CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	July 30, 2021
From	Marina Zemskova, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	BLA 761177
Applicant	Ascendis Pharma
Date of Submission	6/25/2020
PDUFA Goal Date	9/25/2021 (based on 3-month clock extension)
Proprietary Name	Skytrofa
Established or Proper Name	Lonapegsomatropin-tcgd
Dosage Form(s)	Lyophilized powder available in single-dose, dual-chamber, prefilled cartridges. The following strengths for injection are available: 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 Indication(s)/Population(s)	Treatment of pediatric patients who have growth failure due to growth hormone deficiency
Applicant Proposed Dosing Regimen(s)	0.24 mg/kg/week
Recommendation on Regulatory Action	*Approval*

Material Reviewed/Consulted	**Names of discipline reviewers**
Medical Officer Review	Shivangi Vachhani
Statistical Review	Alexander Cambon, Feng Li
Pharmacology Toxicology Review	Jeffrey Quinn, Todd Bourcier
OPQ Review	Zhong Zhao, Susan Kirshner, Candace Gomez-Broughton, Mekonnen Lemma Dechassa, Ramesh Potla, Michael R.Shanks, Reyes Candau-Chacon, Virginia Carroll, Viviana Matta
CDRH Review	Shanly Chen, Rumi Young
Clinical Pharmacology Review	Sang Chung, Justin Earp, Jayabharathi Vaidyanathan, Doanh Tran
OPDP	Charuni Shah, Melinda McLawhorn
OSE/DMEPA	Jason Flint, Ebony Whaley, Lolita White
DPMH	Wenjie Sun, Ethan D. Hausman, Miriam Dinatale, Shetarra Walker, Lynne P. Yao, John J. Alexander
DRM	Naomi Boston, Brad Moriyama

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
CDRH= Center for Devices and Radiological Health
DMEPA=Division of Medication Error Prevention and Analysis
DPMH=Division of Pediatric and Maternal Health
DRM=Division of Risk Management

Benefit-Risk Assessment Framework

The Applicant proposes lonapegsomatropin-tcgd, a long-acting recombinant human growth hormone (hGH) that is covalently bonded via a TransCon linker to a methoxypolyethylene glycol (mPEG) carrier, as a weekly treatment for pediatric patients who have growth failure due growth hormone deficiency (GHD). The proposed product is a biologic-device combination containing a glass dual-chamber cartridge with the drug product lonapegsomatropin-tcgd and an auto-injector. The proposed dose is 0.24 mg/kg/week administered subcutaneously. Currently approved formulations for this condition require daily or every-other-day injections.

Pediatric GHD (PGHD) is a well-characterized condition and can be idiopathic or secondary to congenital (e.g., pituitary hypoplasia, various genetic causes) or acquired causes (e.g., trauma, infection, tumors). PGHD deficiency results in inadequate circulating growth hormone (GH) and insulin-like growth factor 1 (IGF-I) levels leading to delayed growth in children with opened epiphysis, short final adult height and diminished quality of life.

Professional guidelines recommend GH replacement therapy in children with GHD. Exogenous treatment with hGH aims at mimicking the function of endogenous GH secretion (i.e., a replacement therapy) leading to normalization of IGF-1 levels and improvement in growth velocity. As per the GH Research Society (2000) and Pediatric Society (2016), the primary objectives of the therapy of children with GHD are normalization of height during childhood and attainment of normal adult height.

Multiple hGH products are currently approved and marketed in the US for treatment of pediatric patients with growth failure due to GHD.[1] Documentation of a drug-induced improvement in annualized growth velocity (AGV) has been used as a validated surrogate of benefit to establish the efficacy and support the approval of these hGH formulations. GH and IGF-1 deficiencies in these patients are associated with delayed growth. Replacement of missing hormones with hGH leads to the improvement in hormone-associated delay in AGV and confers the benefit of increased height of these drugs in this population. Trials that have supported approval of these drugs have shown that all approved hGH products improve AGV and other growth parameters (e.g., height, height standard deviation scores (SDS)) via IGF-1 mediated action of GH at the growth plate. It is notable that the first approved hGH products in children with GHD demonstrated the effect of hGH on final adult height in studies of long duration (up to 8 years). These long-term studies demonstrated that rhGH-induced changes in AGV observed during the first year of treatment were sustained over the years of treatment and ultimately translated into increased final adult height. Therefore, FDA has accepted short-term changes in AGV that are non-inferior to the active comparator (approved hGH with known effect on AGV) as a surrogate endpoint to evaluate the efficacy of the products with a native GH sequence for the treatment of short stature in pediatric patients with GHD. In this context, requirement of longer trials would be an unnecessary burden. Given the history of this class of products and because PGHD is a rare disease, FDA has accepted a single adequate and well-controlled study for the approval of hGH products with native GH sequence for the PGHD indication.

Benefits

CT-301 was a phase 3, randomized, active-controlled, open-label, 52-week study comparing the efficacy and safety of lonapegsomatropin-tcgd with Genotropin. One hundred and sixty-one treatment-naïve subjects with short stature due to PGHD were enrolled in the study and randomized in 2:1 ratio to receive lonapegsomatropin-tcgd or Genotropin, respectively. In this trial, lonapegsomatropin was demonstrated to be non-inferior to Genotropin in the improvement in AGV. The mean treatment difference in AGV at Week 52 between lonapegsomatropin-tcgd and

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

Genotropin groups was 0.8 cm/year (95% CI 0.13; 1.47), p=0.009. The upper bound of the 95% CI was <2, meeting non-inferiority. In addition, a test for superiority was prespecified and controlled for type 1 error using a hierarchical testing approach. Analyses of secondary endpoints demonstrated that lonapegsomatropin-tcgd therapy in subjects with PGHD also increased height SDS at the end of 52 weeks and was similar to Genotropin: mean height SDS at baseline were approximately - 3 SDS in each group and normalized by the end of 52 weeks of treatment (1.1 SDS in lonapegsomatropin-tcgd group and 0.96 SDS in Genotropin group at the end of treatment). Short stature in pediatric patients is defined as a height below 2 SDS for age, sex, and race. In addition, height SDS is widely used in clinical practice to evaluate the appropriate growth of children at various stages of development. Thus, changes in height SDS were traditionally accepted and used as a supportive growth endpoint in studies evaluating the effect of hGH on growth in pediatric patients with GHD. The improvement in the growth parameters also positively correlated with normalization in IGF-1 SDS, indicating that lonapegsomatropin-tcgd effectively replaces the missing hormone associated with deficient state in these patients. The overall data in this trial establish the benefit of lonapegsomatropin-tcgd therapy in the treatment of pediatric patients with GHD. However, it should be also noted that the ultimate goal of treatment is the improvement in growth and final height, and the target IGF-1 levels to optimize the balance between height gain and potential risks are not established to date[2]. There is also no correlation between levels of IGF-1 and final height. Thus, the assessment of treatment efficacy in clinical practice should not be based on IGF-1 levels, but rather on AGV and height.

Studies CT-302 and CT-301EXT CT-301 provide supportive evidence of effectiveness; the results demonstrated improvement in growth parameters in children 1 year and older with PGHD treated with lonapegsomatropin-tcgd. In study CT-302, mean AGV was 8.72 cm/year (95% CI: 8.55, 9.77), mean change in height SDS was 0.25 (00.2) (95% CI: 0.21, 0.29) at Week 26. The LS means (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. In study CT-301EXT, mean (SD) AGV was 8.8 (2.2) cm/year, mean change in height SDS from baseline was 0.27 (0.19) and IGF-1 SDS was 1.2 (1.34), respectively. However, these results should be interpreted with caution because of multiple factors, including that the studies were not designed to evaluate efficacy, did not have a placebo arm, dose was titrated based on IGF-1, and all subjects had been exposed to other hGH therapies prior to the enrollment. (b) (4)

The (b) (4) lonapegsomatropin-tcgd provides a significant improvement in growth over Genotropin in pediatric patients with GHD. However, (b) (4) (b) (4) a single trial comparing the effect of two drugs on a surrogate endpoint, AGV, and the observed difference of 0.86 cm/year in AGV at 12 months is small and of unclear clinical significance. It remains unknown whether this difference will ultimately translate to a difference in final adult height. In addition, statistical significance was not consistent between all subgroups, e.g., in subjects > 6 years old, in female subjects, in subjects from US lonapegsomatropin-tcgd was not superior to Genotropin. (b) (4)

Risks

The risks associated with the use of lonapegsomatropin-tcgd are expected to be generally consistent with the risks known to be associated with the hGH class of drugs. These risks include such common adverse events (AE) as headache and edema and more rare serious adverse events of intracranial hypertension, adrenal insufficiency, hyperglycemia, lipodystrophy, scoliosis, slipped capital femoral epiphysis (SCFE), injection site reactions, increased risk of immunogenicity and development of new tumors.

