (3.19)	2.13 (3.28)

Source: Summary of Clinical Safety, page 81

Figure 12: Distribution of average Hemoglobin A1c over 52 weeks by treatment group



Source: JMP clinical, medical reviewer generated graph.

Table 43: Shift in assessments of glucose metabolism compared to baseline in subjects with normal levels at baseline.

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	N	n (%)	N	n (%)
Hemoglobin A1c (%) elevation				
Week 5	104	0 (0%)	56	0 (0%)
Week 13	104	1 (1%)	55	0 (0%)
Week 26	104	0 (0%)	56	0 (0%)
Week 39	104	0 (0%)	56	0 (0%)
Week 52	104	0 (0%)	54	0 (0%)
Glucose (mmol/L) elevation				
Week 5	102	5 (4.9%)	55	3 (5.5%)
Week 13	103	5 (4.9%)	55	2 (3.6%)
Week 26	103	6 (5.8%)	56	0 (0%)
Week 39	102	7 (6.9%)	56	2 (3.6%)
Week 52	103	2 (1.9%)	54	1 (1.9%)
Insulin (pmol/L) elevation				
Week 5	104	2 (1.9%)	54	3 (5.6%)

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
Week 13	102	5 (4.9%)	55	2 (3.6%)
Week 26	102	3 (2.9%)	56	0 (0%)
Week 39	102	15 (14.7%)	54	2 (3.7%)
Week 52	103	4 (3.9%)	53	0 (0%)
Insulin (pmol/L) reduction				
Week 5	104	16 (15.4%)	54	1 (1.9%)
Week 13	102	2 (2%)	55	3 (5.5%)
Week 26	102	3 (2.9%)	56	1 (1.8%)
Week 39	102	0 (0%)	54	1 (1.9%)
Week 52	103	5 (4.9%)	53	0 (0%)

N = total number of subjects with non-missing value at given visit, n = number of subjects with laboratory abnormality, (%) = proportion of subjects experiencing the event.
Source: derived from various tables submitted by the Applicant

None of the subjects shifted from normal to high hemoglobin A1c. Three subjects, all on lonapegsomatropin-tcgd, experienced hemoglobin A1c levels >6.1% during the trial CT-301. Two of these subjects, had elevated hemoglobin A1c levels at baseline, and during the trial, hemoglobin A1c levels increased from 6.2% to 6.4% in one subject and from 6.4% to 6.7% in second subject. Third subject had a normal hemoglobin A1c level of 5.1% at baseline and was found to have an elevation to 7.7% on study day 85. However, this was likely a laboratory error given the glucose level assessed on the same day was normal, and hemoglobin A1c repeated 1 week later was 5%.

There were 2 subjects with an elevated hemoglobin A1c level at baseline, and the levels remained stable throughout the trial for both these subjects.

> *Medical reviewer's comments: Overall, the mean fasting plasma glucose and Hemoglobin A1c levels were stable, changes were small and of unknown clinical significance. No hyperglycemia symptoms were reported in any of subjects. None of the subjects had a shift from normal to elevated Hemoglobin A1c levels, and the 2 subjects who were found to have a persistently elevated hemoglobin A1c level had an elevated level at baseline as well.*

IGF-1 Levels

Prolonged exposures to elevated IGF-1 levels are a potential safety concern. IGF-1 levels were thus monitored throughout the clinical program of lonapegsomatropin-tcgd.

Trial CT-301:

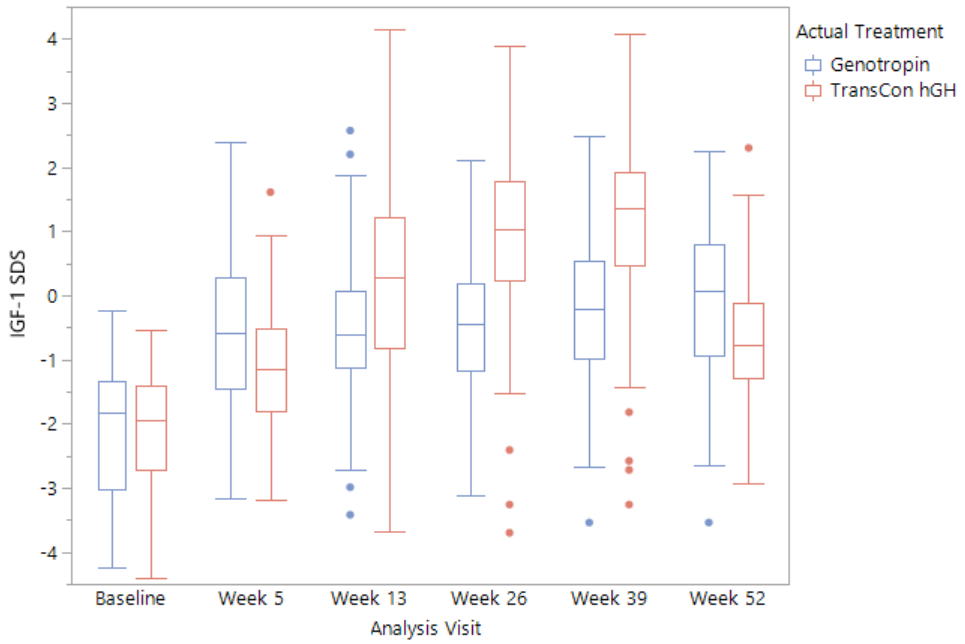
During the trial CT-301, the mean IGF-1 SDS was within reference range (-2 ≤ SDS ≤ +2) in both lonapegsomatropin-tcgd and Genotropin groups throughout the 52 weeks (Table 44 and Figure 13)

Table 44: Average IGF-1 SDS by visit

Visit	Lonapegsomatropin LS Mean (SE) [95% CI] N=105	Genotropin LS Mean (SE) [95% CI] N=56	Estimate of Difference[a] in LS Means (SE) [95% CI]	*P* Value
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]	<0.0001
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]	<0.0001
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]	<0.0001
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]	<0.0001

Source: Clinical Study Report for Study CT-301, page 91

Figure 13: Distribution of average IGF-1 SDS over 52 weeks by treatment group



Source: JMP clinical, medical reviewer generated graph.

At any given point during the 52 weeks of the trial, there were 37 (35.2%) subjects in lonapegsomatropin-tcgd group, compared to 2 (3.6%) subjects in Genotropin group, that experienced IGF-1 level > +2 SDS. To further evaluate if the elevation in IGF-1 levels were associated with adverse events, the AEs reported by subjects in the lonapegsomatropin-tcgd group when IGF-1 was > +2 SDS were reviewed in detail. Out of the 37 subjects who experienced an elevation in IGF-1 of >+2 SDS, 25 (67.6%) did not experience any concurrent AEs. Adverse events experienced by more than 1 subject in the setting of elevated IGF-1 of > +2 SDS were iron deficiency anemia (2 subjects, 5.4%) and secondary hypothyroidism (2 subjects, 5.4%) and were most likely not related to the elevated IGF-1 levels. These rates were similar to the rates observed in all subjects during this trial (Table 45).

Table 45: Adverse events experienced by subjects in the lonapegsomatropin-tcgd group, in the setting of IGF-1 SDS >+2, compared to all subjects during the 52 weeks of trial CT-301

Preferred term	Subjects on lonapegsomatropin-tcgd with IGF-1 SDS >+2 (N = 37) n (%)
Any Adverse Event	12 (32.4%)
Secondary hypothyroidism	2 (5.4%)
Iron deficiency anemia	2 (5.4%)
Nasopharyngitis	1 (2.7%)
Headache	1 (2.7%)
Cough	1 (2.7%)
Arthralgia/Pain in extremity	1 (2.7%)
Seasonal allergy	1 (2.7%)
Skin papilloma	1 (2.7%)
Increased eosinophil count	1 (2.7%)
Tachycardia	1 (2.7%)
Molluscum contagiosum	1 (2.7%)

Table derived by medical reviewer after reviewing the list adverse events experienced by subjects when their IGF-1 SDS level was >+2
In bold are AEs that are known to be associated with GH drug class

Given the IGF-1 levels were measured as trough levels at Weeks 5 and 52, and as peak levels at Weeks 13, 26, and 39 for subjects in the lonapegsomatropin-tcgd group, the Applicant used a nonlinear population PD model to obtain average IGF-1 SDS values over one week in these subjects. In contrast, a similar model was not used for subjects in Genotropin group as the IGF-1 levels were measured at any time during the week for these subjects.

When IGF-1 measurements were assessed as average IGF-1 over 1 week based on the Applicant's nonlinear population PD model, a total of 8 (7.6%) subjects in lonapegsomatropin-tcgd arm and 2 (3.6%) subjects in Genotropin arm had an IGF-1 level > +2 SDS at any point during the trial, with the level just above the upper limit of +2 for majority of these subjects. Additionally, IGF-1 level averaged over 1 week > +2 SDS for at least two consecutive visits was present in 3 (2.9%) subjects in lonapegsomatropin-tcgd arm and 1 (1.8%) subject in Genotropin arm. All these eight subjects in the lonapegsomatropin-tcgd group had undergone a dose increase based on weight bracket during the prior visit. All subjects were asymptomatic or experienced AEs not related to elevated IGF-1 levels (nasopharyngitis, cough, tachycardia) and none experienced any adverse event that could be attributed to elevated IGF-1 levels.

Trial CT-302:
The proportion of subjects with IGF-1 SDS value >2 increased from 21.9% at baseline to 38.7% at Week 26, and the proportion of subjects with IGF-1 SDS value >3 increased from 3.4% at baseline to 15.5% at Week 26. There was a persistent increase in these values through the trial (Table 46). At any given point during the trial, 56.8% and 25.3% of subjects had IGF-1 values >2 and >3, respectively (Table 47).

Table 46: Serum IGF-1 SDS categories by visit

IGF-1 SDS Category	Baseline (N=146) n (%)	Week 13 (N=144) n (%)	Week 26 (N=142) n (%)
<-2.0	0	0	1 (0.7)
≥-2.0 and ≤0	40 (27.4)	18 (12.5)	12 (8.5)
≥0 and ≤2.0	74 (50.7)	71 (49.3)	74 (52.1)
>2.0	32 (21.9)	55 (38.2)	55 (38.7)
>2.0 but not at Baseline	—	31 (21.5)	34 (23.9)
>3.0	5 (3.4)	17 (11.8)	22 (15.5)
>3.0 but not at Baseline	—	15 (10.4)	21 (14.8)

Source: Clinical Study Report for CT-302, page 65

Table 47: Proportion of subjects with serum IGF-1 SDS >+2 and >+3

IGF-1 SDS Category	Total (N=146) n (%)
>2.0	83 (56.8)
>2.0 at both Weeks 13 and 26 but not at baseline	15 (10.3)
>3.0	37 (25.3)
>3.0 at both Weeks 13 and 26 but not at baseline	7 (4.8)

Source: Clinical Study Report for CT-302, page 65

Cumulative phase 3 program:
At any point during the phase 3 program, there were a total of 202 subjects who experienced IGF-1 > +2 SDS. Of these, 79 (39%) subjects experienced adverse event(s) at the time of elevated IGF-1 levels. According to the Applicant's analysis, adverse events occurred at a similar rate in subjects with IGF-1 >+2 SDS compared to subjects with IGF-1 < +2 SDS, with the exception of SOC of metabolism and nutritional disorders (6 subjects vs. 0 subjects, respectively) and preferred terms hyperglycemia (1), iron deficiency (1), dehydration (1) and vitamin D deficiency (3).

Medical reviewer's comments:
Overall, IGF-1 levels above the normal range of +2 SDS were not associated with an increased risk of adverse events. In trial CT-301, treatment with lonapegsomatropin-tcgd was associated with a greater rate of elevation in IGF-1 SDS compared to treatment with Genotropin (35.2% vs. 3.6%). However, when a population-based PD model was used in the lonapegsomatropin-tcgd group to obtain the average IGF-1 SDS value over one week, majority of these levels were found to be within the normal range of <+2, and the difference between the two groups was smaller (7.6% vs. 3.6%). All 8 subjects in lonapegsomatropin-tcgd group who had an elevated IGF-1 level averaged over one week had undergone a dose increase based on weight bracket during the prior visit, and none of these subjects experienced any adverse event that could be attributed to elevated IGF-1 levels.

Phosphate Levels
Treatment with GH therapy is associated with phosphate retention. Phosphate levels were thus monitored throughout the trial CT-301.

An increase in phosphate levels from baseline was observed in both treatment groups. Even though the mean change from baseline was comparable between both the treatment groups at Week 52 (Table 48), a greater number of subjects in the lonapegsomatropin-tcgd group presented with elevated phosphate levels throughout the trial (Table 49, Table 50 and Figure 14).

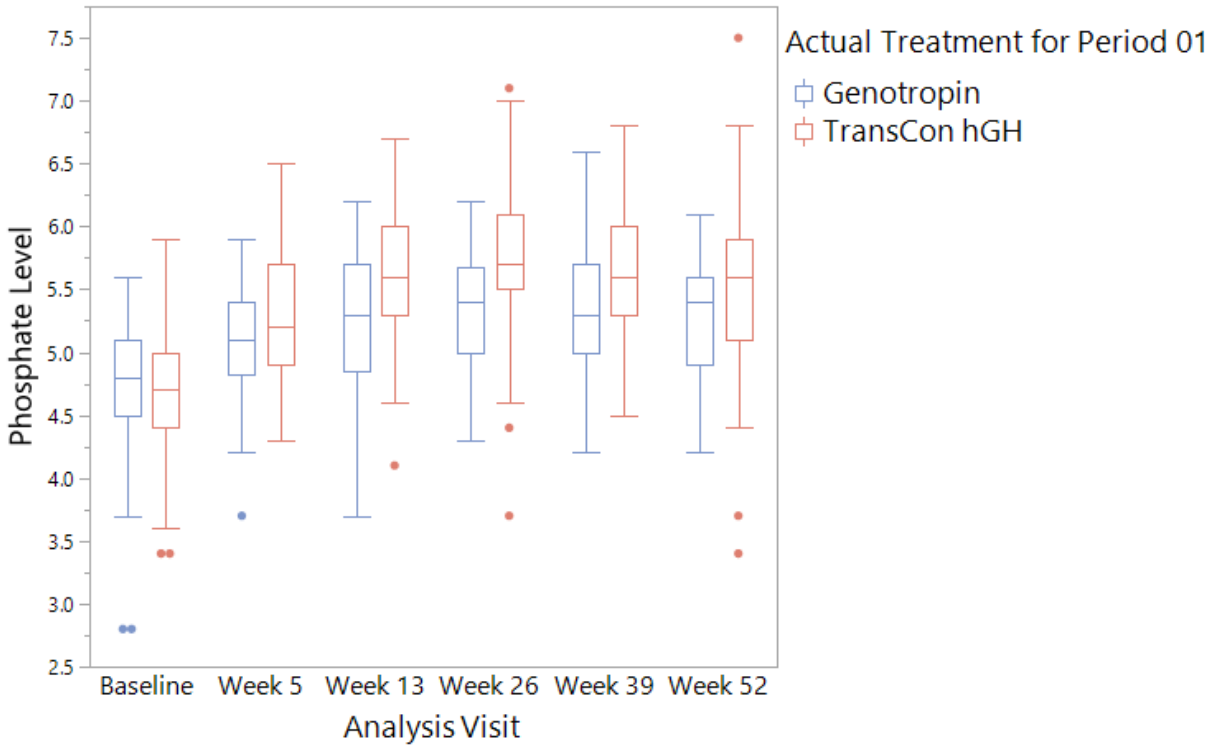
Table 48: Mean Alkaline Phosphate and Phosphate levels throughout the trial CT-301

	Lonapegsomatropin-tcgd		Genotropin	
	Mean Value	Change from Baseline	Mean Value	Change from Baseline
Phosphate (mg/dL)				
Baseline	4.67		4.72	
Week 5	5.31	0.64	5.09	0.37
Week 13	5.62	0.94	5.28	0.56
Week 26	5.77	1.1	5.32	0.6

	Lonapegsomatropin-tcgd		Genotropin	
Week 39	5.63	0.96	5.32	0.6
Week 52	5.52	0.85	5.31	0.61

Source: derived from various tables submitted by the Applicant

Figure 14: Comparison of Phosphate levels at various visits during trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Of note, a higher percentage of subjects shifted from normal to elevated phosphate levels in the lonapegsomatropin-tcgd group compared to Genotropin group throughout the trial (Table 49).