[2] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. 2016. Horm Res Paediatr;86:361-397

The most common AEs that occurred more frequently in subjects treated with lonapegsomatropin-tcgd compared to subjects treated with Genotropin in Study CT-301 were pyrexia (15% of subjects compared to 9% on Genotropin), hemorrhage (including epistaxis, hemorrhage due to contusion, petechiae and eye hemorrhage; 7% vs 2% on Genotropin), viral infection (15% vs 11% on Genotropin), arthralgia and arthritis (6% vs 2% on Genotropin), cough (10% vs 7% on Genotropin), nausea and vomiting (10% vs 7% on Genotropin), abdominal pain (6% vs 4 % on Genotropin), and diarrhea (6% vs 5% on Genotropin). Adrenal insufficiency, intracranial hypertension, pancreatitis, slipped capital femoral epiphyses are rare but serious AEs associated with use of all hGH. Mild adrenal insufficiency was reported in 2 subjects treated with lonapegsomatropin-tcgd and 1 subject treated with Genotropin, respectively. No adrenal crisis was reported in any of subjects. Injection site reactions occurred in 4 subjects treated with lonapegsomatropin-tcgd; 2 of these subjects developed lipoatrophy. No cases of intracranial hypertension, pancreatitis, or slipped capital femoral epiphysis were reported during the study in any of the treatment groups. Although definitive conclusions regarding the effect of lonapegsomatropin on tumor development is limited because of the relatively short duration of the trials, the overall incidence of neoplasms reported was low in the clinical program. No malignant tumors were reported; five subjects treated with lonapegsomatropin-tcgd and one subject treated with Genotropin developed benign tumors.

With all hGH formulations, there is a concern for chronically elevated IGF-1 levels above the normal range, as they may be associated with various AEs characteristic of acromegaly, including headache, intracranial hypertension, edema, and tumors. Therefore, IGF-1 levels are monitored during the treatment with the goal to not exceed +2 SDS - +3 SDS. In study CT-301, 39 subjects had at least one IGF-1 value > +2 SDS (37 subjects treated with lonapegsomatropin-tcgd and 2 subjects treated with Genotropin). All levels normalized with or without dose adjustments. All subjects with excessive IGF-1 (above the pre-specified threshold) were asymptomatic. Small, intermittent, and asymptomatic increases in blood phosphate and alkaline phosphatase levels of unknown clinical significance were observed in subjects treated with lonapegsomatropin-tcgd (86% vs 36% of subjects, respectively); the events resolved without dose adjustment or treatment.

Lastly, this product contains mPEG. mPEG accumulation associated with vacuolation of cells of choroid plexus was noted in animal studies that led to concern that accumulation of mPEG may be associated with various neurological symptoms in humans. However, the team concluded that asymptomatic accumulation of mPEG in cells of choroid plexus in animals is not associated with potential risk(s) to human at the proposed dose based on the following:1) nonclinical findings were observed at higher than human exposure at the proposed dose and were not associated with neurotoxicity; 2) clinical pharmacology analysis confirmed the low predicted mPEG levels at the proposed doses; 3) no neurological AEs that may be suggestive of mPEG were detected in clinical program. (b) (4)

As with all therapeutic proteins, there is potential for immunogenicity that may decrease efficacy of the drug and/or induce various hypersensitivity reactions. The submitted immunogenicity data do not raise any concerns. The frequency of antidrug antibodies was low and within the expected range: anti-hGH antibodies were observed in 7% of subjects treated with lonapegsomatropin and 4% of subjects treated with Genotropin. Two lonapegsomatropin-treated subjects had anti-mPEG antibodies, which were transient. No neutralizing antibodies developed during the clinical program. There was no impact of antibodies on growth parameters, IGF-1 levels, or PK parameters. All allergic reactions were mild, no severe hypersensitivity reactions were reported.

Overall, the types and frequencies of lonapegsomatropin-tcgd -related AEs seen in the clinical program are consistent with the known safety profile of the hGH drug class. No new safety signals were identified with use of lonapegsomatropin-tcgd or mPEG in subjects with PGHD in the clinical program. Product labeling will be used to

mitigate the known risks associated with lonapegsomatropin-tcgd in the PGHD population. (b) (4) (b) (4)

In conclusion, safety and efficacy data from the single pivotal, randomized, active control phase 3 study conducted to support the approval of lonapegsomatropin-tcgd for the proposed indication have demonstrated that the benefits outweigh the potential risks in this population. Specifically, lonapegsomatropin-tcgd provides a benefit in the improvement in AGV in patients with PGHD that is expected to translate to improvement in final adult height. Safety issues were consistent with the expected class specific side effects (e.g., headache, arthralgia); no new safety issues were identified. Safety issues will be mitigated through labeling. Thus, I recommend approval of lonapegsomatropin-tcgd for the proposed indication.

However, I recommend limiting approval to pediatric patients > 1 year old. The Applicant did not submit data to support the effective and safe use of lonapegsomatropin-tcgd in pediatric subjects with PGHD < 1 year old in the clinical program. In addition, the indication should be also restricted to children with body weight > 11.5 kg based on the currently on the currently available lowest dosage strength of cartridge (3 mg) and on the weight-based dosing recommendations.

Lastly, I do not recommend (b) (4)

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• PGHD is a well-characterized condition that may be idiopathic or secondary to congenital or acquired causes. • GH deficiency results in inadequate circulating GH and IGF-I levels. • Low levels of GH and IGF-1 in patients with PGHD adversely affect linear growth and ultimately result in short stature. • Guidelines on the treatment of pediatric patients with GHD issued by professional societies[3][4] recommend treating pediatric patients with proven GHD to normalize height during childhood and attain normal adult height.	• PGHD is associated with delayed growth and ultimately short final adult height due to low GH/IGF-1 levels.
Current Treatment Options	• Multiple recombinant human growth hormone (rhGH; somatropin) products are FDA-approved for the treatment of short stature associated with PGHD and on the U.S. market. All approved hGH products require daily or every other day injections via the subcutaneous route. • Treatment with hGH is a replacement therapy that mimics the action of endogenous GH leading to increase in IGF-1 levels and improvement in linear growth and ultimately final adult height. • The first approved hGH formulations were studied in clinical trials until final adult height was achieved and demonstrated that improved AGV was sustained over the years of treatment and ultimately improved/normalized final adult height.	• Multiple hGH products are approved for the treatment of PGHD. • Replacement therapy with rhGH aims to mimic the action of endogenous GH, leading to an increase in IGF-1 levels that act on growth plates and improve linear growth. • In this population, there is evidence that hGH-induced improvement in AGV sustained over the years of treatment and leads to the improvement in final adult height. • A long-acting formulation of hGH has the potential to reduce discomfort and increase compliance by requiring less frequent injections, a particular advantage in the pediatric population.

[3] GH RESEARCH SOCIETY. Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society. *The Journal of Clinical Endocrinology & Metabolism*. 2000; 85: 3990–3993

[4] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H. on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. Horm Res Paediatr. 2016;86:361-397

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• AGV at week 52 was the primary endpoint in Study CT-301. The results demonstrated that the effect of lonapegsomatropin-tcgd on AGV is non-inferior to the effect of Genotropin: the mean treatment difference in AGV between lonapegsomatropin-tcgd and Genotropin groups was 0.8 cm/year (95% CI 0.13; 1.47), p=0.009. • Height SDS increased in lonapegsomatropin-tcgd treated subjects by 1.1 at week 52 compared to baseline values. Similar improvement in height SDS was observed in the Genotropin group (0.96). • The improvement in IGF-1 levels supports the claim that the drug effectively replaces the deficient hormone. Mean IGF-1 SDS increased during the study in all subjects and were in 0-2 SDS range in 70% of subjects treated with lonapegsomatropin and in 60% of subjects with Genotropin at the end of 52 weeks. However, it should be noted that normalization of IGF-1 is not the ultimate goal of treatment and there is no known correlation between IGF-1 levels and final height. • Secondary superiority analysis comparing lonapegsomatropin to Genotropin demonstrated more pronounced effect of lonapegsomatropin-tcgd on AGV over Genotropin. However, the superiority was demonstrated in a single study only and by comparison of the effect of the drugs on AGV, not a difference in final height. The observed treatment difference is relatively small and therefore the difference in this one trial has unclear clinical significance.	• Treatment with lonapegsomatropin-tcgd increases annual growth velocity at week 52; the improvement in AGV is within prespecified non-inferiority margins compared to Genotropin. • An improvement in growth parameters (AGV, height SDS) is consistent with that found with other hGH products in patients with PGHD. (b) (4) • Clinically, the assessment of treatment efficacy should not be based on IGF-1 levels, but rather on AGV and height. IGF-1 levels should be monitored for safety reasons as well as to ensure compliance with the treatment.
Risk and Risk Management	• The safety profile of lonapegsomatropin-tcgd has been generally well-characterized and is consistent with the drug class. • No new safety signals for lonapegsomatropin-tcgd in the PGHD population were identified in the clinical program. • The most common AEs associated with use of lonapegsomatropin-tcgd in study CT-301 were pyrexia (15% of subjects), infection viral (15.2%), cough (10.5% of subjects), nausea and vomiting (10.5% of subjects), hemorrhage that included epistaxis, petechia, eye hemorrhage and contusion-induced (6.7%% of subjects), and arthralgia, abdominal pain, and diarrhea (5.7% of subjects, each. • AEs of adrenal insufficiency were mild and occurred in 2 subjects treated with lonapegsomatropin-tcgd. No adrenal crisis was reported in any of subjects.	• Treatment with lonapegsomatropin-tcgd is associated with headache, arthralgia, lipoatrophy, adrenal insufficiency, hypothyroidism, and injection site reactions. All risks are consistent with the drug class and are monitorable. Monitoring and interventions will be recommended in labeling to address these risks. • Potential risks of tumorogenesis, intracranial hypertension, slipped capital epiphysis, pancreatitis are expected for the rhGH class of drugs and will be mitigated through the labeling. Like other drugs in the class, lonapegsomatropin-tcgd will be contraindicated in patients with active malignancies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Injection site reactions occurred in 4 subjects treated with lonapegsomatropin-tcgd. Of these, 2 subjects developed lipoatrophy. • Intracranial hypertension, slipped capital epiphyses, or pancreatitis were not reported in the development program. • No increased risk of tumorogenesis with lonapegsomatropin-tcgd use was observed in the clinical program. • Chronically elevated IGF-1 levels above the normal range (> +2SDS) are associated with potential risk for various AEs including headache, intracranial hypertension, edema, tumors, etc. In study CT-301, 7.6% of subjects had at least one IGF-1 value >+2SDS. All levels normalized without or with next dose adjustments. All subjects were asymptomatic. • The immunogenicity data did not raise any particular concerns. No severe allergic reactions were reported. • mPEG accumulation associated with vacuolation of cells of choroid plexus was noted in animal studies. 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 doses associated with mPEG accumulation. No unexpected neurological signals that are potentially associated with mPEG accumulation were detected in subjects treated with lonapegsomatropin in the clinical program. Most of the neurologic AEs were rare and occurred in one subject each (attention deficit disorder, affect lability, depressive symptom, tremor, enuresis, tonic-clonic seizure) and were likely related to an underlying medical condition (e.g., seizure disorder). The only AEs that occurred in more than one subject was headache (12.4% in lonapegsomatropin-tcgd group vs. 14.3% - in Genotropin group, respectively) and dizziness (1.9% in lonapegsomatropin-tcgd group vs. 1.8 % - in Genotropin group). Headache is a known effect of hGH treatment, and headache and dizziness are also frequently seen in this age group. There was no imbalance in frequency of these AEs between lonapegsomatropin-tcgd group and the Genotropin group. • Labeling will be sufficient to mitigate the risks associated with use of lonapegsomatropin-tcgd in patients with PGHD.	• Increase in IGF-1 levels above the normal range is a monitorable risk. The risk is mitigated by the monitoring IGF-1 levels and dose adjustment. • Nonclinical, clinical pharmacology, and clinical data overall support a minimal mPEG-related risk at the proposed dose that does not require labeling. • No risks identified require risk management beyond labeling.

1. Background

On June 25, 2020 Ascendis Pharma submitted a Biologics License Application (BLA) for lonapegsomatropin-tcgd, a long-acting recombinant human growth hormone (rhGH) derivative, under Section 351(a) of the Public Health Service Act in support of the following indication: Treatment of pediatric patients who have growth failure due growth hormone deficiency.

Lonapegsomatropin-tcgd (ACP-011) is a long-acting hGH derivative that is bonded via a TransCon linker to a methoxypolyethylene glycol (mPEG) carrier. Following subcutaneous administration, the linker auto-hydrolyzes and releases unmodified active rhGH over time, allowing for once-weekly dosing. Lonapegsomatropin-tcgd also has an extended circulation time due to decreased renal clearance.

Pediatric growth hormone deficiency (PGHD) is a well-characterized condition that results from insufficient production of growth hormone (GH) from the somatotroph cells of the anterior pituitary gland. PGHD can be idiopathic or secondary to congenital (e.g., pituitary hypoplasia, empty sells, various genetic causes) or acquired causes (e.g., trauma, infection, tumors). PGHD deficiency results in inadequate circulating GH and insulin-like growth factor 1 (IGF-I) levels and results in delayed growth and short stature in children with open epiphyses.

Over the last decades, physicians and professional societies have recommended hGH (somatropin) therapy for the treatment of PGHD. Exogenous hGH treatment aims at mimicking the function of GH secretion (i.e., a replacement therapy), leading to normalization of IGF-1 levels and improvement in linear growth and final adult height. Guidelines on the treatment of pediatric patients with GHD issued by professional societies[5] [6]recommend treating pediatric patients with confirmed GHD to normalize height during childhood and to attain normal adult height. Treatment of PGHD with hGH should be discontinued once the epiphyses are closed, and patients should be reevaluated at that time for GHD. GHD may (e.g., congenital) or may not (e.g., idiopathic) persist into adult life and the objectives of treatment of GH treatment in adults are different.

Several hGH products are approved for the treatment of short stature associated with GHD in children and are on the US market.[7] While clinical development programs for these products have demonstrated improvement in annualized growth velocity (AGV), the first approved products also evaluated the improvement in final adult height and, thus, established AGV as a surrogate endpoint for final height improvement for studies evaluating efficacy of hGH in PGHD (refer to **Error! Reference source not found.Error! Reference source not found.** section below). The safety profile of these products is well-characterized and known adverse effects include hypothyroidism, glucose intolerance, slipped capital femoral epiphysis, scoliosis, fluid retention, arthralgia, carpal tunnel syndrome, myalgias, risk of neoplasm, intracranial hypertension and immunogenicity.

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[5] GH RESEARCH SOCIETY. Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society. *The Journal of Clinical Endocrinology & Metabolism*. 2000; 85: 3990–3993

[6] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H. on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. Horm Res Paediatr. 2016;86:361-397

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

All approved hGH products require daily or every other day injections via the subcutaneous route. A long-acting form of hGH has the potential to reduce discomfort and increase compliance by requiring less frequent injections, an advantage particularly in the pediatric population.

Basis of approval for hGH products intended to treat PGHD

The safety and efficacy of products containing rhGH as an active ingredient are well-established in PGHD and other indications such as the treatment of short stature in pediatric patients with other non-GHD states and for the replacement of endogenous growth hormone in adults with GHD; however, these indications are not relevant to the current application for lonapegsomatropin-tcgd, and thus, will not be discussed in this memo.