Table 49: Shift in phosphate levels from normal levels at baseline to elevated levels throughout the trial CT-301

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	N	n (%)	N	n (%)
Phosphate elevation				
Week 5	105	25 (23.8%)	56	6 (10.7%)
Week 13	105	49 (46.7%)	56	16 (28.6%)
Week 26	104	61 (58.7%)	56	14 (25%)
Week 39	104	54 (51.9%)	56	14 (25%)

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
Week 52	104	46 (44.2%)	53	16 (30.2%)

N = total number of subjects with non-missing value at given visit, n = number of subjects with laboratory abnormality, (%) = proportion of subjects experiencing the laboratory abnormality.
Source: derived from various tables submitted by the Applicant

Additionally, the number of subjects with normal or low phosphate level at baseline, but at least 1 elevated phosphate level post baseline was higher in the lonapegsomatropin-tcgd group (89 [86.4%] subjects), compared to Genotropin group (33 [60%]). In the lonapegsomatropin-tcgd group, 43 (41.7%) subjects had elevated phosphate levels more than 50% of the times being tested (≥3/5 post baseline visits). Refer to Table 50.

Table 50: Number of post baseline visits with elevated phosphate levels in subjects with normal or low levels at baseline

	Lonapegsomatropin-tcgd (N = 103)	Genotropin (N=55)
All normal readings	14 (13.6%)	22 (40%)
1 elevated reading	20 (19.4%)	13 (23.6%)
2 elevated readings	26 (25.2%)	12 (21.8%)
3 elevated readings	13 (12.6%)	4 (7.2%)
4 elevated readings	25 (24.3%)	2 (3.6%)
5 elevated readings	5 (4.9%)	2 (3.6%)

Source: JMP clinical, medical reviewer generated report.

Medical reviewer's comments:
Treatment with lonapegsomatropin-tcgd was associated with a greater degree and rate of phosphate elevation. Moreover, 86.4% of subjects in lonapegsomatropin-tcgd group had phosphate elevation for >50% of the times they were tested, compared to 14.5% of subjects in Genotropin group. Change in phosphate is known rhGH class adverse event and should thus be labeled under Sections 5.0 and 6.0 Adverse Reactions, for healthcare providers' awareness.

Alkaline Phosphate Levels

GH therapy associated increased skeletal growth can lead to elevated alkaline phosphate. Alkaline phosphate levels were thus monitored throughout the trial CT-301.

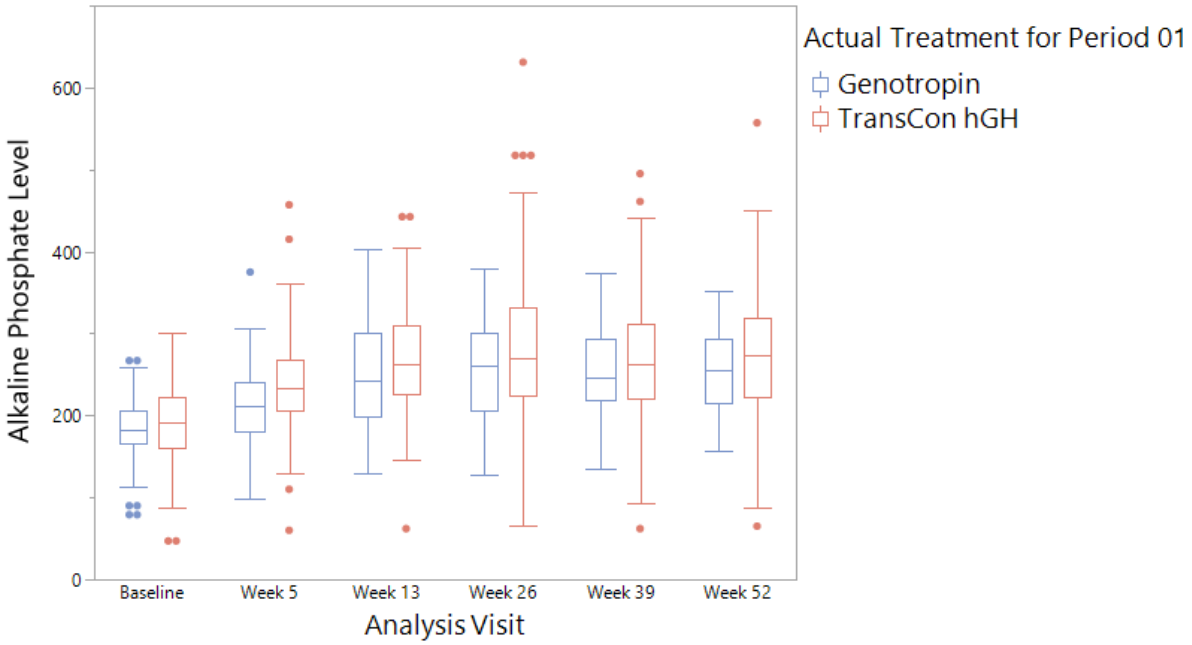
An increase in alkaline phosphate levels from baseline was observed in both treatment groups, and the mean change from baseline was comparable between both the treatment groups at Week 52 (Table 51 and Figure 15).

Table 51: Mean Alkaline Phosphate and Phosphate levels throughout the trial CT-301

	Lonapegsomatropin-tcgd		Genotropin	
	Mean Value	Change from Baseline	Mean Value	Change from Baseline
Alkaline Phosphatase (U/L)				
Baseline	210.2		181.7	
Week 5	240	29.8	210.5	28.9
Week 13	269.3	59	252.6	70.9
Week 26	281.6	71.2	257.6	75.9
Week 39	268.9	58.5	254.1	72.5
Week 52	273.3	62.9	249.6	68.9

Source: derived from various tables submitted by the Applicant

Figure 15: Comparison of Alkaline Phosphate levels at various visits during trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Of note, a higher percentage of subjects shifted from normal to elevated alkaline phosphate levels in the lonapegsomatropin-tcgd group compared to Genotropin group throughout the trial (Table 52).

Table 52: Shift in alkaline phosphate levels from normal levels at baseline to elevated levels throughout the trial CT-301

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	N	n (%)	N	n (%)
Alkaline Phosphatase				
Week 5	105	7 (6.7%)	56	1(1.8%)
Week 13	105	20 (19%)	56	8 (14.3%)
Week 26	104	22 (21.2%)	56	7 (12.5%)
Week 39	104	18 (17.3%)	56	6 (10.7%)
Week 52	104	20 (19.2%)	53	5 (9.4%)

N = total number of subjects with non-missing value at given visit, n = number of subjects with laboratory abnormality, (%) = proportion of subjects experiencing the event.
Source: derived from various tables submitted by the Applicant

Additionally, the number of subjects with normal or low alkaline phosphate level at baseline, but at least 1 elevated alkaline phosphate level post baseline was higher in the lonapegsomatropin-tcgd group (38 [36.5%] subjects), compared to Genotropin group (13 [23.2%]). In the lonapegsomatropin-tcgd group, 16 (15.4%) subjects had elevated phosphate levels more than 50% of the times being tested (≥3/5 post baseline visits). Refer to Table 53.

Table 53: Number of post baseline visits with elevated alkaline phosphate levels in subjects with normal or low levels at baseline

	Lonapegsomatropin-tcgd (N = 104)	Genotropin (N=56)
High at baseline	1	0
All normal readings	66 (63.5%)	43 (76.8%)
1 elevated reading	11 (10.6%)	6 (10.7%)
2 elevated readings	11 (10.6%)	3 (5.4%)
3 elevated readings	6 (5.8%)	2 (3.6%)
4 elevated readings	6 (5.8%)	1 (1.8%)
5 elevated readings	4 (3.8%)	1 (1.8%)

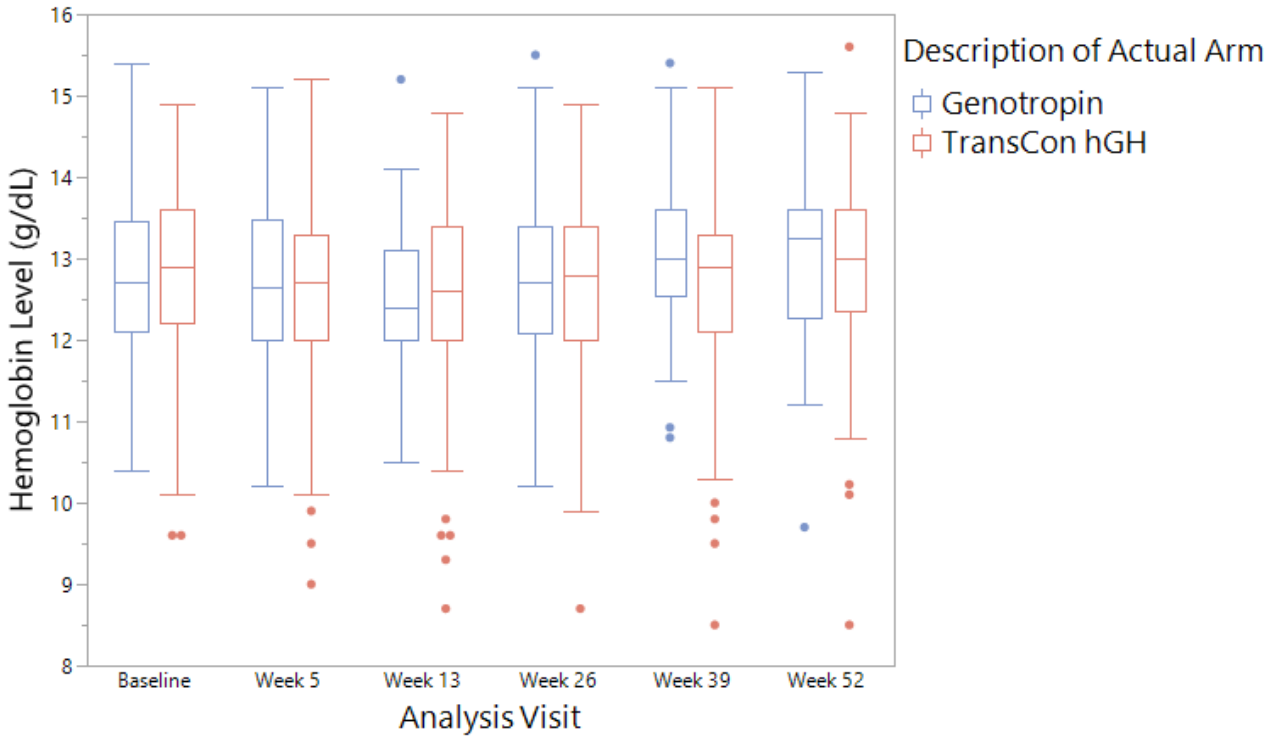
Source: JMP clinical, medical reviewer generated report.

Medical reviewer's comments:
Treatment with lonapegsomatropin-tcgd was associated with a greater degree and rate of alkaline phosphate elevation. Moreover, 15.4% of subjects in lonapegsomatropin-tcgd group had alkaline phosphate elevation for >50% of the times they were tested, compared to 7.1% of subjects in Genotropin group. Change in alkaline phosphate are known adverse event associated with all rhGH products and should be labeled event under Sections 5.0 and 6.0 Adverse Reactions, for healthcare providers' awareness.

Hematology parameters

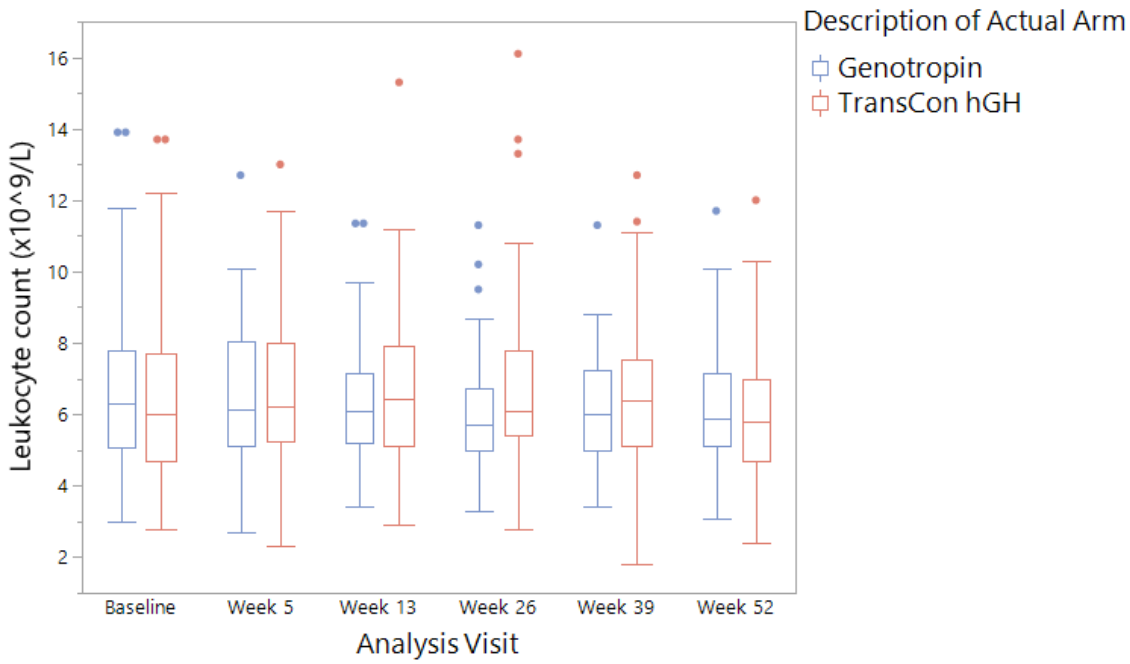
No clinically significant changes in mean hemoglobin, leukocyte, and platelet levels from baseline to end of the trial (Week 52) were observed in either treatment groups. Refer to Figure 16, Figure 17 and Figure 18.