PGHD is associated with delayed growth due to inadequate GH, and improvement in growth is the recommended target for therapeutic intervention in children with GHD. The efficacy of hGH products for the treatment of pediatric patients with growth failure due to GHD has been established using short-term improvement in AGV (1-2 years) as a surrogate of improvement for final adult height. However, earlier pivotal studies with hGH formulations (e.g., Humatrope) in children with GHD were of long duration (up to 8 years and/or until final adult height was achieved) and evaluated the effect of rhGH on final adult height along with AGV. These long-term studies demonstrated that hGH-induced changes in AGV observed during the first year of treatment were sustained over years of treatment and ultimately translated into increased final adult height in pediatric patients with short stature due to GHD.

Exogenous GH treatment in PGHD is a replacement therapy and the overarching goal is to mimic the function of endogenous GH secretion. It is expected that binding of hGH to the human growth hormone receptor (hGHR) will raise IGF-1 levels, which is what occurs physiologically. IGF-1 is the main mediator of the actions of GH at the growth plate, and its actions are ultimately responsible for linear growth. As such, all approved hGH products with the GH native sequence have provided scientific evidence that these products increase IGF-1 levels.

Therefore, FDA accepts AGV at timepoints of 1-2 years as a surrogate endpoint to evaluate the efficacy of products with the native GH sequence intended for the treatment of growth failure in pediatric patients with GHD. This surrogate endpoint is objective and is supported by clear mechanistic rationale and clinical data from longer duration trials that followed patients to final adult height, providing evidence that short-term improvement in AGV translates into the improvement in final adult height, the ultimate goal for therapy. In this population, AGV has therefore supported full approval rather than accelerated approval.

Highlights of Regulatory History (refer to Clinical Review in DARRTS from 2/26/2021 for details)

This memorandum focuses on the product's development as it related to the PGHD indication. The Sponsor initiated the lonapegsomatropin-tcgd (ACP-011) development program (b) (4) using ACP-001, a predecessor molecule containing an (b) (4) kDa mPEG carrier. (b) (4) (b) (4) The Sponsor modified their hGH product and developed ACP-011 that contains a 40 kDa mPEG molecule allowing for a smaller injection volume, a lower viscosity solution compatible with smaller caliber needles and reduced the amount of mPEG administered per dose.

IND 126053 for lonapegsomatropin-tcgd was opened on 9/25/2015 with a phase 1 protocol evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of lonapegsomatropin-tcgd compared to ACP-001 in healthy volunteers (CT-101).

- End-of-Phase 2 (EOP2) meeting (7/27/2016): The Sponsor and FDA discussed the program, including the design of the phase 3 trial for PGHD.
  - FDA overall agreed with the proposed phase 3 study design, study population, duration of 12 months for the core period, the proposed dose (0.24 mg hGH/kg/week) and the proposed primary endpoint of AGV. FDA recommended the primary analysis for efficacy to be conducted in the intention to treat population.
  - FDA disagreed with the proposed duration of the extension period (b) (4) and number of subjects with longer exposure ((b) (4) subjects with > 12 months exposure) and indicated that these data might be insufficient to establish the long-term safety and efficacy of the product. The sponsor agreed to reconsider the duration of the exposure and number of subjects in the extension trial.
  - FDA agreed with the sponsor's plan to provide the data from the phase 1 study (CT-102) and clinical data from at least 20 subjects who used the auto-injector for at least 1 month in the phase 3 extension study (CT-301EXT) to support registration of the lonapegsomatropin-tcgd autoinjector and pen needle combination product configuration.
  - FDA requested the sponsor to submit a human factors validation protocol for the Agency to review and provided elements that should be included in the protocol.

- Phase 3 Protocol: On 9/13/2016, the sponsor submitted the protocol for the Phase 3 study evaluating safety and efficacy of lonapegsomatropin-tcgd compared to Genotropin after 52 weeks of treatment in prepubertal subjects with growth failure due to GHD (CT-301). The protocol incorporated FDA's recommendations provided during the EOP2 meeting. The submission also included the sponsor's justification for the non-inferiority margin (2 cm) and revised approach to the statistical analysis. Dr. Alex Cambon, the biostatistician, concluded that the sponsor's justification for the proposed non-inferiority margin (2 cm/year) addressed ICH E9, ICH E10 and FDA Guidance on Non-Inferiority Trials and was acceptable (refer to review in DARRTS from 10/24/2016).

- A human factors (HF) validation study protocol was submitted on 12/1/2016 and revised further on 3/3/2017. The Sponsor disagreed with DMEPA recommendations to include untrained caregivers and patients in the study and proposed (b) (4) (b) (4) DMEPA disagreed with the sponsor's approach (refer to DMEPA review in DARRTS from 5/3/2018).

- On 7/18/17 and 10/1/2017 the Sponsor submitted two additional phase 3 study protocol: CT-302 (in pediatric subjects > 6 months - 17 years old with short stature due to GHD who were previously treated with other hGH formulations) and CT-301EXT (long term safety and efficacy study in pediatric subjects with short stature due GHD who completed trials CT-301 or CT-302), respectively. Both studies were found to be acceptable as exploratory trials.

- On 6/04/2018, FDA notified the Sponsor that no additional nonclinical studies were required to define the carcinogenic risk related to lonapegsomatropin-tcgd treatment. FDA's reasons for not requiring carcinogenicity studies are detailed in Dr.'s Braithwaite review from 5/29/2018with PEGylated products. Executive Carcinogenicity Assessment Committee (ECAC) was consulted and concurred that approval of a carcinogenicity waiver is warranted for lonapegsomatropin-tcgd.

- FDA reviewed and provided recommendations to the Sponsor regarding the statistical analysis plan (SAP) for study CT-301 (phase 3 pivotal study) on 1/25/2019, 2/19/2019 and 3/28/2019. FDA indicated that ANCOVA model is the preferable method in primary and secondary analyses and that

the imputation method should not rely on a missing at random (MAR) assumption. FDA also defined ITT population as all randomized subjects who receive at least one dose of study drug.

- On 5/29/2019, a Type C meeting was held with the Sponsor and the Office of Biotechnology Products, Office of Pharmaceutical Quality, and Office of Process and Facilities (Division of Microbiology Assessment), who provided recommendations on the bracketing validation strategy, the proposed drug product specification and representation of the strength for the ACP-011 prodrug.

- On 7/9/2019 the Sponsor submitted a request for Fast Track designation (FTD). FDA denied FTD on 9/3/2019 for the following reasons: 1) the current clinical program for ACP-011 was not designed to evaluate and did not demonstrate an effect on a serious aspect of the condition, i.e., final height; 2) there are multiple FDA-approved rhGH formulations for the treatment of PGHD on the market; 3) based on the data submitted, there is no evidence that ACP-011 offers an improved effect on AGV or better toxicity profile over exciting therapy. Lastly, the sponsor also did not provide sufficient evidence that the drug offers improved compliance as one of the potential benefits of the product over existing therapies.

- On 12/4/2019, a meeting was held with the Sponsor and the FDA team from chemistry, manufacturing, and controls. During this meeting FDA and the sponsor discussed CMC information to be included in BLA submission.

- On 12/10/2019, a pre-BLA meeting was held. During this meeting, the Division and the sponsor discussed and agreed on BLA's content and format and the completeness of the different BLA modules. FDA agreed that the size of the safety database appeared to be adequate to support a BLA submission. However, FDA disagreed with the sponsor's strategy to pool efficacy and safety data from three phase 3 studies in subjects with PGHD because of the different study designs and durations and populations studied (treatment-naïve vs previously treated with GH).

- Orphan designation was granted for the treatment of GHD on April 13, 2020.

- The BLA for lonapegsomatropin-tcgd for treatment of growth failure in pediatric patients with GHD was submitted to FDA on 6/26/2020. The submission included a request for priority review. The request was denied for the following reasons: 1) the clinical program completed to date did not evaluate the effect of the drug on a serious aspect of the condition, including physical manifestations (e.g., final adult height or body composition parameters, cognitive deficits); 2) there was no evidence to suggest that treatment with lonapegsomatropin-tcgd offers clinically meaningful improvement in effectiveness (AGV), or a better toxicity profile over the exciting therapy; 3) there was no evidence that lonapegsomatropin-tcgd offers an improved compliance/adherence as a potential benefit over existing therapies.

- The Division extended the user fee goal date to 9/25/2021 due to the submission of a major amendment to the application addressing the CDRH issues.