Figure 16: Comparison of Hemoglobin levels at various visits during trial CT-301



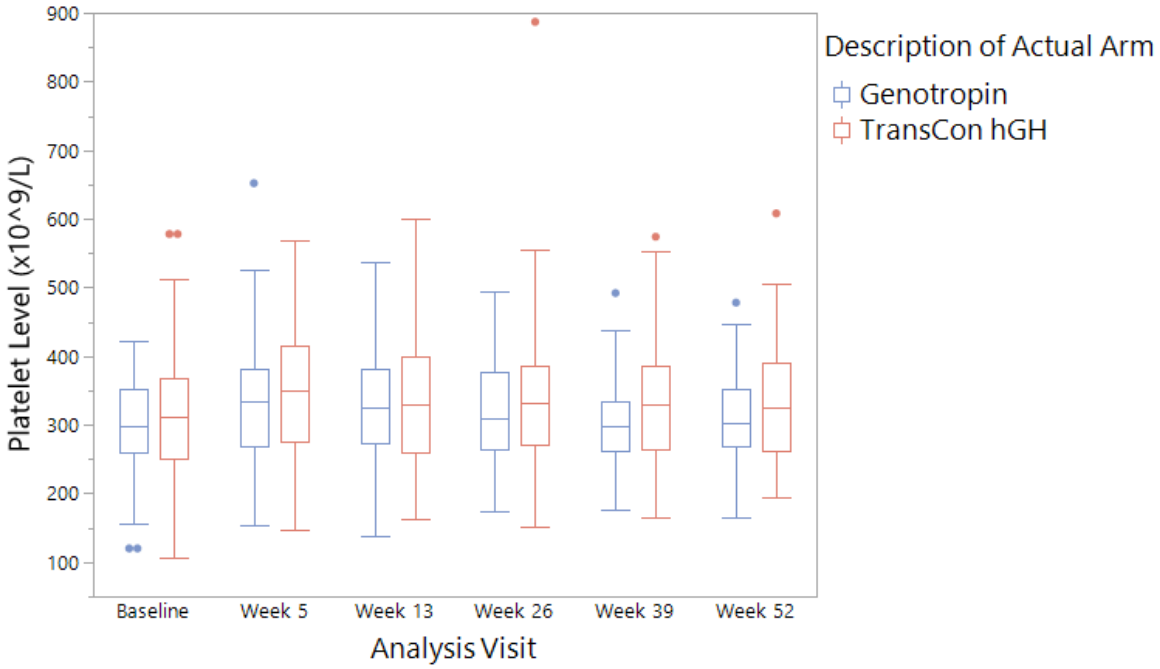
Source: JMP clinical, medical reviewer generated graph.

Figure 17: Comparison of Leukocyte levels at various visits during trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Figure 18: Comparison of Platelet levels at various visits during trial CT-301



Source: JMP clinical, medical reviewer generated graph.

A shift from normal to high hemoglobin levels from baseline to Week 52 was not seen in any of the subjects in either treatment groups. The number of subjects who shifted from normal to low hemoglobin levels from baseline to Week 52 were similar between the two treatment groups as follows: lonapegsomatropin-tcgd: 4 (4.4%) subjects; Genotropin: 1 (1.9%) subject.

The number of subjects who shifted from normal to low leukocyte levels from baseline to Week 52 were as follows: lonapegsomatropin-tcgd: 10 (10.1%) subjects; Genotropin: 3 (5.8%). However, this rise was intermitted, without any gradual increase pattern, as at various other points during the trial, a greater number of subjects in the Genotropin group shifted from normal to low leukocyte. For example, the number of subjects who shifted from normal to low leukocyte levels from baseline to Week 39 were 4 (4.2%) in lonapegsomatropin-tcgd group and 5 (8.9%) in Genotropin group. Additionally, the number of subjects with normal leukocyte level at baseline, but at least 1 low leukocyte level post baseline was lower in the lonapegsomatropin-tcgd group (22 [25.9%] subjects), compared to Genotropin group (15 [32.6%]).

A shift from normal to low platelet levels was not observed during the trial. The number of subjects who shifted from normal to high platelet levels from baseline to Week 52 were similar between the two treatment groups as follows: lonapegsomatropin-tcgd: 6 (6.1%) subjects; Genotropin: 1 (1.9%).

Table 54: Number of subjects with a shift in hematology parameters from normal at baseline to abnormal at Week 52

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	N	n (%)	N	n (%)
Hemoglobin (shift to low)				
Week 52	100	4 (4%)	54	1 (1.9%)
Hemoglobin (shift to high)				
Week 52	100	0 (0%)	54	0 (0%)
Leukocyte ($x10^3$/microliter) (shift to low)				
Week 52	99	10 (10.1%)	52	3 (5.8%)
Platelet ($x10^9$/L) (shift to low)				
Week 52	99	0 (0%)	52	0 (0%)
Platelet ($x10^9$/L) (shift to high)				
Week 52	99	6 (6.1%)	52	1 (1.9%)

N = total number of subjects with non-missing value at given visit, n = number of subjects with laboratory abnormality, (%) = proportion of subjects experiencing the event.
Source: derived from various tables submitted by the Applicant

Table 55: Mean change from baseline in hematology parameters

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	Mean Value	Change from Baseline	Mean Value	Change from Baseline
Hemoglobin (g/dL)				
Baseline	12.82		12.8	
Week 52	12.89	0.06	12.96	0.16
Leukocyte ($x10^3$/microliter)				
Baseline	6.28		6.55	
Week 52	5.97	-0.4	6.28	-0.32
Platelets ($x10^9$/L)				
Baseline	315.7		301.4	
Week 52	331.4	13	310.6	10.1

Source: derived from various tables submitted by the Applicant

Table 56: Number of post baseline visits with low leukocyte levels in subjects with normal levels at baseline

	Lonapegsomatropin-tcgd (N = 85)	Genotropin (N=46)
All normal readings	63 (74.1%)	31 (67.4%)
1 low reading	13 (15.3%)	9 (19.6%)
2 low readings	6 (7.1%)	6 (13%)
3 low readings	2 (2.4%)	0 (0%)
4 low readings	1 (1.2%)	0 (0%)
5 low readings	0 (0%)	0 (0%)

Source: JMP clinical, medical reviewer generated report.

Medical reviewer's comments:
There were no clinically meaningful changes in any of the hematology parameters. Intermittent reduction in hemoglobin and leukocyte levels and intermitted increase in platelet levels occurred throughout the trial in both treatment groups, without any gradual pattern. The mean hemoglobin, leukocyte and platelet levels remained stable throughout the trial.

Lipid parameters

The mean values for various lipid parameters such as total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides remained within normal limits and were similar between both treatment groups. There was no significant pattern of shift from normal at baseline to high levels at Week 52 for various lipid parameters such as total cholesterol, LDL, and triglyceride levels.

The number of subjects who shifted from normal to high total cholesterol levels from baseline to Week 52 were as follows: lonapegsomatropin-tcgd 2 (1.9%) subjects and Genotropin 0 (0%) subjects.

The number of subjects who shifted from normal to high LDL cholesterol levels from baseline to Week 52 were as follows: lonapegsomatropin-tcgd 0 (0%) subjects and Genotropin 1 (1.9%) subjects.

The number of subjects who shifted from normal to high triglyceride levels from baseline to Week 52 were as follows: lonapegsomatropin-tcgd 3 (2.9%) subjects and Genotropin 4 (7.5%) subjects.

The number of subjects who shifted from normal to low HDL levels from baseline to Week 52 were as follows: lonapegsomatropin-tcgd 5 (4.8%) subjects and Genotropin 3 (5.7%) subjects.

Table 57: Number of subjects with a shift in lipid parameters from normal at baseline to abnormal at Week 52

Assessment endpoint	Lonapegsomatropin-tcgd		Genotropin	
	N	n (%)	N	n (%)
Total Cholesterol - shift to high				
Week 52	104	2 (1.9%)	53	0 (0%)
LDL (shift to high)				
Week 52	104	0 (0%)	53	1 (1.9%)
HDL (shift to low)				
Week 52	104	5 (4.8%)	53	3 (5.7%)
Triglycerides (shift to high)				
Week 52	104	3 (2.9%)	53	4 (7.5%)

N = total number of subjects with non-missing value at given visit, n = number of subjects with laboratory abnormality, (%) = proportion of subjects experiencing the event.
Source: derived from various tables submitted by the Applicant

Medical reviewer's comments:
There were no clinically meaningful changes in any of the lipid parameters. Intermittent elevations in total cholesterol, LDL and triglyceride levels occurred throughout the trial in both treatment groups, without any gradual pattern. Treatment with lonapegsomatropin-tcgd was not associated with a greater elevation of different lipid parameters when compared to Genotropin.

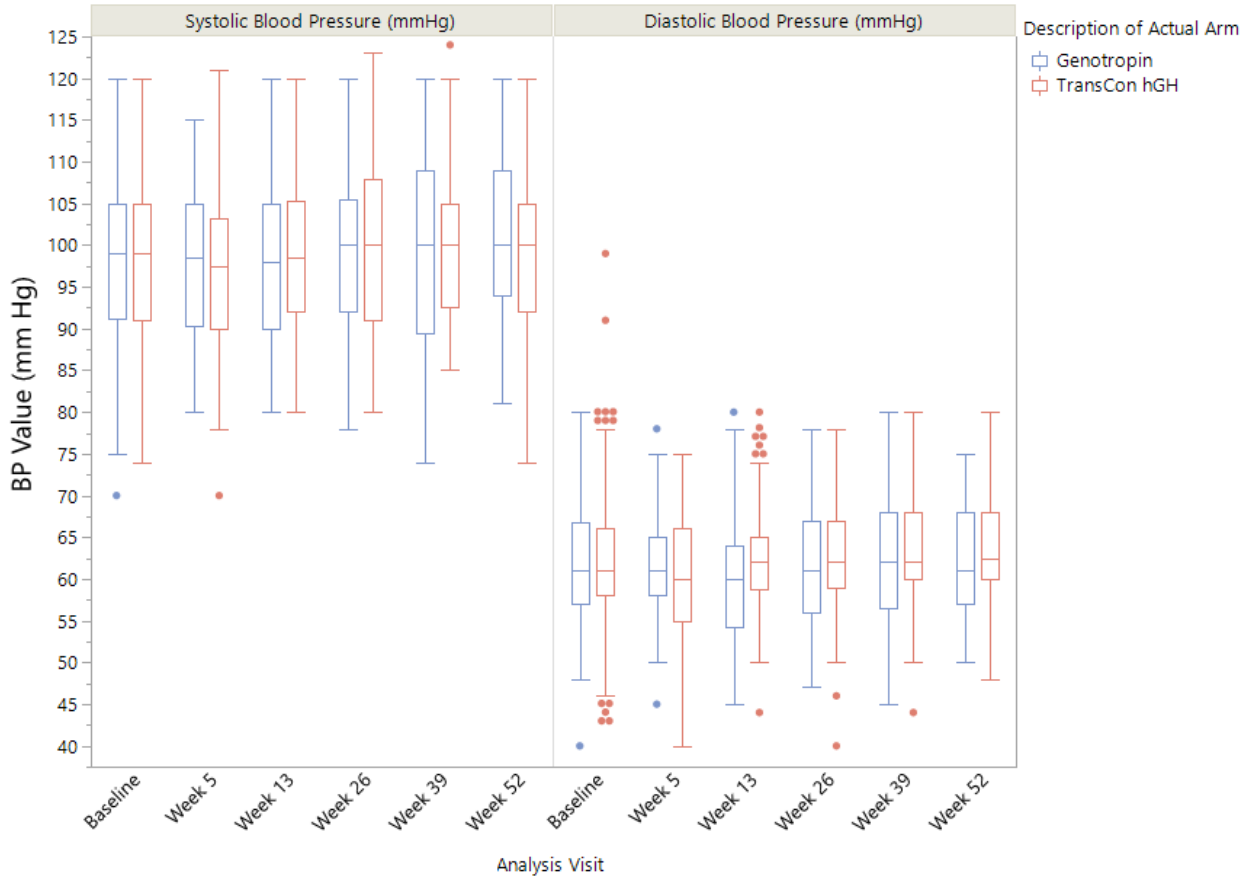
8.4.7. Vital Signs

Vital signs were assessed by this medical reviewer, by analyzing the data from trial CT-301, using

JMP Clinical software.

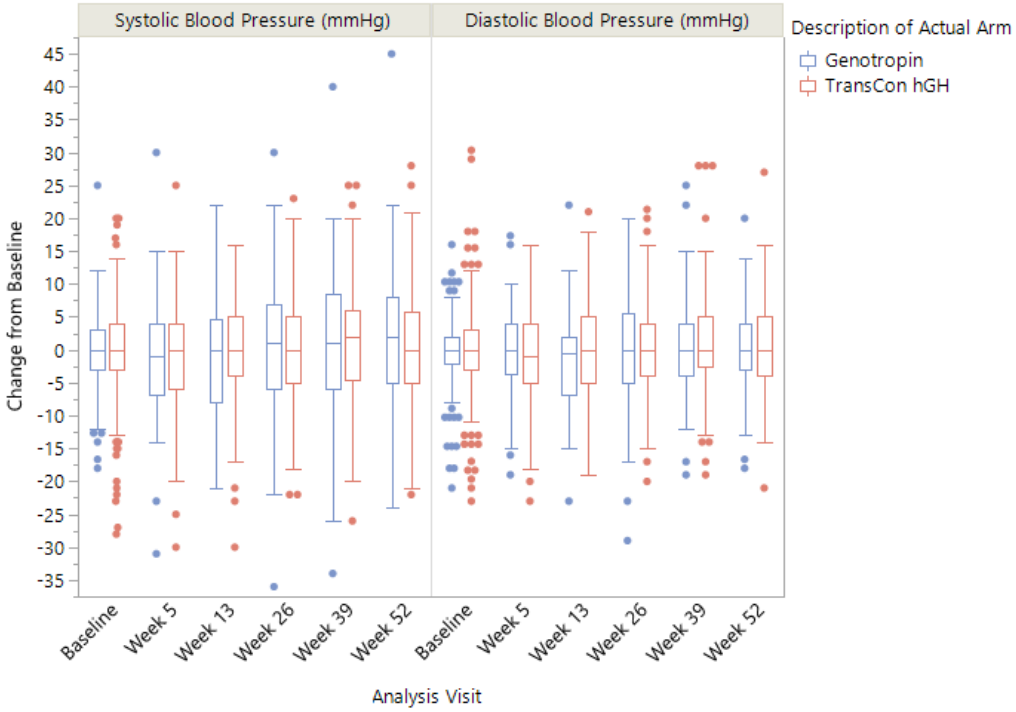
The systolic and diastolic blood pressure (BP) measurements as well as BMI were stable throughout the trial, and similar between both the treatment groups (Figure 19, Figure 20 and Figure 21). Other vital signs measurements including heart rate, respiratory rate, and body temperature were also similar between the two treatment groups and were generally stable throughout the trials when compared to baseline (not shown).

Figure 19: Blood Pressure measurements (mmHg) by visit - Trial CT-301



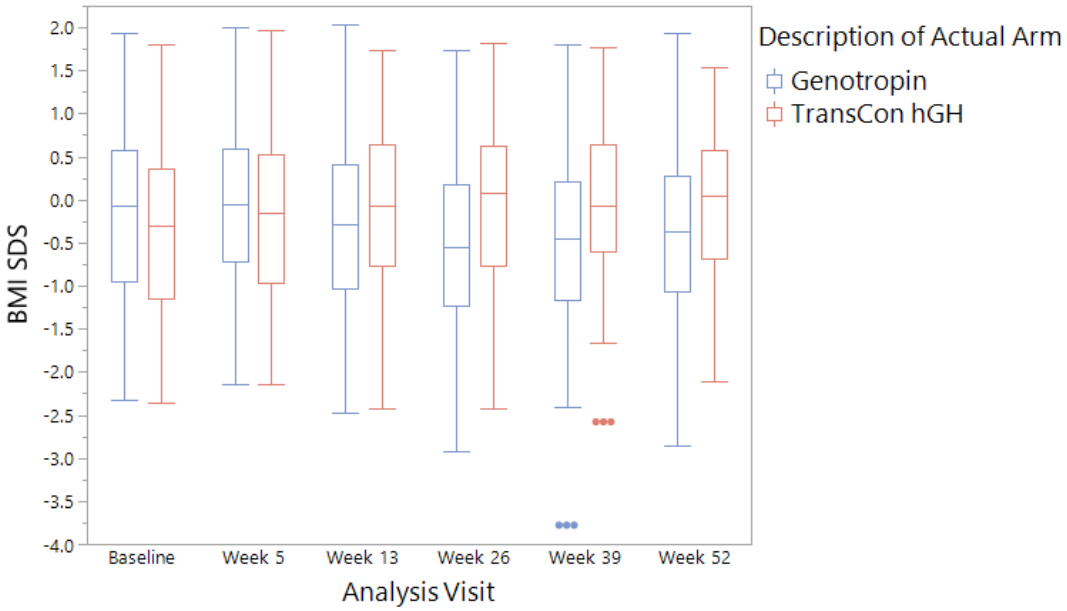
Source: JMP clinical, medical reviewer generated graph.

Figure 20: Change from baseline in BP measurements by visit – Trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Figure 21: BMI SDS by visit - Trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Medical reviewer's comments:
Vital sign measurements were stable from baseline throughout the trial, and there were no significant differences between the lonapegsomatropin-tcgd and Genotropin treatment groups.

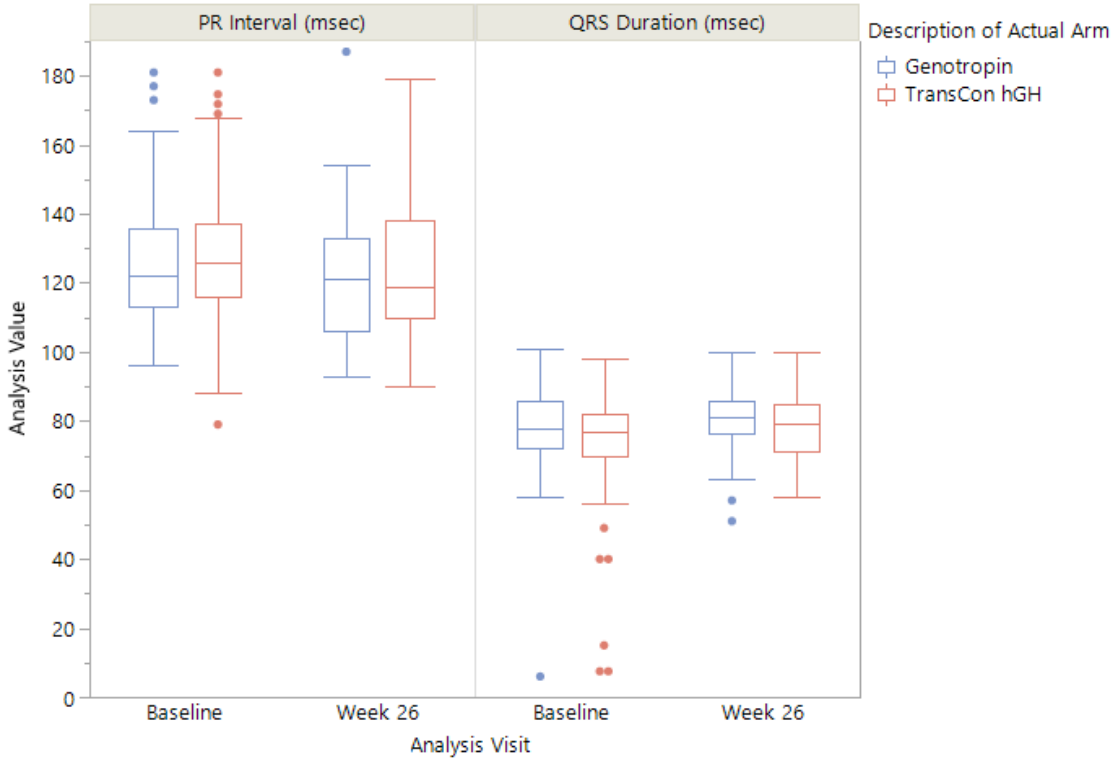
8.4.8. Electrocardiograms (ECGs)

ECGs were obtained during trials CT-101, CT-004 and CT-301.

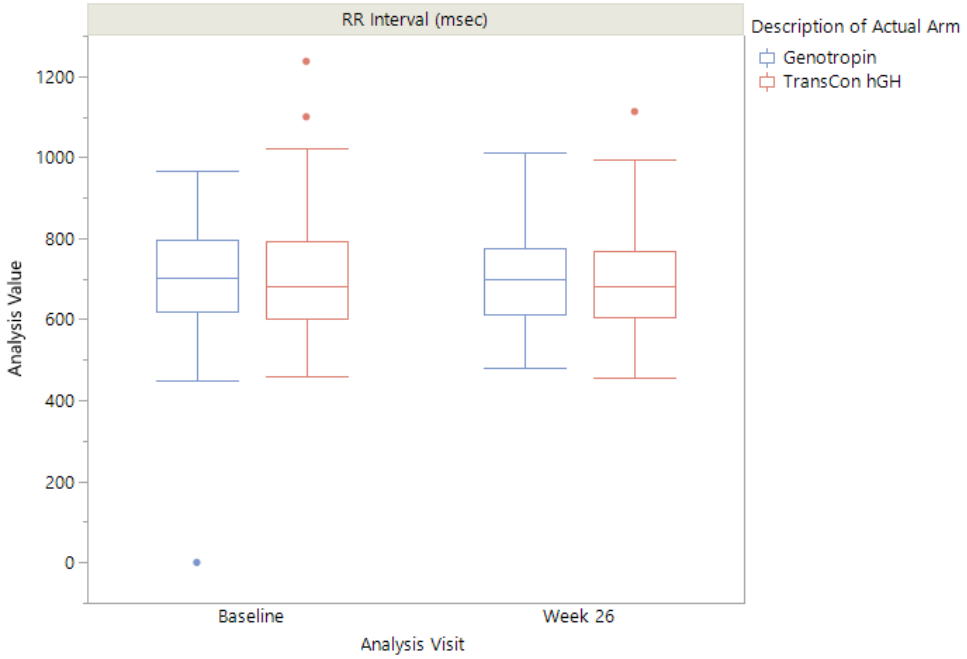
During the trial CT-301, ECG was obtained at baseline and at Week 26 in all subjects. Additionally, in the PK/PD subset of 11 subjects in the lonapegsomatropin-tcgd group, ECG was also obtained as serial measurements (pre-dose and 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours after dosing) at Week 13. All ECGs were recorded after the subject had been at rest for at least 2 minutes, and all ECGs were read centrally.

Various ECG parameters such as PR interval, QRS duration, RR interval and heart rate remained within normal range and were similar between both treatment groups.

Figure 22: PR interval and QRS duration by visit - Trial CT-301

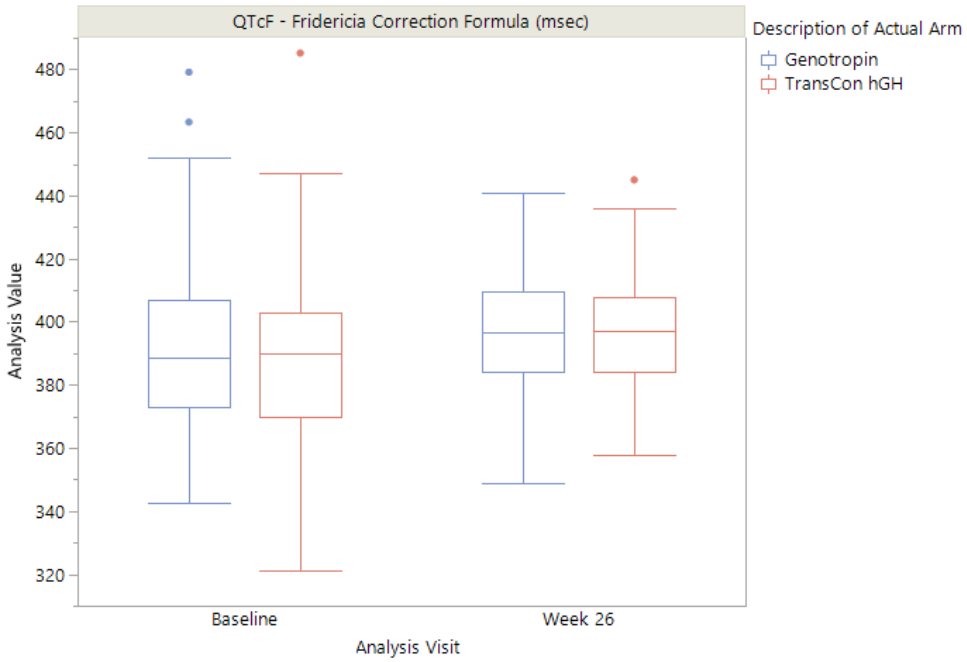


Source: JMP clinical, medical reviewer generated graph.
Figure 23: RR interval by visit - Trial CT-301



Source: JMP clinical, medical reviewer generated graph.

Figure 24: QTcF interval by visit - Trial CT-301



Source: JMP clinical, medical reviewer generated graph.

8.4.9. QT

The Applicant did not conduct a dedicated QT study. According to ICH E14, large targeted proteins (i.e. lonapegsomatropin-tcgd) "have a low likelihood of direct ion channel interactions and a thorough OQ/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies". [25]

This plan was discussed with Agency during the EOP2 meeting, and the Division recommended collecting ECG at the expected steady-state time of C_{max} in all subjects (refer to letter dated 08/25/2016 in DARRTS under IND 126053) The Applicant collected ECGs in a PK/PD subset of 11 subjects in the lonapegsomatropin-tcgd group during the pivotal phase 3 trial CT-301, In order to bracket the presumed C_{max} for lonapegsomatropin-tcgd, ECGs were obtained in the PK/PD subjects at Week 13, at the following timepoints: pre-dose and 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 hours after dosing.

The FDA Interdisciplinary Review Team (IRT) was consulted to provide recommendations regarding the Applicant's ECG assessment and product labeling (see review in DARRTS, dated 11/25/2020). Findings and recommendations from this consult as summarized below.

According to the IRT-QT review team, even though the peak concentration (C_{max} 2480 ng/mL; lonapegsomatropin-tcgd) observed at the highest dose studied (0.42 mg/kg; single dose) offers only ~2-fold margin over the therapeutic exposure (C_{max}: 1230 ng/mL), based on the submitted ECG data, there is no evidence of unexpected or important effects of lonapegsomatropin-tcgd on the QTc interval at the proposed therapeutic dose.

IRT-QT review team agreed with the Applicant's proposal of not including any QT labeling language in Section 12.2 (Cardiac Electrophysiology) of the label, which is consistent with the labeling practices for large molecules for which a dedicated QT study is generally not required.

8.4.10. Immunogenicity

[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e14-clinical-evaluation-qtqtcinterval-prolongation-and-proarrhythmic-potential-non-antiarrhythmic-1

Antidrug antibodies (ADA) including anti-hGH, anti-lonapegsomatropin-tcgd, anti-PEG and neutralizing ADA were monitored at the screening visits, and in addition, at weeks 1, 5, 13, and every 3 months thereafter during trial CT-301, and every 3 months during trials CT-302 and CT-301EXT.

During trial CT-301, the rate of positive anti-hGH binding antibodies post-baseline was similar between lonapegsomatropin-tcgd and Genotropin groups (6.7% vs. 3.6%) and these were all transient (defined as <16 weeks between the first and last antibody positive post-treatment samples). None of the subjects developed anti-hGH neutralizing antibodies. In the lonapegsomatropin-tcgd group, anti-lonapegsomatropin-tcgd binding antibodies were positive in 4 (3.8%) subjects and anti-mPEG antibodies were positive in 2 (1.9%) subjects post-baseline.

As of the Day 120 data cut (June 1, 2020), out of the 305 subjects with GHD who were exposed to lonapegsomatropin-tcgd during the phase 3 program, 21 (6.9%) subjects developed antidrug antibody (anti-hGH, anti-lonapegsomatropin-tcgd or anti-mPEG). All antibodies detected were of low titer (≤ 400); no neutralizing antibodies were detected. None of these subjects experienced any hypersensitivity adverse events or injection site reactions at the time of the detection of positive antibodies. There was no evidence of decreased efficacy in subjects with positive antidrug antibodies. The last recorded AHV for these subjects was within the range of 3.8 to 13.3 cm/year, with a mean (SD) of 8.1 (2.1) cm/year, and median of 7.97 cm/year. This was lower than the mean (SD) AHV of 11.17 (0.23) cm/year that was observed at week 52 in the subjects treated with lonapegsomatropin-tcgd in trial CT-301. However, AHV is expected to decrease after 1st year of treatment with rhGH, and the AHV in subjects with positive antidrug antibodies was comparable to the AHV observed in subjects enrolled in extension trial CT-301EXT. In trial CT-301EXT, subjects who were treated with lonapegsomatropin-tcgd in the parent trial CT-301 and continued on treatment had a mean (SD) AHV of 9.42 (0.21) at Week 78, and subjects who were either treated with Genotropin in parent trial CT-301 or with lonapegsomatropin-tcgd in parent trial CT-302 had a mean (SE) AHV of 8.36 (0.24) cm/year.

Medical reviewer's comments:
The incidence of anti-hGH binding antibodies was similar between lonapegsomatropin-tcgd and Genotropin groups (6.7% vs. 3.6%), and all antibodies were transient (defined as <16 weeks between the first and last antibody positive post-treatment samples). Overall, the incidence of antidrug antibodies in subjects who received lonapegsomatropin-tcgd during the entire phase 3 program was low (6.9%). Additionally, all antibodies detected were of low titer (≤ 400) and non-neutralizing. Lastly, there was no evidence of increased rate of hypersensitivity or injection site reactions, or decreased efficacy in these subjects. According to the clinical pharmacology reviewer, there were no observed effects on safety, efficacy, IGF-1 or PK.