2. Product Quality

The review team from Office of Pharmaceutical Quality (OPQ)/ Office of Biotechnology Products (OBP) recommends approval of this application (refer to OPQ executive summary from 3/22/2021). The Office of

Pharmaceutical Quality and Office of Compliance has determined the manufacturing facilities are acceptable (refer to OPQ review from 6/7/21).

Fujifilm Diosynth Biotechnologies UK Limited (FEI 3007182567), Billingham, United Kingdom, proposed for (b) (4) lonapegsomatropin DS manufacture was found to be acceptable based on the review of the requested manufacturing site records under section 704(a)(4) (refer to OPQ review from 6/4/21). Vetter Pharma-Ferintigung GmbH&Co.KG (FEI 3005987757) in Ravensburg, Germany, the facility intended for the manufacturing and visual inspection of lonapegsomatropin-tcgd dual-chamber cartridge drug product, was found to be acceptable by OPQ based on its history and a waiver granted by the Office of Pharmaceutical Manufacturing Assessment (OPMA)/OBP (refer to the review from 4/22/2021). All other proposed manufacturing and testing facilities were found to be acceptable based on their Current Good Manufacturing Practice (CGMP) compliance status and recent relevant inspectional coverage.

The drug substance is produced (b) (4)

Based on the stability data that has been submitted, the OBP reviewer recommends a shelf-life of (b) (4) months for the drug substance when stored at < (b) (4) °C.

The final drug product (DP) is provided in a prefilled dual-chamber glass cartridges (DCC) that is designed for use with a reusable auto-injector for subcutaneous administration. The dual chamber cartridges are packed with sterile single-use disposable needles that are not attached to the cartridge; the auto-injector is packed separately. A shelf-life of 36 months was granted for the drug product when stored at the recommended storage condition of 2-8^{0}C of which up to 6 months can be stored at up to 30^{0}C. In-use stability data supports the use of the reconstituted product within 4 hours at 30°C. The viscosity of the DP depends on storage temperature; thus the reviewer recommends placement of the DP in room temperature for at least 15 minutes before use to reduce the viscosity of DP.

Overall, there are no approvability issues with regard to the manufacture of the drug substance, drug product, excipients, impurities, extractables, or leachables.

Device

The lonapegsomatropin-tcgd is a drug-device combination product containing glass dual-chamber cartridge with the drug product lonapegsomatropin-tcgd and auto-injector (**Figure 1. Lonapegsomatropin-tcgd Autoinjector and dual-chamber cartridgeFigure 1**). Drs. Shanly Chen and Rumi Young from the Center for Devices and Radiological Health (CDRH) reviewed the proposed device, auto-injector, and recommend approval (refer to the review from 6/22/2021).

Figure 1. Lonapegsomatropin-tcgd Autoinjector and dual-chamber cartridge

(b) (4)

Source: CDRH review.

The auto-injector is intended to be used multiple times, for up to 4 years, by a single user. The reviewer concluded that the Applicant's proposed cleaning instructions have been adequately tested and are acceptable. The drug product is enclosed within the cartridge and not in contact with the device. The overall risk is low "in the sterility context."

The dual-chamber cartridge is intended to connect to a sterile needle prior to the insertion of the cartridge in the auto-injector. The electronics and software in the auto-injector control the penetration and injection of the drug product. The auto-injector reconstitutes the drug product by automatic mixing (4-8 minutes) followed by manual mixing. There are two mixing steps (auto-4-8 minutes and manual). There were two 2 changes to the device used in the trial. These changes were implemented based on feedback from users during the CT301EXT study. (b) (4)

The Applicant adequately identified all health hazards that may be associated with use of the auto-injector (pain, skin irritation, needle injury, contamination, electrical shock, airway obstruction due to wires, overdose, underdose, etc.) and provided a mitigation plan, which the reviewer found to be acceptable. The reviewer also confirmed that all component materials have been evaluated for biocompatibility and do not pose a risk of cytotoxicity, skin irritation or skin sensitization, or any other biological hazard when used as intended.

The Applicant evaluated the PK comparability between lonapegsomatropin-tcgd delivered by the syringe/needle (clinical product) and the to-be-marketed auto-injector (to-be-marketed product) in the phase 1 study CT-301 and that was also used in study CT-301EXT. The CDRH reviewer agrees with the Clinical Pharmacology reviewers that the to-be-marketed drug product was successfully bridged to the clinical product in this study (refer to *Clinical Pharmacology* Section below).

Dr. Young reviewed the essential performance requirements of this device, i.e., dose accuracy, activation force, injection force and injection time ([redacted] (b) (4) seconds). To allow the administration of lonapegsomatropin-tcgd solution that has high viscosity, the injection time was extended to [redacted] (b) (4) seconds to deliver the required volume of the product with the maximum force permitted. The reviewer confirmed that the Applicant verified that the cartridge will expel the required volume with the proposed force and time of injection.

Multiple concerns associated with device performance and delivery of accurate dose were identified, including: [redacted] (b) (4) During the review cycle, the Applicant provided the additional information to address these concerns; see CDRH review for a detailed discussion of the initially identified deficiencies and the Applicant's responses. The CDRH team reviewed all submitted data and concluded that all issues that could affect approvability of the device were adequately addressed and recommend approval. They also concluded that the remained unresolved issues (information required to demonstrate that alarms are complaint and validated to be complaint to IEC 6061-1-8:2006 and A1:2012 and validation testing that implements Corrective and Preventive Action (CAPA) changes are effective at preventing the [redacted] (b) (4) problem) can be addressed post-approval through a post-marketing commitment.

During the review of the application, Dr. Young noted that two facilities, Ascendis Pharma and Sharp Corporation, did not require inspection given the responsibilities of these sites and recent inspections. However, the last inspection of the third site, Philips-Medisize A/S, a facility "which will be handling most of the work involved in Auto-injector", [redacted] (b) (4) OPQ reviewers also found these facilities to be acceptable (refer to OPQ review from 6/7/21).

Human Factors

In their initial review of this application, Drs. Jason Flint and Ebony Whaley from the Division of Medical Errors Prevention and Analysis (DMEPA) found that the results of the human factors (HF) validation study could not support the safe and effective use of the proposed combination product user interface by the intended users due to multiple deficiencies, including: [redacted] (b) (4), use of leading language in the study script, concerns with using the second injection that may affect the recall of the errors, lack of assessment of the use of two cartridges per patient, and concerns with using the video. In addition, instructions for use and quick reference

guide were modified following completion the study, but those revisions were not evaluated in the subsequent studies. Thus, the reviewers recommended to address all concerns by conducting a new HF validation study (refer to FDA's Advice/ Information request Letter sent to the Applicant on 1/14/2021).

The revised protocol was submitted to FDA on 2/11/2021; DMEPA reviewed the protocol and provided further comments and suggestions (refer to FDA Letter from 3/31/2021). The Applicant submitted the results of the new HF validation study to FDA on 5/11/2021. According to the DMEPA team, the Applicant addressed all identified concerns in the new study. Review of the new study results and updated IFU and QRG confirmed that there do not appear to be any residual human factor issues that would preclude approval (refer to DMEPA review in DARRTS from 7/14/2021). However, the reviewers recommended to add the caution statement to the IFU and ORG Step 5 *Turn the auto injector up and down*, to further support the safe and effective use of the product and to minimize the risk of medications errors. This statement warns users to avoid the power button during this step to avoid inadvertently aborting the injection. The reviewers indicated that this change can be implemented without additional HF validation testing to be submitted for review. The above recommendation was sent to the Applicant on 7/12/2021. The Applicant accepted all DMEPA recommendations.

3. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers, Drs. Jefferey Quinn and Todd Bourcier, recommend approval without additional studies (refer to the review in DARRTS from 03/01/2021). There are no outstanding nonclinical issues.

The Applicant conducted all the required non-clinical studies, including pharmacokinetic and toxicokinetic studies evaluating lonapegsomatropin-tcgd and the products of its autocleavage (hGH, (b) (4) (b) (4) e; TransCon linker released during autocleavage), mPEG linker (b) (4) (b) (4) as well as mPEG to support the chronic use of lonapegsomatropin-tcgd in patients with PGHD. All studies were conducted using the subcutaneous route of administration.