8.5. Analysis of Submission-Specific Safety Issues

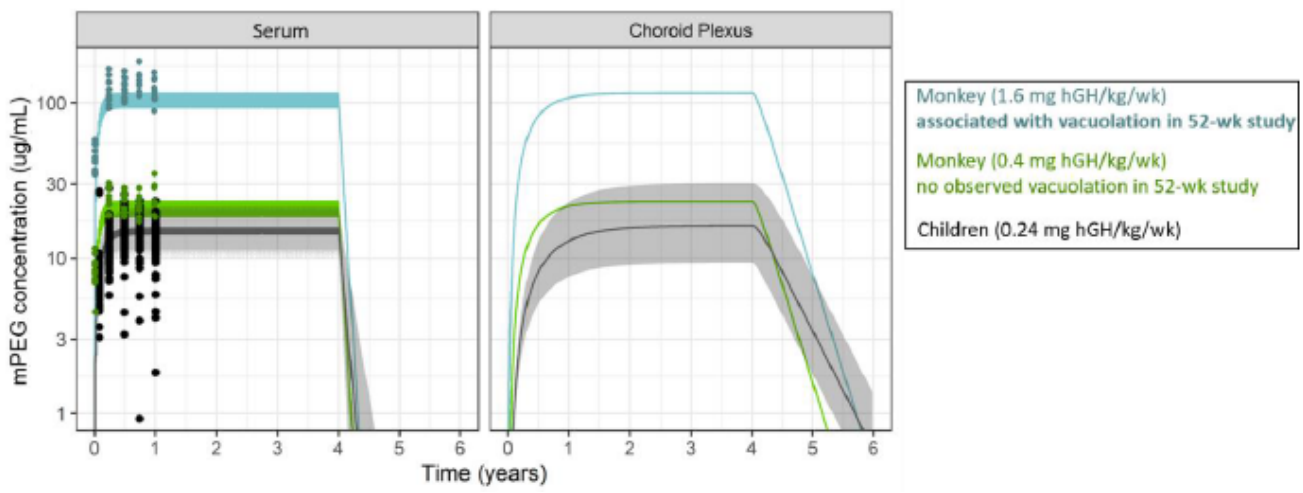
8.5.1. Risks associated with pegylated therapy

In non-clinical studies, large parenteral doses of high molecular weight PEG have been associated with cellular vacuolation of macrophages or interstitial cells of various organs such as liver, spleen, kidney, and epithelial cells of the choroid plexus. Given lonapegsomatropin-tcgd consists of somatropin transiently conjugated to a 40 kDa mPEG carrier, risks associated with pegylated therapy were analyzed and are summarized below. Refer to the review by non-clinical reviewer Dr. Jeffrey Quinn and clinical pharmacology reviewer Dr. Sang Chung for further details.

In the non-clinical studies of lonapegsomatropin-tcgd in rats and monkeys, mPEG staining in brain tissues was observed at 1.2 mg hGH/kg dose equivalent in the 26-week study (doses studied were 1.2, 2.4 and 4.8 mg hGH/kg dose equivalent). Also, vacuolization of the choroid plexus was observed at the 1.6 mg hGH/kg dose equivalent in the 52-week study in monkeys (doses studied were 0.4, 1.6 and 4.8 mg hGH/kg dose equivalent), and at the 1.2 mg hGH/kg dose equivalent in the 26-week study in rats (doses studied were 1.2, 2.4 and 4.8 mg hGH/kg dose equivalent). Additionally, after the 27-week recovery period in rats, and 52-week recovery period in monkeys, there was a persistence of mPEG association with several cell types and vacuolation of the choroid plexus, indicating only a partial recovery upon withdrawal of lonapegsomatropin-tcgd. However, mPEG staining and vacuolation were not associated with a distortion of the cytoplasmic or nuclear compartments, degeneration, necrosis, or inflammation. Additionally, there was no evidence of signs of neurotoxicity such as tremors, convulsions, reactivity to handling or unusual behavior. In both rats and monkeys, the level of mPEG in cerebral spinal fluid did not exceed lower limit of quantification.

As per the clinical pharmacology and nonclinical reviewers, the predicted median steady state level of mPEG in the choroid plexus of children at the proposed dose of 0.24 mg hGH/kg/week is 2-fold lower than the predicted steady state levels in the choroid plexus of monkeys at the NOEL of 0.4mg/hGH/kg/week, whereas the test article-related microscopic findings in the brain (vacuolation of epithelial cells and/or macrophages within the choroid plexus) were observed in male and female monkeys dosed at ≥1.6 mg hGH/kg/week for 52 weeks. Refer to Figure 25. Hence, the anticipated risks at the proposed therapeutic dose of 0.24 mg hGH/kg/week may be considered minimal.

Figure 25: Predicted mPEG (lines) and individual observed mPEG (symbols) in serum and choroid plexus of children and cynomolgus monkey following 3 doses



Source: adapted from Dr. Sang Chung's clinical pharmacology review

Division of Neurology was also consulted to provide inputs on the potential risk associated with accumulation of mPEG in the brain, and whether the pediatric population is at an increased risk for the neurologic deficits (refer to consult by clinical reviewer David Hosford, MD, PhD dated 01/14/2021 and by nonclinical reviewer David Hawver, PhD dated 01/19/2021 in DARRTS).

According to the nonclinical reviewer with the Division of Neurology, compared to the serum mPEG exposures in children at the proposed dose of 0.24 mg hGH/kg/week, the NOAELs in the 26-week study in rat, 26-week study in monkey and 52-week study in monkey were associated with exposure margins of 3.5x, 35x, and 34x, respectively. These studies included extensive neurohistophathology evaluations but were limited by a lack of neurological testing, neurobehavioral assessments, and analysis of CSF composition. However, based on the relatively large exposure margins achieved in the nonclinical studies in monkey, and the lack of evidence that minimal to moderate accumulation of mPEG is adverse in the absence of any other abnormalities, the proposed human dose carries a low mPEG associated risk. Thus, additional nonclinical studies may not be needed.

According to the clinical reviewer with the Division of Neurology, currently there are 6 marketed pegylated products that are known to cause mPEG accumulation and choroid plexus epithelial cell vacuolation in nonclinical studies. To date, there are no clear safety risks associated with mPEG accumulation in the brain with these products, and headaches are the only clinical events that have a low likelihood association. Tonic-clonic seizures may be associated with mPEG accumulation. However, this association is at a much lower possibility and is easily ascertainable by routine adverse event assessments. Even though there is paucity of data regarding the safety of pegylated compounds in children, the 3-year history of Rebinyn, an approved treatment of hemophilia B, without any associated central nervous system adverse events in children is reassuring.

The Division of Pediatric and Maternal Health (DPMH) was also consulted to provide inputs on the potential risks associated with mPEG accumulation in the brain, in pediatric population. The DPMH review was pending at the time of this review completion. (b) (4)

DMPH was thus unable to provide any comments on the safety or toxicity of mPEG, and differed to the recommendations provided by the pharmacotoxicology and the Division of Neurology reviewers.

During the clinical studies of lonapegsomatropin-tcgd, treatment with lonapegsomatropin-tcgd was not associated with an increased risk of central nervous system related adverse events compared to Genotropin. Headaches were the only adverse events in the nervous system disorders or psychiatric disorders System Organ Class, that were observed in ≥2% of subjects, and were present at a similar rate in both lonapegsomatropin-tcgd (12.3%) and Genotropin (14.3%) groups. Refer to Table 58.

Table 58: TEAEs observed in the System Organ Class of Nervous system disorders or Psychiatric disorders during Trial CT-301

Treatment Emergent Adverse Event	Lonapegsomatropin-tcgd (N = 105) n (%)	Genotropin (N = 56) N (%)
Headache	13 (12.4%)	8 (14.3%)
Dizziness	2 (1.9%)	1 (1.8%)
Attention Deficit/Hyperactivity Disorder	1 (0.95%)	1 (1.8%)
Affect liability	1 (0.95%)	0
Depressive Symptom	1 (0.95%)	0
Enuresis	1 (0.95%)	0
Tremor	1 (0.95%)	0

N = total number of subjects in each treatment group. n = number of subjects experiencing the event, (%) = proportion of subjects experiencing the event.
Source: Medical reviewer generated report using JMP clinical

Hence, the anticipated risks of mPEG at the proposed therapeutic dose of 0.24 mg hGH/kg/week may be considered minimal.

8.5.2. Increased risk of Neoplasms

Growth hormone treatment has been associated with an increased risk of neoplasms. There was a low incidence of neoplasms reported with use of lonapegsomatropin-tcgd in clinical program, with no difference between treatment groups. During trial CT-301, the rate of skin papilloma was similar between both treatment groups as follows: lonapegsomatropin-tcgd group 2 (1.9%) subjects and Genotropin group 1 (1.8%) subject. During the phase 3 program of lonapegsomatropin-tcgd, a total of 5 (1.6%) subjects treated with lonapegsomatropin-tcgd experienced a TEAE in the SOC of Neoplasms: 4 (1.3%) subjects (2 subjects in CT-301, 1 subject in CT-302 and 1 subject in CT-301EXT), developed skin papilloma and 1 (0.3%) subject in CT-301 with a prior history of osteochondroma developed osteoma.

8.5.3. Glucose Intolerance

Decreased insulin sensitivity and glucose metabolism due to GH related insulin antagonistic effects in liver and other tissues is a known class effect of rhGH formulations. During the phase 3 program, mean glucose, insulin, and hemoglobin A1c values remained stable from baseline in subjects who were treated with lonapegsomatropin-tcgd. During the trial CT-301, three subjects, all on lonapegsomatropin-tcgd, experienced hemoglobin A1c levels >6.1%. However, two of these subjects, had elevated hemoglobin A1c levels at baseline, and the third subject likely had a laboratory error. There were 2 subjects with an elevated hemoglobin A1c level at baseline, and the levels remained stable throughout the trial for both these subjects. Refer to Section 8.4.6 for further details.

8.5.4. Severe hypersensitivity

Serious systemic hypersensitivity reactions such as anaphylactic reactions and angioedema have been reported with other GH therapies. During the trial CT-301, hypersensitivity reactions were observed in 6 (5.7%) of subjects in lonapegsomatropin-tcgd group and 4 (7.1%) of subjects in Genotropin group. However, none of these reactions were characterized as severe reactions. Out of the 305 subjects exposed to lonapegsomatropin-tcgd during the phase 3 trials, hypersensitivity reactions were observed in 11 (3.6%) subjects and none of these were characterized as severe reactions.

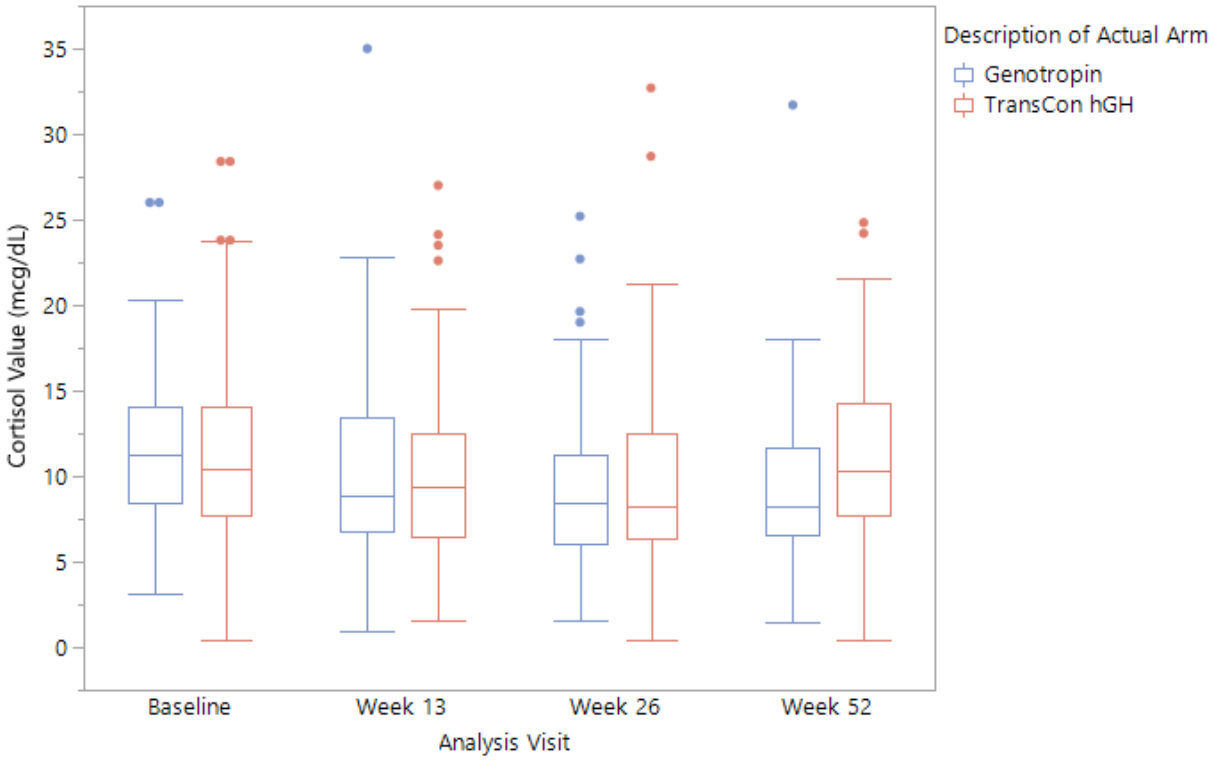
8.5.5. Intracranial hypertension

Due to an increased risk of intracranial hypertension with GH therapy, fundoscopic examinations were conducted at regular intervals during trials CT-301 and CT-302, and if indicated, in trial CT-301EXT. None of the subjects were found to have abnormal fundoscopic examinations, or any evidence of intracranial hypertension. Additionally, the rate of headaches was similar between the lonapegsomatropin-tcgd group (12.4%) and Genotropin group (14.3%) during trial CT-301. A total of 36 (11.8%) of subjects experienced headaches during the phase 3 program, and none of them were severe in nature and were not associated with visual changes.

8.5.6. Hypoadrenalism

Treatment with GH can unmask underlying adrenal insufficiency. However, treatment with lonapegsomatropin-tcgd was not associated with an increased risk of hypoadrenalism when compared to Genotropin. During trial CT-301, the mean cortisol levels were stable, and similar between both treatment groups (Figure 26). However, it should be noted that diagnosis of adrenal insufficiency can be based only on the results of ACTH stimulation test due to the variation in cortisol levels through the day. During the trial CT-301, there were 2 (1.9%) subjects in lonapegsomatropin-tcgd group and 1 (1.8%) subject in Genotropin group who experienced adverse event of hypoadrenalism (as reported by the Sponsor). It is not clear whether the diagnosis of adrenal insufficiency was based on cortisol levels and response to ACTH stimulation test, or presence symptoms alone. Throughout the phase 3 program, a total of 3 (1%) subjects treated with lonapegsomatropin-tcgd experienced hypoadrenalism, including 1 subject who experienced adrenal crisis. None of the events met the criteria for serious adverse event. Adrenal insufficiency was of moderate severity in 2/3 subjects, and of mild severity in 1/3 subjects. At the end of the trial, the outcome was listed as unknown for 1 subject, not recovered for 1 subject, and recovered for 1 subject. All three subjects required concomitant treatment with glucocorticoids, and none of the subjects required a change in dose of lonapegsomatropin-tcgd.

Figure 26: Comparison of Cortisol levels at various visits during trial CT-301

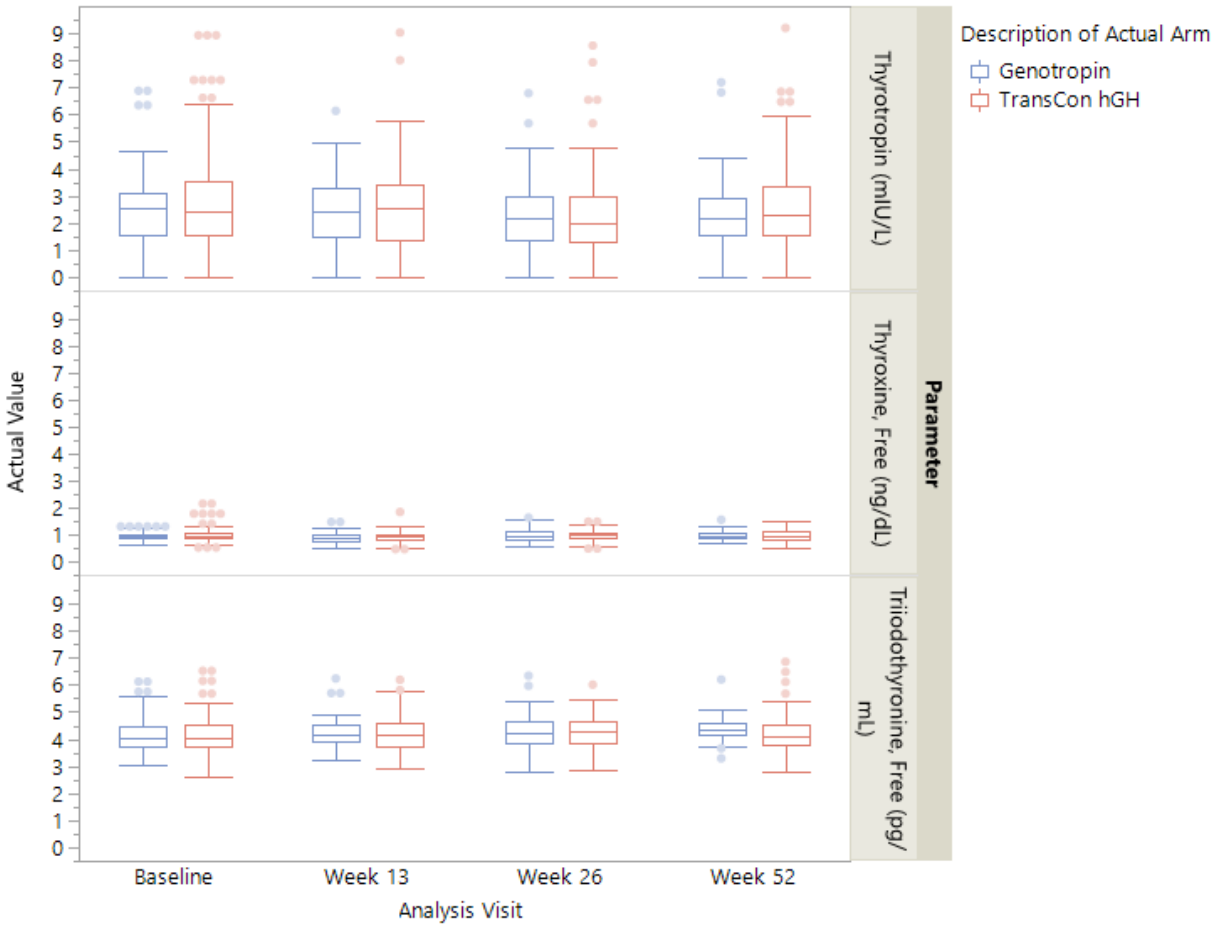


Source: JMP clinical, medical reviewer generated graph.

8.5.7. Hypothyroidism

Since treatment with GH can unmask underlying hypothyroidism, thyroid stimulating hormone (thyrotropin), free thyroxine and free triiodothyronine levels were assessed throughout the trial. During trial CT-301, the mean thyroid hormone levels were stable, and similar between both treatment groups (Figure 27). Treatment with lonapegsomatropin-tcgd was not associated with an increased risk of hypothyroidism when compared to Genotropin. The rates of new onset secondary hypothyroidism were similar between both treatment groups as follows: lonapegsomatropin-tcgd 6 (5.7%) and Genotropin 4 (7.1%). All subjects were asymptomatic

Figure 27: Comparison of Thyroid Function Tests at various visits during trial CT-301



Source: JMP clinical, medical reviewer generated graph.

8.5.8. Fluid retention

GH therapy has been associated with an increased risk of fluid retention. During the trial CT-301, only one subject in the Genotropin group experienced facial edema.

8.5.9. Slipped capital femoral epiphyses

Slipped capital femoral epiphyses was not observed in any subjects during the clinical development of lonapegsomatropin-tcgd.

8.5.10. Progression of pre-existing scoliosis in pediatric subjects

Throughout the phase 3 program, 1 (0.3%) subject on lonapegsomatropin-tcgd developed scoliosis on day 106 of treatment, which was mild and did not require any further treatment. No adjustment was made to the study dose. Additionally, this subject was enrolled in trial CT-302, and had been treated with another GH therapy prior to enrollment. There were 2 subjects who had preexisting scoliosis, and did not experience any worsening with lonapegsomatropin-tcgd treatment

8.5.11. Pancreatitis

None of the subjects experienced pancreatitis during the clinical development of lonapegsomatropin-tcgd.

8.5.12. Lipoatrophy/Injection Site Reactions

During trial CT-301, 2 (1.9%) subjects in lonapegsomatropin-tcgd group developed injection site reaction of injection site atrophy and injection site urticaria, respectively. In comparison, 1 (1.8%) subject in Genotropin group developed injection site reaction of urticaria. Out of the 305 children with GHD exposed to lonapegsomatropin-tcgd during the phase 3 development, 4 (1.3%) developed following injection site reactions: lipoatrophy (2), urticaria (1) and pain (1).

8.5.13. Arthralgia

During the trial CT-301, arthralgia occurred at a similar frequency in the lonapegsomatropin-tcgd (5.7%) and Genotropin groups (1.8%). Out of the 305 subjects who were treated with lonapegsomatropin-tcgd during the three phase 3 trials, a total of 14 (4.6%) subjects experienced arthralgia.

8.6. Safety Analyses by Demographic Subgroups

The Applicant also presented the safety data as a subgroup analysis conducted on Safety Pool II, which consisted of 305 subjects who were exposed to lonapegsomatropin-tcgd during the phase 3 development. Subgroups included age (<3 years, ≥3 to <6 years, ≥6 to <11 years for girls and ≥6

to <12 years for boys, and ≥11 years for girls and ≥12 years for boys); gender (male vs. female); region (U.S. vs non-US); and completion status (2-year lonapegsomatropin-tcgd completer, non-2-year lonapegsomatropin-tcgd completer). Refer to Table 59

Table 59: AE by subgroup analysis

Subgroup	N (%)	Any TEAE	Severe TEAE
Overall	305	221 (72.5%)	4 (1.3%)
Age			
<3 years	4	4 (100%)	0
≥3 to ≤6 years	54	44 (81.5%)	0
≥6 to <11 years for girls and ≥6 to <12 years for boys	149	105 (70.5%)	3 (2%)
≥11 years for girls and ≥12 years for boys	98	68 (69.4%)	1 (1%)
Gender			
Male	240	170 (70.8%)	4 (1.7%)
Female	65	51 (78.5%)	0
Region			
US	179	144 (80.4%)	2 (1.1%)
Non-US	126	77 (61.1%)	2 (1.6%)
Completion Status			
2-year lonapegsomatropin-tcgd completer	46	39 (84.8%)	2 (4.3%)

Source: Summary of Clinical Safety, Page 104

8.6.1. Safety Analysis by Age

The rate of TEAE was greater in younger subjects, and a decrease in rate was observed with age, with the rate in subjects <3 years old of 100% and in subjects ≥11 years old of 69.4% (Table 59). The rate of severe TEAE was similar between all age groups. Higher rate of TEAE in subjects <3 years old may be given the phase 3 clinical program of lonapegsomatropin-tcgd only enrolled 4 subjects <3 years old.

8.6.2. Safety Analysis by Gender

There were more male (78.7%) than female (21.3%) subjects in the phase 3 program of lonapegsomatropin-tcgd. Overall, the rate of TEAE was slightly greater in females (78.5%) compared to males (70.8%). The rate of severe TEAE was similar between the 2 groups.

8.6.3. Safety Analysis by Region

Given majority of the subjects in the US were enrolled in trail CT-302, a greater number of subjects in the US had previously been treated with hGH therapy compared to non-US subjects (83.8% vs 37.3%). The rate of TEAE was slightly greater in US subjects compared to non-US subjects (80.4% vs. 61.1%). Refer to Table 59

8.6.4. Safety Analysis by Completion Status

Out of the 46 (15%) subjects who completed 2 years of lonapegsomatropin-tcgd treatment, 39 (84.8%) subjects experienced at least one TEAE, and 2 (4.3%) subjects experienced a severe TEAE. These rates were similar to the overall rates for any TEAEs (72.5%) and severe TEAE (1.3%).

8.7. Specific Safety Studies/Clinical Trials

No specific safety studies/clinical trials were conducted for lonapegsomatropin-tcgd

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

According to the nonclinical reviewer, lonapegsomatropin-tcgd, hGH, or the products of its autocleavage carry a minimal genotoxic or carcinogenic potential in children with GHD.

A low incidence of neoplasms was noted during the clinical development program of lonapegsomatropin-tcgd with no significant difference between study groups (see Section 8.5.2 above, for details).

8.8.2. Human Reproduction and Pregnancy

There were no exposures to lonapegsomatropin-tcgd in pregnant or lactating women during the development program.

The Division of Pediatric and Maternal Health (DPMH) review was pending at time of this review completion. However, no issues that preclude approvability of this drug were identified to date by Dr. Ethan Hausman.

8.8.3. Pediatrics and Assessment of Effects on Growth

This application is for a pediatric indication (b) (4)

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

During the lonapegsomatropin-tcgd clinical development program, 2 subjects enrolled in trial CT-301 experienced an accidental overdose as follows: a 5-year old female received 5.8 times the recommended dose for 3 weeks and a 9-year old male received 3.3 times the recommended dose for 3 weeks. Neither of these subjects experienced any AEs or significant laboratory abnormalities. The proposed label adequately indicates that inappropriate use of lonapegsomatropin-tcgd may result in significant negative health consequences, which is consistent with other GH products.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

None. Lonapegsomatropin is not currently approved or marketed in any country.

8.9.2. Expectations on Safety in the Postmarket Setting

No potential safety issues have been identified during this review.

8.9.3. Additional Safety Issues From Other Disciplines

None. Refer to Section 4 for further details.

8.10. Integrated Assessment of Safety

Adequate number of pediatric subjects with GHD were exposed to lonapegsomatropin-tcgd during the clinical development program. The safety areas of special interest are summarized below and include potential risks associated with mPEG, GH class effects, injection site reactions and immunogenicity.

Potential risks of mPEG:
High molecular weight PEG has been associated with cellular vacuolation of macrophages or interstitial cells of various organs, such as liver, spleen, kidney, and epithelial cells of the choroid plexus in animal studies. Lonapegsomatropin-tcgd-related microscopic findings in the brain such as vacuolation of epithelial cells and/or macrophages within the choroid plexus were observed in monkeys dosed at ≥1.6 mg hGH/kg/week dose equivalent for 52 weeks, and in rats dosed at the 1.2 mg hGH/kg dose equivalent for 26 weeks. However, both monkey and rat species did not present with any neurological deficits that could be directly linked to mPEG accumulation in the brain. Additionally, the predicted median steady state level of mPEG in the choroid plexus of children at the proposed dose of 0.24 mg hGH/kg/week is 2-fold lower than the predicted steady state levels in the choroid plexus of monkeys at the NOEL of 0.4mg/hGH/kg/week. Hence, the anticipated risks of vacuolation in choroid plexus at the proposed therapeutic dose of 0.24 mg hGH/kg/week may be considered minimal and does not require mitigation of the risk through the labeling at this time.

Risks of Neoplasms:
At this time, there is no clear evidence that GH therapy leads to tumor development in children with or without a history of prior malignancy.[26,27,28,29] However, due to the mitogenic and antiapoptotic activity of GH and IGF-1, there is a theoretical concern for neoplasia development with GH therapy, and treatment with GH therapy is contraindicated in patients with active malignancy.[30] Therefore, the 'Warnings and Precautions' section for all rhGH therapies labels includes a potential risk of neoplasms. Overall, there was a low rate of neoplasms during the clinical development of lonapegsomatropin-tcgd, with a similar rate between Genotropin and lonapegsomatropin-tcgd (see Section 8.5 for further details).

Thus, based on the lonapegsomatropin-tcgd clinical development program, there was no evidence of an increased risk of neoplasm with lonapegsomatropin-tcgd compared to other GH

[26] Wilton P, et al. Growth hormone treatment in children is not associated with an increase in the incidence of cancer: Experience from KIGS. *The Journal of Pediatrics*. 2010; 157:265-270
[27] Tuffli GA, et al. Lack of increased risk for extracranial, nonleukemic neoplasms in recipients of recombinant deoxyribonucleic acid growth hormone. *Journal of Clinical Endocrinology and Metabolism*. 1995; 80:1416-1422
[28] Moshang T, et al. Brain tumor recurrence in children treated with growth hormone: the National Cooperative Growth Study experience. *The Journal of Pediatrics*. 1996; 128:S4-S7
[29] Swerdlow A, et al. Growth Hormone treatment of children with brain tumors and risk of tumor recurrence. *The Journal of Clinical Endocrinology and Metabolism*. 2000; 85:4444-4449
[30] Chae HW, et al. Growth hormone treatment and risk of malignancy. *Korean Journal of Pediatrics*. 2015; 52:41-46

formulations, and inclusion of the risk of neoplasms in the 'Warnings and Precautions' section of the label should be sufficient to alert the providers of this potential risk.

Glucose Intolerance:
Decreased insulin sensitivity and glucose metabolism due to GH related insulin antagonistic effects in liver and other tissues is a known class effect of rhGH formulations. Overall, the mean fasting plasma glucose and Hemoglobin A1c levels were stable, and no significant glucose excursions were noted. None of the subjects had a shift from normal to elevated Hemoglobin A1c levels. There were 2 subjects with an elevated hemoglobin A1c level at baseline, and the levels remained stable throughout the trial for both these subjects.

The number of subjects who shifted from normal to high glucose levels were similar in both groups at Week 52. Even though a greater number of subjects in lonapegsomatropin-tcgd group shifted from normal to high insulin levels at Week 39 (14.7% vs. 3.7%), a similar rate of shift from normal to high glucose levels was not observed at Week 39 (6.9% vs 3.6%). Additionally, this difference in shift from normal to high insulin levels was smaller at Week 52 (3.9% vs. 0%) and may thus be a temporary effect.

In conclusion, the impact of lonapegsomatropin-tcgd on glucose metabolism that was observed during the clinical development program was consistent with the rhGH therapy class effect. Consistent with the labels of other rhGH therapies, risk of glucose intolerance should thus be included in the label.

Hypoadrenalism and hypothyroidism:
Treatment with GH can unmask underlying adrenal insufficiency and/or hypothyroidism.

Treatment with lonapegsomatropin-tcgd was not associated with an increased risk of hypoadrenalism when compared to Genotropin. AE of 'hypoadrenalism' occurred at a similar frequency between the lonapegsomatropin-tcgd group and Genotropin group (1.9% vs 1.8%). Out of the 305 subjects exposed to lonapegsomatropin-tcgd during the phase 3 program, 3 (1%) subjects reported the AE of 'adrenal insufficiency', including 1 subject who experienced adrenal crisis. None of the events met the criteria for serious adverse event. Adrenal insufficiency was of moderate severity in 2/3 subjects, and of mild severity in 1/3 subjects. At the end of the trial, the outcome was listed as unknown for 1 subject, not recovered for 1 subject, and recovered for 1 subject. All three subjects required concomitant treatment, and none of the subjects required a change in dose of lonapegsomatropin-tcgd.

Overall, the mean thyroid hormone levels were stable, and similar between both treatment groups, and treatment with lonapegsomatropin-tcgd was not associated with an increased risk of hypothyroidism when compared to Genotropin (5.7% vs 7.1%).