The reviewers note that the predecessor of lonapegsomatropin-tcgd, ACP-001, was used in the early development program. In vitro studies using ACP-001 demonstrated that the pharmacology of ACP-011 (lonapegsomatropin-tcgd) and ACP-001 were comparable with regards to the mass and integrity of released hGH, in vitro dissociation (kd) from the hGHR and potency of released hGH. Overall, the reviewers concluded that "based upon the overall similarity of the kinetics of the released hGH and subsequent insulin-like growth factor 1 (IGF-1) response as well as the associated efficacy and safety profiles observed in nonclinical studies and in a clinical phase 1 trial, data obtained for ACP-001 was [sic] considered directly applicable to lonapegsomatropin".

In-vitro studies have demonstrated that ACP-001 exhibits reduced binding to hGHR with minimal activity compared to unconjugated hGH. Once hGH is released from lonapegsomatropin-tcgd following hydrolysis, it is fully active (as unmodified hGH). The nonclinical data indicate that the pharmacodynamics and biological activity of hGH released from lonapegsomatropin "are comparable to those of other hGH products". Once a week administration of ACP-001 to hypophysectomised rats and normal monkeys resulted in increases in body weight and IGF-1 levels.

ACP-001 did not have any effect on the hERG current.

The toxicity of the product was assessed in a series of repeat-dose toxicity studies in rats and monkeys. The reviewers indicated that no effects on the central nervous (CNS), respiratory, or cardiovascular systems were observed in monkey and/or rat studies.

The reviewers also concluded that the toxicology profile observed with lonapegsomatropin-tcgd was related to the pharmacological effects of growth hormone and with cellular uptake of the released mPEG moiety at lonapegsomatropin-tcgd dose levels ≤ 4.8 mg/kg/week (20-fold above the expected clinical therapeutic dose level of 0.24 mg hGH/kg/week). Details of the effect on GH and mPEG follow.

GH

In monkeys, treatment related effects were exudate, galactocele, vacuolation, hyperplasia in the mammary gland and increase in body weight and organ weight. These effects were not considered as adverse but rather consistent with the pharmacological effect of hGH. Anti-drug antibodies (anti-hGH and anti-mPEG) were not detected in monkeys.

In rats, administration of lonapegsomatropin-tcgd was associated with changes in body weight/organ weight only. The reviewers noted that the results of the rat study were confounded by the development of antidrug antibodies (ADA) in the majority of animals that affected the exposure to lonapegsomatropin. However, they concluded that the exposure and PD activity were maintained at human dose and the study was overall informative with regards to the risk assessment of lonapegsomatropin-tcgd.

mPEG

Nonclinical findings indicated that mPEG was found in injection site tissues and in choroid plexus cells. mPEG cleared from all tissue sites, but the choroid plexus epithelium retained a minimal to mild level of mPEG cellular vacuolation. The nonclinical review team concluded that presence of mPEG and cellular vacuolation of the choroid plexus epithelium in rats and monkeys represents minimal-to-no risk to children with GHD based on the following considerations:

- Minimal vacuolation of the choroid plexus epithelium was observed histologically in cynomolgus monkeys after 52 weeks dosing at an exposure of 9-10-fold higher than the clinical dose.
- The presence of mPEG and choroid plexus epithelial vacuolation was not associated with histological evidence of structural changes to tissue architecture, degeneration, necrosis, or inflammation, and no clinical signs of neurotoxicity were observed in the animals (e.g. tremors, convulsions, reactivity to handling or unusual behavior). In other words, not adverse…
- mPEG was not detected in the cerebral spinal fluid above the lower limit of quantification (LLOQ, 500 ng/mL)

The reviewers also indicated that the mPEG weekly dose level administered to children with PGHD at the clinical dose was 8-fold below the theoretical threshold (3.7 mg PEG (40 kDa)/kg/QW or 0.4 mcmol PEG/kg/month) recommended by the Committee for Medicinal Products for Human Use (CHMP 2012) for choroid plexus epithelial cell vacuolation.[8] In addition, systemic mPEG concentrations at steady state (15 μg/mL) in children with PGHD administered lonapegsomatropin-tcgd were 7-fold below the mPEG

[8] CHMP Safety Working Party's response to the PDCO regarding the use of PEGylated drug products in the pediatric population, November 16, 2012.

exposure vacuolation threshold (100 μg/mL) defined by Jacobsen/Bjørnsdottir (FDA Briefing Document[9] and BioSafe EU, 2017[10]). Refer to the further discussion on risk of mPEG accumulation in *Safety* Section below.

Local tolerance studies in monkeys and mice showed no adverse injection site reactions.

Fertility studies performed in rats demonstrated no evidence of impaired fertility at doses up to 20-fold the clinical dose of 0.24 mg hGH/kg/week.

There was no evidence of embryo-fetal or neonatal harm in embryofetal development studies in rats at doses up to 13-fold the clinical dose of 0.24 mg hGH/kg/week. In a pre-and post-natal developmental study in rats, there were no adverse effects on the pregnant/lactating female at doses up to 13-fold the clinical dose of 0.24 mg hGH/kg/week.

No carcinogenicity studies with lonapegsomatropin-tcgd were conducted for the reasons described in the ***Error! Reference source not found.***Section above.

Lastly, the reviewers indicated that there were no novel excipients and no impurities of concerns for lonapegsomatropin-tcgd in the drug substance and drug product.

Overall, the available evidence provided in the pivotal toxicity studies is consistent with a low risk associated with potential mPEG accumulation at the proposed human dose. Clinical issues related to mPEG are discussed in Clinical Pharmacology and Clinical sections below.

4. Clinical Pharmacology

The Clinical Pharmacology review was completed by Drs. Sang Chung, Justin Earp and Jayabharathi Vaidyanathan. The team recommends approval of lonapegsomatropin-tcgd without additional post-approval studies. There are no outstanding clinical pharmacology issues. For a detailed discussion, please refer to the Clinical Pharmacology review in DARRTS dated 3/4/2021.

Overall, the clinical pharmacology review concludes that PK/PD of lonapegsomatropin-tcgd has been adequately characterized in the Applicant's studies in healthy volunteers (two studies, CT-101 and CT-102) and in subjects with PGHD (four studies: CT-004, CT-2301, CT-301EXT and CT-302).

The reviewers also note that the predecessor of lonapegsomatropin-tcgd (ACP-011), ACP-001, was used in phase 1 study in healthy volunteers and in phase 2 study in subjects with PGHD (CT-004). The Applicant conducted a phase 1 study (CT-101) to evaluate PK comparability between the two molecules, ACP-001 and ACP-011. Based on the results from this study, the reviewers concluded that PK parameters of ACP-001 and ACP-011 were comparable and clinical information obtained with ACP-001 was applicable to lonapegsomatropin-tcgd (Table 1**Error! Reference source not found.**).

[9] Jacobsen H, Bjørnsdottir I. FDA Briefing Document Prepared for the Blood Products Advisory Committee April 4, 2017, BLA 125611, Coagulation Factor IX (Recombinant), GlycoPEGylated N9-GP Novo Nordisk, Inc. 2017.
[10] Jacobsen H, Bjørnsdottir I. Learnings from recent regulatory submission with 40 kDa PEGylated coagulation factor IX (N9-GP) PK and Safety. In: Presented at: BioSafe European Annual General Membership Meeting, November 14-15, 2017.