Lipoatrophy and injection site reactions:
Rate of injection site reactions was similar between lonapegsomatropin-tcgd and Genotropin groups (1.9% vs 1.8%). Overall, treatment with lonapegsomatropin-tcgd was not associated with an increased rated of injection site reactions. Out of the 305 children with GHD exposed to lonapegsomatropin-tcgd during the phase 3 development, 4 (1.3%) developed following injection site reactions: lipoatrophy (2), urticaria (1) and pain (1).

Severe hypersensitivity:
Serious systemic hypersensitivity reactions such as anaphylactic reactions and angioedema have been reported with other GH therapies. The rate of hypersensitivity reactions was similar between the lonapegsomatropin-tcgd and Genotropin groups (5.7% vs 7.1%). Throughout the phase 3 clinical program, hypersensitivity reactions were observed in 11 (3.6%) subjects who were exposed to lonapegsomatropin-tcgd, and none of these were characterized as severe reactions.

Intracranial hypertension:
GH therapy is associated with an increased risk of intracranial hypertension. However, none of the subjects treated with lonapegsomatropin-tcgd during the phase 3 program were found to have abnormal fundoscopic examinations, or any evidence of intracranial hypertension, and the rate of headaches was similar between the lonapegsomatropin-tcgd group (12.4%) and Genotropin group (14.3%) during trial CT-301. A total of 36 (11.8%) of subjects experienced headaches during the phase 3 program, and none of them were severe in nature and no visual changes were reported.
Other adverse events related to GH class
Other adverse events that are associated with GH treatment include fluid retention, slipped capital femoral epiphyses, pancreatitis, progression of pre-existing scoliosis and arthralgia. Out of the 305 subjects who were treated with lonapegsomatropin-tcgd during the three phase 3 program, none of the subjects developed fluid retention, slipped capital femoral epiphyses or pancreatitis, and 1 (0.3%) subject developed mild scoliosis which did not require any further treatment. Arthralgia occurred at a similar frequency in the lonapegsomatropin-tcgd and Genotropin groups (5.7% vs. 1.8%), and throughout the phase 3 program, a total of 14 (4.6%) subjects experienced arthralgia.

The Applicant has proposed including fluid retention, slipped capital femoral epiphyses, and progression of preexisting scoliosis in the label, which is consistent with the labels of other rhGH therapies.

Adverse events observed more frequently in subjects treated with ACP-011 compared to subjects treated with Genotropin:

- Gastrointestinal events: Gastrointestinal adverse events including abdominal pain, constipation, diarrhea, dyspepsia, nausea, and vomiting were more frequent in the

lonapegsomatropin-tcgd group compared to Genotropin group (20% vs. 10.7%), and all of these events were of mild severity, were temporary and resolved without dose changes.

- Pyrexia: Pyrexia was reported at a greater frequency in the lonapegsomatropin-tcgd group compared to the Genotropin group (15.2% vs 8.9%). All events resolved without additional treatment and were mild.

- Hemorrhage: Hemorrhage was reported at an increased frequency in the lonapegsomatropin-tcgd group compared to Genotropin group (6.7% vs. 1.8%). However, in the lonapegsomatropin-tcgd group, the etiologies of hemorrhage were epistaxis (3), contusion (2), petechiae (1) and eye hemorrhage (1), and these events were unlikely to be related to the study drug. Additionally, in 3 subjects, hemorrhage was related to either a fall (1 subject with contusion) or concurrent infection (2 subjects with epistaxis), where as in 4 (3.8%) subjects, hemorrhage which was unexplained. None of these subjects had abnormal platelets (coagulation markers were not tested during this trial). All events resolved without treatment.

- Infection, viral: Rate of viral infections was greater in the lonapegsomatropin-tcgd group (15.2% vs 10.7%). However, infections may be more common in pediatric subjects in general, and concomitant leukopenia was present in 4 (25%) of these subjects.

- Cough: Cough was reported in 11(10.5%) of subjects in the lonapegsomatropin-tcgd group, compared to 4 (7.1%) of subjects in Genotropin group.

In conclusion, although the above AEs were seen more frequently in subjects treated with lonapegsomatropin-tcgd compared to Genotropin group, these events were most likely not associated with lonapegsomatropin-tcgd itself. The discrepancy in the rates of these AEs is not clear and may be due to the fact that more subjects were treated with lonapegsomatropin-tcgd in the trials. In addition, gastrointestinal symptoms, fever, viral infections are in general seen frequently in this age group. More importantly, all AEs were mild, were of short duration and resolved without treatment or dose change and can be mitigated through the appropriate labeling.

Immunogenicity:
The incidence of anti-hGH binding antibodies was similar between lonapegsomatropin-tcgd and Genotropin groups (6.7% vs. 3.6%). Out of the 305 subjects treated with lonapegsomatropin-tcgd during the phase 3 program, antidrug antibodies were present in 21 (6.9%) subjects. All antibodies detected were of low titer (≤ 400) and non-neutralizing. There was no evidence of increased rate of hypersensitivity or injection site reactions, or decreased efficacy in these subjects.

Changes in phosphate and alkaline phosphate:
Treatment with lonapegsomatropin-tcgd was associated with a greater degree and rate of phosphate and alkaline phosphate elevation compared to Genotropin. Moreover, 86.4% of subjects in lonapegsomatropin-tcgd group had phosphate elevation for >50% of the times they were tested, compared to 14.5% of subjects in Genotropin group. Similarly, 15.4% of subjects in lonapegsomatropin-tcgd group had alkaline phosphate elevation for >50% of the times they were tested, compared to 7.1% of subjects in Genotropin group. However, the elevations occurred on an intermittent basis, were mild and not progressive, and of unknown clinical significance. Overall, changes in phosphate and alkaline phosphate are known class effect for all GH formulations and listed in Warnings and Precaution section of all approved GH labels. Thus, I agree that these events should be included in section 5 of lonapegsomatropin-tcgd label.

In conclusion, overall, the safety profile of lonapegsomatropin-tcgd was well characterized in clinical development program. AEs observed with lonapegsomatropin-tcgd were consistent with the AEs associated with rhGH therapy class. These include potential increased risk of neoplasm, glucose intolerance, hypoadrenalism, hypothyroidism, injection site reactions and hypersensitivity reactions. Treatment with lonapegsomatropin-tcgd was not associated with increased risk of well-known AEs including an increased risk of neoplasm and was not associated with any new significant safety signals.

In general, the AEs observed are predictable, well-known class effects of GH therapies, can be adequately identified and managed by the health care providers. The safety profile of lonapegsomatropin-tcgd is acceptable given its potential benefits and the expected class effects will be mitigated through the labeling.

However, due to the lack of safety data of lonapegsomatropin-tcgd in subjects <1-year-old, the drug should be indicated only for pediatric subjects >1-year-old with growth failure due to GHD. Lonapegsomatropin-tcgd is a long acting growth hormone therapy, which consists of somatropin transiently conjugated to mPEG carrier via a proprietary TransCon linker. The major concern with use of this drug in subjects < 1 year old is that safety profile has not been evaluated and remains unknown in this age group (e.g., effect of mPEG, elevated IGF-1 levels above normal). Additionally, the PK/PD profile of lonapegsomatropin-tcgd in subjects <1-year-old is unknown and there is no predictive model that may evaluate PK/PD profile of lonapegsomatropin-tcgd in subjects <1-year-old. Hence, it is not clear if subjects <1-year-old have a similar, greater, or lower IGF-1 response to lonapegsomatropin-tcgd compared to subjects ≥1-year-old. If subjects < 1 year old exhibit an exaggerated IGF-1 response after treatment with lonapegsomatropin-tcgd, given lonapegsomatropin-tcgd has a longer half-life than the currently available daily GH therapies, any adverse events observed may not be easily reversible upon discontinuation of the drug.

9. Advisory Committee Meeting and Other External Consultations

Not applicable for this submission

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

- INDICATIONS AND USAGE:
  - I recommend that lonapegsomatropin-tcgd is indicated for the treatment of pediatric patients >1 year of age, who have growth failure due to inadequate secretion of endogenous growth hormone. The pivotal trial CT-301 included subjects aged 3.3 to 13.1 years old, and the supportive trial CT-302 enrolled subjects 1.2 to 17.4 years old. Lonapegsomatropin-tcgd is a long acting growth hormone therapy, which consists of somatropin transiently conjugated to mPEG carrier via a proprietary TransCon linker. Given subjects <1-year-old were not enrolled in the clinical development program of lonapegsomatropin-tcgd, safety of this drug cannot be assessed in this patient population at this time.
- DOSAGE AND ADMINISTRATION:
  - Lonapegsomatropin-tcgd is available in cartridges at 9 dosage strengths, with the lowest available dosage strength of 3 mg hGH. Based on the currently available dosage strengths and based on the weight-based dosing recommended by the Applicant in the label, the drug cannot be used in patients whose weight is <11.5 kg. The Applicant needs to clarify how to dose patients who are >1-year-old and weigh <11.5 kg. Alternatively, the labeled indication needs to include a lower weight limit of 11.5 kg.
  - I do not recommend to individualize and titrate the dosage of lonapegsomatropin-tcgd based on etiology of GHD, treatment goals, expected sensitivity to therapy, and clinical response. In the pivotal phase 3 trial, subjects did not undergo dose titration, and all subjects were treated at a fixed dose of 0.24 mg hGH/kg/week.
  - I do not agree with the Applicant's recommendation (b) (4) Given the pivotal phase 3 trial only included subjects with open epiphyses, lonapegsomatropin-tcgd should be discontinued once epiphyseal fusion has occurred.

- CONTRAINDICATIONS:
  - I recommend including acute critical illness and active proliferative or severe non-proliferative diabetic retinopathy in the contraindications. These contraindications are consistent with GH class labelling.
- WARNINGS AND PRECAUTIONS:
  - I recommend that consistent with GH class labelling, acute critical illness and active malignancy are included in the Warnings and Precautions section.
- ADVERSE REACTIONS:
  - I recommend that adverse reactions that occurred at >5% frequency, and more frequently in lonapegsomatropin-tcgd treated patients than the daily Somatropin treated patients are included in the 'Clinical Trial Experience' subsection. These adverse events were obtained using FMQ analysis. Refer to Section 8.4.5 for further details.
  - I also recommend including elevated phosphate and alkaline phosphate in the adverse reactions section, as more subjects treated with lonapegsomatropin-tcgd shifted from normal baseline levels to elevated phosphate and alkaline phosphate levels at the end of the trial compared to daily somatropin group (44.2% vs. 30.2% and 19.2% vs. 9.4%, respectively).
- CLINICAL STUDIES:

(b) (4)

11. Risk Evaluation and Mitigation Strategies (REMS)

Not required for this submission.

12. Postmarketing Requirements and Commitments

Not required for this submission.

13. Appendices

Appendix 1: Schedule of Events for Lonapegsomatropin-tcgd group during trial CT-301

Visit	Screening[1] (-6-0 weeks)	1[1] (Week 1)	2 (Week 5)	3 (Week 13)	4 (Week 26)	5 (Week 39)	6 (Week 52)
Trial Day (Lonapegsomatropin subjects)		1 (Predose, Morning)	29 (Predose, Morning)	87-88[2] (48-72 h postdose, Morning)	178-179 (48-72 h postdose, Morning)	269-270 (48-72 h postdose, Morning)	365 (164-172 h postdose, Morning)
Visit Window (weeks)				+2	±1	±1	+1
Informed consent	x						
Medical history	x						
Concomitant medication and adverse events		x	x	x	x	x	x
Review of subject diary			x	x	x	x	x
Height and weight measurement	x	x	x	x	x	x	x
Physical examination and vital signs[3]	x	x	x	x	x	x	x
Pubertal status	x				x		x
GH-stimulation test(s)[4,5]	x						
Assessment of adrenal status[6,7]	x						
Karyotype testing[8]	x						
12-lead ECG[9]	x	x		x[10]	x		
X-ray of left hand and wrist[4]	x						x
Sellar MRI[4]	x						
Fundoscopy[11]	x				x		x
Safety laboratory parameters[12]	x	x	x	x	x	x	x
Fasting required	x	x			x		x
Hormone status[13]	x	x		x	x		x
Bioanalytical samples[14]	x	x	x	x	x	x	x
Anti-transglutaminase antibodies[4]	x						
Anti-hGH and anti-mPEG antibodies	x[15]	x	x	x	x	x	x
PK/PD Sampling (PK/PD subset)[16]				x[10]			
Drug administration training[17]		x					

Adjustment of dose to body weight				x	x	x	
Study drug administration at site[17]		x	x	x[16]			
Visit Window (weeks)				**+2**	**±1**	**±1**	**+1**
Postdose vital signs[3]		x[18]		x[19]			
Injection site reaction assessment		x[18]	x	x	x	x	x

Source: Clinical Study Report for CT-301, page 41

[1] Following randomization, it is recommended to start V1 within 2 weeks from the time of randomization.
2 Lonapegsomatropin-tcgd PK/PD subset subjects will start Visit 3 predose on Day 85.
3 Vital signs: Heart rate, blood pressure, respiratory rate, and body temperature. Subjects should rest for at least 5 minutes before vital sign assessment.
4 These diagnostic assessments may be performed prior to screening within approximately 6 months with proper documentation and approval by the Medical Expert.
5 Sex hormone priming suggested (but not required) to be performed in girls over the age of 10 and boys over the age of 11.
6 8:00 AM cortisol (e.g., baseline for GH stimulation test) < 7 mcg/dL requires an ACTH stimulation test. 8:00 AM cortisol ≥ 7 mcg/dL satisfies inclusion. This assessment may be performed prior to screening within approximately 3 months with proper documentation and approval by the Medical Expert.
7 These assessments may be performed prior to screening within approximately 3 months with proper documentation and approval by the Medical Expert.
8 Karyotype evaluation in girls. Results prior to screening may be accepted if well documented; the final decision rests with the Medical Expert.
9 Subjects should rest for at least 2 minutes before ECG assessment. Screening ECG is locally read; all other ECGs to be read centrally.
10 At predose and 8, 12, 16, 24, 36, 48, 72, 96, 120 and 168 h post dose for lonapegsomatropin-tcgd PK/PD subset subjects.
11 Should be performed at any time if clinically indicated.
12 Hematology (blood smears will be performed locally for back-up analysis), blood chemistry, lipid, and glucose metabolism (fasting glucose, insulin, HbA1c, and OGTT can be assessed locally at any time in case of suspicion of glucose intolerance).
13 Hormone status: TSH, fT3, fT4, and morning cortisol.
14 Bioanalytical samples for lonapegsomatropin-tcgd, hGH, mPEG, IGF-1 and IGFBP-3: IGF-1 and mPEG will be analyzed at screening and V1 through V6. Lonapegsomatropin-tcgd, hGH, and IGFBP-3 analysis only at V1 to V6. Screening mPEG levels only to be analyzed after randomization.
15 The analysis of the anti-hGH and anti-mPEG antibodies may only be conducted after randomization and are not required for eligibility verification.
16 Only for lonapegsomatropin-tcgd PK/PD subset subjects.
17 Training on study drug preparation and administration (V1 - during first administration and further as needed).
18 At 15 min, 1 h and 2 h post dose.
19 At 15 min, 1 h, 2 h and 24 h post dose for lonapegsomatropin-tcgd PK/PD subset subjects; time point for other subjects as they attend to site.