Table 1. Statistical Assessment of PK and PD parameters Between ACP-001 (Treatment A) and ACP-011 (Treatment B)

Analyte	Adjustment	Parameter (unit)	Geometric LS Means N	(A)	N	(B)	Ratio (%) of Geometric LS Means (B/A)	90% CI of Ratio of Geometric LS Means	Intra-Subject %CV
hGH	Absolute	AUC_{0-168} (h*ng/mL)	28	595	27	623	104.64	(94.91, 115.37)	21.25
		AUC_{0-336} (h*ng/mL)	28	616	27	645	104.72	(91.73, 119.55)	29.16
		C_{max} (ng/mL)	28	11.7	27	13.3	113.70	(103.91, 124.40)	19.61
IGF-1	Absolute	$AUEC_{0-168}$ (h*ng/mL)	28	88400	26	87600	99.07	(96.84, 101.35)	4.81
		$AUEC_{0-336}$ (h*ng/mL)	27	144000	26	138000	95.55	(93.56, 97.59)	4.36
		E_{max} (ng/mL)	28	678	27	695	102.55	(99.71, 105.46)	6.04
	Baseline-adjusted	$AUEC_{0-168}$ (h*ng/mL)	28	54400	27	54000	99.17	(94.57, 103.99)	10.24
		$AUEC_{0-336}$ (h*ng/mL)	28	75900	27	70500	92.86	(87.11, 98.99)	13.83
		E_{max} (ng/mL)	28	475	27	493	103.71	(99.21, 108.42)	9.57

Treatment A: A single SC dose of ACP-001 0.24 mg hGH/kg. Treatment B: A single SC dose of ACP-011 0.24 mg hGH/kg.
Source: Clinical Pharmacology Review, Table 10.

Pharmacokinetics

The PK profile of a single dose of lonapegsomatropin-tcgd following subcutaneous administration was evaluated in healthy subjects (CT-101) at dose levels of 0.24-0.42 hGH mg/kg. The steady state PK was evaluated in subjects with PGHD (study CT-104 and CT-301).

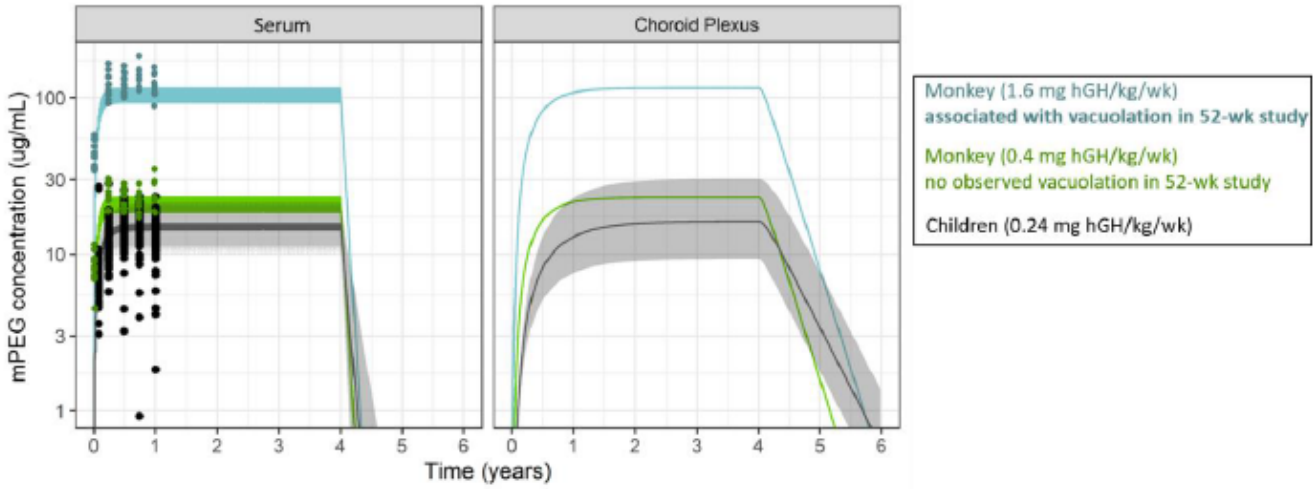
Following single dose administration of 0.24 mg hGH/kg of lonapegsomatropin-tcgd to healthy volunteers, the $t_{1/2}$ of hGH, lonapegsomatropin-tcgd, and mPEG was 51.9, 25.4 and 508 hours, respectively. T_{max} was 16, 36 and 240 hours for hGH, lonapegsomatropin-tcgd, and mPEG, respectively. The PK of hGH, lonapegsomatropin and mPEG was greater than dose-proportional following single doses of 0.24, 0.3 and 0.42 mg hGH/kg (Table 1). In healthy volunteers AUC_{0-168} for hGH, lonapegsomatropin-tcgd, and mPEG increased 2.5-, 5.3-, and 3.3-fold, respectively, with a 1.8-fold increase in dose. However, the reviewers noted that PK-dose proportionally is not clinically relevant since there is no proposed dose adjustment.
Steady state in subjects with PGHD is achieved following 13 weekly doses (CT-004 and CT-301). There was no significant accumulation for hGH or lonapegsomatropin-tcgd. However, the accumulation of mPEG was observed at steady state.

Based on population PK analyses, the estimated volume of distribution (V/F) in subjects with PGHD for hGH, lonapegsomatropin-tcgd and mPEG is 61.8, 1.3 and 3.5 L, respectively. Lonapegsomatropin-tcgd is metabolized via auto-hydrolysis to mPEG40-TransCon, a leaving group (b) (4) (b) (4) and hGH. hGH elimination involves protein catabolism in liver and kidneys. mPEG is excreted intact into urine. The $t_{1/2}$ of hGH released from lonapegsomatropin-tcgd in healthy volunteers is 20.5 hours.

mPEG accumulation

As described in the nonclinical section above, mPEG was associated with cellular vacuolation in epithelial cells of choroid plexus in monkeys and rats. Because the drug has a long half-life and will be administered chronically, the Applicant conducted additional modeling and simulation analyses evaluating the relationship between estimated exposure in serum and choroid plexus and extrapolated information using animal scale up related to "No Observed Vacuolation" from non-clinical models, which utilizes similar approaches of non-clinical risk assessment as is done with NOAEL (**Figure 2**). Clinical pharmacology reviewers verified the Applicant's analyses and concluded that the predicted median steady state level of mPEG was 2-fold lower that the predicted steady state levels in the choroid plexus of monkeys at the no observed effect level (NOEL) 0.4 mg/hGH/kg/week for the drug-related microscopic findings in the brain observed at doses 1.6 mg hGH/kg/week in monkeys and rats. The Clinical Pharmacology team concluded that given the nonclinical and clinical data, the modeling and simulation supports that the proposed dosing confers minimal risk.

Figure 2. Predicted mPEG (lines) and individual observed mPEG (symbols) in serum (left) and choroid plexus (right) of children (BW = 22 kg, black) and cynomolgus monkey (BW = 3 kg, green and cyan) following 3 doses.



0.24 mg hGH/kg in children (black), 0.4 mg hGH/kg in monkey (green, No Observed Vacuolation) and 1.6 mg hGH/kg in monkey (cyan)
Source: Clinical pharmacology review, figure 4.

PD parameters (PD)

Data from study CT-104 demonstrated a dose-dependent increase in IGF- levels in subjects with PGHD (

Figure 3). IGF-1 AUC was similar between 0.21 and 0.30 mg hGH/kg/week indicating that IGF-1 response reached an apparent plateau from 0.21 mg hGH/kg/week.

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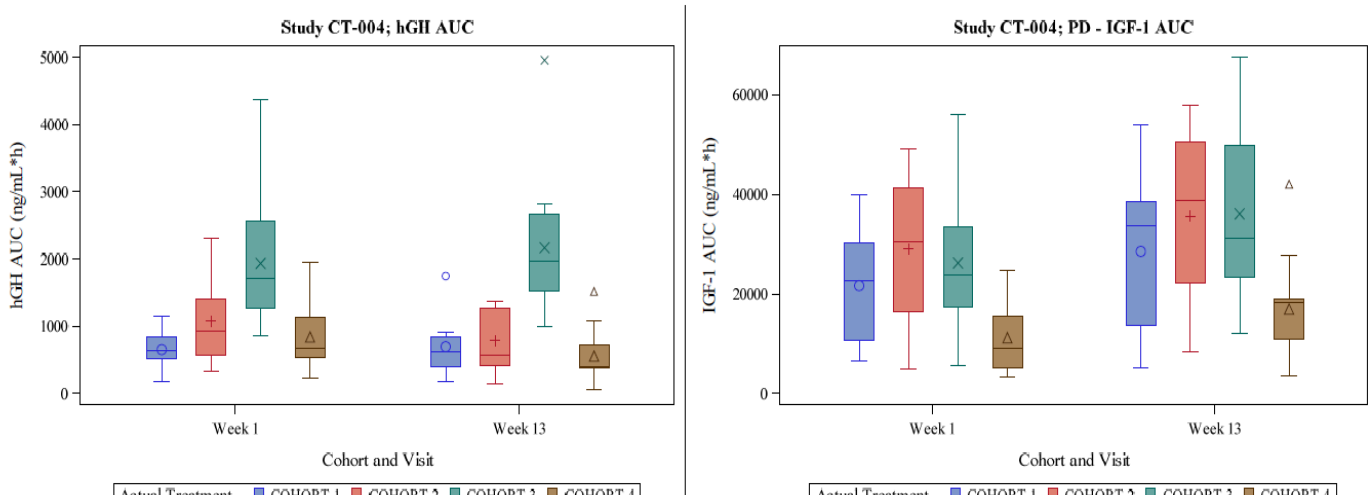
Figure 3. Box plot of AUC (hGH; left, IGF-1; right) by cohort and visit; AUC0-168h for cohort 1-3, $AUC_{0\text{-}24h}$ x 7 for cohort 4 (Study CT-004)



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: Clinical Pharmacology review, figure 6.