Appendix 2: Schedule of Events for Genotropin group during trial CT-301

Visit	Screening[a] (-6-0 weeks)	1[a] (Week 1)	2 (Week 5)	3 (Week 13)	4 (Week 26)	5 (Week 39)	6 (Week 52)
Trial Day (Genotropin subjects)		1 (Predose, Morning)	29-35 (Morning)	85-91 (Morning)	176-182 (Morning)	267-273 (Morning)	365 (Morning)
Visit Window (weeks)				+2	±1	±1	+1
Informed consent	x						
Medical history	x						
Concomitant medication and adverse events		x	x	x	x	x	x
Review of Subject Diary			x	x	x	x	x
Height and weight measurement	x	x	x	x	x	x	x
Physical examination and vital signs[b]	x	x	x	x	x	x	x
Pubertal status	x				x		x
GH-stimulation test(s)[c,d]	x						
Assessment of adrenal status[e,f]	x						
Karyotype testing[g]	x						
12-lead ECG[h]	x	x			x		
X-ray of left hand and wrist[c]	x						x
Sellar MRI[c]	x						
Fundoscopy[i]	x				x		x
Safety laboratory parameters[j]	x	x	x	x	x	x	x
Fasting required	x	x			x		x
Hormone status[k]	x	x		x	x		x
Bioanalytical samples[l]	x	x[m]	x	x	x	x	x
Anti-transglutaminase antibodies[c]	x						
Anti-hGH and anti-mPEG antibodies	x[n,o]	x[o]	x[o]	x[o]	x[o]	x[o]	x[o]
Drug administration training[p]		x					
Adjustment of dose to body weight				x	x	x	
Study drug administration at site[p]		x[q]					
Postdose vital signs[b]		x[r]					
Injection site reaction assessment		x[r]	x	x	x	x	x

Source: Clinical Study Report for CT-301, page 43

[a] Following randomization, it is recommended to start V1 within 2 weeks from the time of randomization.
[b] Vital signs: Heart rate, blood pressure, respiratory rate, and body temperature. Subjects should rest for at least 5 minutes before vital sign assessment.
[c] These diagnostic assessments may be performed prior to screening within approximately 6 months with proper documentation and approval by the Medical Expert.
[d] Sex hormone priming suggested (but not required) to be performed in girls over the age of 10 and boys over the age of 11.
[e] 8:00 AM cortisol (e.g., baseline for GH stimulation test) < 7 mcg/dL requires an ACTH stimulation test. 8:00 AM cortisol ≥ 7 mcg/dL satisfies inclusion. This assessment may
be performed prior to screening within approximately 3 months with proper documentation and approval by the Medical Expert.
[f] These assessments may be performed prior to screening within approximately 3 months with proper documentation and approval by the Medical Expert.
[g] Karyotype evaluation in girls. Results prior to screening may be accepted if well documented; the final decision rests with the Medical Expert.
[h] Subjects should rest for at least 2 minutes before ECG assessment. Screening ECG is locally read; all other ECGs to be read centrally.
[i] Should be performed at any time if clinically indicated.
[j] Hematology (blood smears will be performed locally for back-up analysis), blood chemistry, lipid, and glucose metabolism (fasting glucose, insulin, HbA1c, and OGTT can be assessed locally at any time in case of suspicion of glucose intolerance).
[k] Hormone status: TSH, fT3, fT4, and morning cortisol.
[l] Bioanalytical samples for hGH, mPEG, IGF-1 and IGFBP-3. IGF-1 will be analyzed at screening and V1 through V6 (excluding V1-2h post dose). hGH and IGFBP-3 will be analyzed at V1 predose through V6; V1-2h post dose sample will only be analyzed for hGH. mPEG samples are taken at screening and V1 predose only, to assist interpretation of anti-mPEG antibody data.
[m] V1: predose and 2 h post dose sample.
[n] The analysis of the anti-hGH and anti-mPEG antibodies may only be conducted after randomization and are not required for eligibility verification.

[o] Analysis for anti-mPEG antibodies will only be performed at screening and V1 (predose) in support of assessment of a trial specific assay cut-point.
[p] Training on study drug preparation and administration (V1 - during first administration and further as needed).
[q] Dosing for Genotropin subjects allowed in the morning.
[r] At 15 min, 1 h, and 2 h post dose.

Appendix 3: Schedule of Events during trial CT-302

	SCREENING	VISIT 1	CMAX VISIT[a]	VISIT 2	VISIT 3/ET[b]
	Weeks -4 to -1	Week 1	Week 4 (+ 1 Week)	Week 13 (± 1 Week)	Week 26 (± 1 Week)
	Morning	*Predose, Morning*	*1-2d Postdose, Morning*	*5d ± 1d Postdose, Morning*	*5d ± 1d Postdose, Morning*
Informed consent	X				
Medical history	X				
Concomitant medication	X	X	X	X	X
Vital sign measurements[c]	X	X		X	X
Height[d] and weight	X	X		X	X
Limited physical examination	X	X		X	X
Pubertal status assessment	X	X		X	X
Bone age x-ray[e]	X				
Fundoscopy[f]	X				X
Blood sample collection	X[g]		X[h]	X[i]	X[j]
Trial drug and subject diary dispensing		X		X	
Drug preparation/administration training		X			
Subject diary training		X			
CSDS-P		X[k]		X[l]	X
CSDS-C[m]		X[k]		X[l]	X
C&OS-P		X[k]		X[l]	
On-site trial drug administration		X			
Local tolerability assessment[n]		X			
PQ-P[o]				X[l]	
PQ-C[m,o]				X[l]	
Adverse events[p]			X	X	X
Trial drug compliance[q]			X	X	X
Dose adjustment[r]				X	

Source: Clinical Study Report for CT-302, page 34

Abbreviations: C&OS-P = Convenience & Overall Satisfaction domains of the abbreviated 9-item Treatment Satisfaction Questionnaire for Medication; Cmax = maximum
observed concentration; CSDS-C = Child Sheehan Disability Scale – Child; CSDS-P = Child Sheehan Disability Scale – Parent; d = day; ET = Early Termination; FT3 = free triiodothyronine; FT4 = free thyroxine; HbA1c = hemoglobin A1c; hCG = human chorionic gonadotropin; hGH = human growth hormone; IGF-1 = insulin-like growth
factor 1; IGFBP-3 = insulin-like growth factor binding protein-3; mPEG = methoxypolyethylene glycol; PEG = polyethylene glycol; PQ-C = Preference Questionnaire – Child;
PQ-P = Preference Questionnaire – Parent; (b) (4) TSH = thyroid stimulating hormone.
a Subjects <3 years old at Visit 1 performed the Cmax Visit. Subjects ≥3 years old at Visit 1 did not perform the Cmax Visit.
b An ET Visit was to be performed for all subjects exiting the trial and was to include all procedures listed for Visit 3. Stopping trial drug did not require termination from the trial and, therefore, did not require an ET Visit.
c Vital sign measurement included heart rate, blood pressure, respiratory rate, and body temperature, which were to be performed after the subject had rested for at least 5 minutes.
d Height was to be measured at each visit at approximately the same time of day, preferably by the same auxologist.
e Locally read bone age x-ray was only required at Screening if the subject was at Tanner stage 4 and an x-ray performed within the past 52 weeks showing a bone age delay of ≥6 months was not available.
f Fundoscopy may also have been performed at any time, if clinically indicated.

g Blood samples collected at Screening were to be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. The analyses of antibodies against hGH and PEG were only to be conducted after enrollment and were not required for eligibility verification. Data were used to support evaluation of antibody detection after dosing. Female subjects of child-bearing potential were also to have blood samples tested for hCG.
h Blood samples collected at the Cmax Visit were to be tested for the following: hGH, IGF-1, and IGFBP-3, and hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c).
i Blood samples collected at Visit 2 were to be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects <3 years old at Visit 1 were also to have blood samples tested for mPEG. Female subjects of child-bearing potential were also to have blood samples tested for hCG.
j Blood samples collected at Visit 3 were to be tested for the following: IGF-1 and IGFBP-3, antibodies against hGH and PEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Subjects ≥9 years old at Visit 1 were also to have blood samples tested for (b) (4). Subjects <3 years old at Visit 1 were also to have blood samples tested for mPEG. Female subjects of child-bearing potential were also to have blood samples tested for hCG.
k At Visit 1, the CSDS-P, CSDS-C, and C&OS-P were only to be completed for subjects treated with daily hGH before enrollment.
l The CSDS-P CSDS-C, C&OS-P, PQ-P, and PQ-C were to be completed (as applicable) within the subject diary immediately before the sixth dose of trial drug and again at Visit 2.
m The CSDS-C and PQ-C were only to be completed by subjects ≥9 years old at Visit 1.
n Local tolerability assessments at the injection site were to be performed at the time of injection and 15 minutes, 1 hour, and 2 hours after dosing.
o The PQ-P and PQ-C were only to be completed for subjects treated with daily hGH before enrollment.
p Adverse event review included review of subject diary and physical examination of injection sites.
q Trial drug compliance included review of subject diary and returned trial drug.
r Dose adjustments at visits were based on subject weight at visits. However, dose adjustments may have occurred between visits

Appendix 4: Schedule of Events during trial CT-301EXT

	VISIT 1[a]	VISIT 2	VISIT 3	VISIT 4	VISIT 5/CV/ETV[b]
	Week 1 Day 1	Week 13 (± 2 weeks)	Week 26 (+ 2 Weeks)	Week 39 (± 2 Weeks)	Week 52 (± 2 Weeks)
	Morning	5d ±1d Postdose, Morning	5d ±1d Postdose, Morning	5d ± 1d Postdose, Morning	5d ± 1d Postdose, Morning
Informed consent	X				
Interval history, medications and health status review[c]	X				
Vital sign measurements[d]	X	X	X	X	X
Height[e] & weight	X	X	X	X	X
Physical examination	X	X	X	X	X
Pubertal status assessment	X	X	X	X	X
Blood sample collection – A[f]	X	X	X	X	X
Blood sample collection – B[g]	X		X		X
Bone age x-ray[h]	X				X
Investigational product preparation/administration training	X				
Training on GH Auto-Injector[i]	(X)	(X)	(X)	(X)	(X)
Trial diary training	X				
C&OS-P[j]	X[k]	X			
CSDS-P[j]	X[k]	X			
CSDS-C[j,l]	X[k]	X			
PQ-P[j]		X			
PQ-C[j,l]		X			
DUQ[j]		X			
Investigational product dose adjustmentm	X	X	X	X	X
Local tolerability assessmentn	X	X	X	X	X
Investigational product & subject diary dispensing	X	X	X	X	X
Investigational product complianceo		X	X	X	X
Concomitant medications		X	X	X	X
Adverse eventsp		X	X	X	X

Source: Clinical Study Report for CT-301EXT, page 32

Abbreviations: AE = adverse event; C&OS-P = convenience & overall satisfaction domains of the abbreviated Treatment Satisfaction Questionnaire for Medication version 9;
CSDS-C = Child Sheehan Disability Scale – Child; CSDS-P = Child Sheehan Disability Scale – Parent; CV = Completion Visit; d = day; DUQ = Device Usability Questionnaire; ETV = Early Termination Visit; FT3 = free triiodothyronine; FT4 = free thyroxine; GH = growth hormone; HbA1c = hemoglobin A1c; hCG = human chorionic gonadotropin; hGH = human growth hormone; IGF-1 = insulin-like growth factor-1; IGFBP-3 = insulin-like growth factor binding protein-3; mPEG = methoxypolyethylene glycol; PEG = polyethylene glycol; PQ-C = Preference Questionnaire – Child; PQ-P = Preference Questionnaire – Parent; TSH = thyroid stimulating hormone.

[a] In nearly all cases, Visit 1 of this extension trial was the same day as the final visit of the prior trial, and the first dose occurred as soon as possible. A period of up to approximately 6 weeks between the final visit of the prior trial and first dose (Day 1) of the extension trial was acceptable. Visit 1 assessments were to be performed unless they were performed for the final visit of the prior trial. In the unusual event there is a gap of approximately 4-6 weeks, then all Visit 1 assessments were to be repeated for Day 1 except physical exam, blood collection and bone age x-ray.

[b] After Visit 5, visits continued every 3 months. A CV/ETV was performed for all subjects either completing the trial or terminating trial participation prematurely. The visit should include all procedures listed for Visit 5, as applicable.

[c] Interval history, medications and health status included disease states diagnosed since the initiation of the prior trial (e.g., new onset migraines) collected as medical history; medical history from the prior trial carried forward into this trial's database; ongoing AEs from the prior trial, which were followed until resolution or stabilization; review of subject diary from the prior trial; and current therapies.

[d] Vital sign measurements include heart rate, blood pressure, respiratory rate, and body temperature, which were performed after the subject had rested for at least 5 minutes.
[e] Height was measured at each visit at approximately the same time of day, preferably by the same auxologist.
[f] Blood sample collection A includes IGF-1, IGFBP-3, antibodies against hGH and PEG, and hCG for females of child-bearing potential. If warranted, lonapegsomatropin-tcgd, hGH, and PEG serum levels may be analyzed for the interpretation of immunogenicity titers.
[g] Blood sample collection B included mPEG, hormone/glycemic status (TSH, FT4, FT3, morning cortisol, and HbA1c), chemistry, hematology, and lipid panel. Fasting was not required.
[h] Bone age x-ray was not required at Visit 1 if there was documentation of a bone age x-ray performed within the previous 52 weeks. However, if a subject's prior documented bone age was >12.0 years, and it was performed >9 months prior to Visit 1, a bone age x-ray was to be performed within approximately 4 weeks of Visit 1. Bone age x-ray may have been performed at any time, if clinically indicated.
[i] Once available, transition to the GH Auto-Injector was to occur in the US (only) at the next regularly scheduled trial visit when thorough training on preparation and administration was to occur.
[j] At Visit 1, the C&OS-P, CSDS-P, and CSDS-C were to be completed for all subjects
[k] For subjects who were treated with Genotropin in the parent trial (CT-301), C&OS-P, CSDS-P, CSDS-C, PQ-P, and PQ-C were to be completed (as applicable) within the subject diary immediately prior to the sixth dose of investigational product, and in clinic at Visit 2, prior to review of the subject diary, AEs, and concomitant medications. For subjects transitioning to the GH Auto-Injector, C&OS-P, CSDS-P, and CSDS-C were to be completed (as applicable) within the subject diary immediately prior to the sixth dose after transition to the GH Auto-Injector, and again in clinic at the following scheduled visit, prior to review of the subject diary, AEs, and concomitant medications. Additionally, for subjects transitioning to the GH Auto-Injector, the DUQ was to be completed within the subject diary on the day of the sixth dose of investigational product, and in clinic at Visit 2, prior to review of the subject diary, AEs, and concomitant medications.
[l] CSDS-C and PQ-C should only be completed by subjects ≥9 years old at the time of Visit 1, and/or at the transition to the GH Auto-Injector, as applicable.
[m] Dose adjustments at visits were typically based on subject weight at visits. However, dose adjustments may have occurred between visits in accordance with the protocol.
[n] Local tolerability assessment at the injection site was to be performed at time of injection, and by the trial staff at visits.
[o] Investigational product compliance included review of subject diary and returned investigational product.
[p] Adverse event review included review of subject diary and physical examination of injection sites. Adverse events that were considered mild and not related to investigational product were not reported on the AE case report form.

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): CT-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 346		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: __X__ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) __0__		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CT-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: __130__		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): ___0__		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): __1__		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: __X__ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S		

Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) __0___		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): CT-301EXT

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _234__		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): ___0__		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): __1__		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: __X__ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) __0__		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHIVANGI R VACHHANI
02/26/2021 05:07:03 PM

MARINA ZEMSKOVA
02/26/2021 06:08:12 PM