Intrinsic factors

The proposed dosing is weight-based. The intrinsic factors (e.g., age, sex, race or renal function) that could influence exposure and activity were evaluated using the results from the phase 1 study (CT-101) and population PK/PD analyses of data from phase 3 studies. The results of these analyses demonstrated that no dose adjustment is necessary for the investigated covariates in addition to the body weight-based dosing.

These recommendations (based on body weight only) are also consistent with dosing recommendations for all other hGH formulations and with the professional societies' guidelines on treatment of PGHD. [11] [12]

The impact of renal function on hGH, lonapegsomatropin-tcgd and mPEG was evaluated using the analysis of relationship between their observed concentrations and estimated creatinine clearance in subjects with PGHD in study CT-301. The results of this analysis indicated that there was no impact of renal function on hGH, lonapegsomatropin-tcgd, or mPEG exposure.

Drug-drug interactions

Drug-drug interactions studies were not conducted in the lonapegsomatropin-tcgd development program. Dr. Chung concludes that the class drug-drug interactions effects for currently marketed daily hGH formulations can be applied for lonapegsomatropin-tcgd. The Clinical Pharmacology reviewers also recommended to address concomitant treatment with CYP450 substrates in the label based on class labeling of all hGH formulations.

QT assessment

No dedicated QTc study for lonapegsomatropin-tcgd was conducted. The interdisciplinary review team consultant indicated that a thorough QT study was not required based on the labeling practice for large molecules and known hGH product class safety information (no QT prolongation) (refer to review in DARRTS from11/25/2020). According to ICH E14 Guidance on QT/QTc evaluation[13], large, targeted proteins (e.g., hGH) "have a low likelihood of direct ion channel interactions and a thorough QT/QTc study is not necessary, unless the potential for proarrhythmic risk is suggested by mechanistic considerations or data from clinical or non-clinical studies". There were no QT-related safety signals in nonclinical studies and lonapegsomatropin-tcgd was negative in hERG assay (refer to Nonclinical Pharmacology/Toxicology section above). The IRT also reviewed ECG data obtained from study CT-101 and concluded that there were no large increases in the QTc interval and none of the subjects had QT-associated adverse reactions. The reviewer concluded that "submitted ECG data do not indicate any unexpected or important effects of lonapegsomatropin-tcgd on the QTc interval at the proposed therapeutic dose". No additional labeling was recommended.

Bridge between the to-be-marketed and clinical trial formulations

The pivotal study CT-301 was conducted using a syringe/needle administration of lonapegsomatropin-tcgd, not the to-be marketed auto-injector. Thus, the Applicant conducted a phase 1 study in healthy volunteers (CT-102) to evaluate the comparability between syringe/needle and to-be-marketed auto-injector. Based on the results of this study, the reviewers concluded that the to-be-marketed drug product was successfully bridged to the clinical product. PK of the lonapegsomatropin-tcgd administered via auto-

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[11] GH RESEARCH SOCIETY. Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society. *The Journal of Clinical Endocrinology & Metabolism*. 2000; 85: 3990–3993

[12] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H. on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. Horm Res Paediatr. 2016;86:361-397

[13] Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, 2005

injector was comparable to using the syringe/needle. The proposed to be-marketed drug product formulation, auto-injector, was also used in a subgroup of subjects with PGHD in study CT-301EXT; no safety issues have been identified to date with the use of the auto-injector (refer to *Clinical/Statistical-Efficacy* section below).

Dosing

Based on the results of PK studies and phase 3 studies, the recommended dose for lonapegsomatropin-tcgd is 0.24 mg hGH/kg/week. The body weight bracketing that is 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. However, the clinical pharmacology reviewer confirmed these deviations in the dosing did not result in different exposure or increased levels of mPEG. Thus, the minor deviations from the proposed dosing due to subject's weight and the proposed body weight bracketing in the label are acceptable and are unlikely to affect safety and/or efficacy of the drug. The reviewers did not recommend different starting doses because "there were no adequate data to support covariates for the different starting dose or dose adjustment during the treatment period in the pivotal Phase 3 study".

The impact of a missing dose on lonapegsomatropin-tcgd concentrations was evaluated by simulations of data from study CT-301 using shorter (7-5-9-7 days schedule) or longer intervals (7-9-5-7 days schedule) between dosing. The results of this analysis demonstrated that there was no significant difference in simulated average IGF-1 SDS among scenarios tested. Based on the results of these analyses, the reviewers have the following recommendations: 1) a dose can be taken within ±2 days of the scheduled day (to ensure that there is a dosing interval of no fewer than 5 days between 2 consecutive doses); 2) if more than 3 days have passed, the dose should be skipped and the next dose should be administered on the regular doing day. These recommendations will be reflected in labeling.

5. Clinical Microbiology

Quality microbiology data were reviewed, and then posted by Drs. Reyes Candau-Chacon and Virginia Carroll (drug product) on 3/23/2021 and 4/30/21 and posted by Dr. Viviana Matta and Virginia Carroll (drug substance) on 6/5/2020. All reviewers recommended approval from a sterility assurance and a microbial control perspective.

Dr. Candau-Chacon noted that the shipping validation under worst-case conditions was not planned by the Applicant; the Applicant provided the qualification of the shipping with a full load and limited exposure at worst-case temperatures (3 hours at 35ºC for summer conditions and 3 hours at -5°C for winter conditions). Thus, the reviewer recommended the following post-marketing commitment (PMC): "Provide the shipping validation report of the bulk drug product in dual-chamber cartridges shipped from (b) (4) (b) (4) performed during winter and summer conditions. The report will be submitted before December 31, 2023". FDA received the Applicant's response with agreement to this PMC on March 4, 2021.

6. Clinical/Statistical- Efficacy

Drs. Vachhani (Clinical) and Cambon (Biostatistical) have reviewed the efficacy data and recommend approval (refer to Clinical Review in DARRTS from 2/26/2021 and Statistical Review in DARRTS from 2/19/2021). The statistical and clinical reviewers concluded, and I agree, that the Applicant has provided the substantial evidence of effectiveness to support approval. Substantial evidence of effectiveness was established from a single adequate and well-controlled (AWC) trial (Study CT-301) and confirmatory

evidence consisting of data providing strong mechanistic support. In PGHD, lonapegsomatropin-tcgd is intended to replace a deficient native hormone – human growth hormone (GH). The Applicant has provided data demonstrating that the active moiety of lonapegsomatropin-tcgd has the same primary amino acid sequence as native human growth hormone and thus is expected to have the same action at the target receptor as native human growth hormone. The structure-function relationship of endogenous GH is well-understood; the wide variety of GH biological effects are achieved through only one mechanism of action, i.e., GH binding to and activation of GHR with subsequent transcription of genes for a variety of proteins, including IGF-1. No alternative receptors mediating GH activity have been identified. GH and IGF-1 stimulate epiphyseal growth plates and formation of new bone resulting in linear growth until fusion of growth plates. Therefore, there is a strong mechanistic understanding of how growth hormone exerts its effect in patients with growth hormone deficiency. Supportive evidence from uncontrolled Studies CT-302 and CT-301EXT also strengthened the conclusion that substantial evidence of effectiveness had been provided but was not necessary for approval. A single AWC plus confirmatory evidence is acceptable for this BLA because PGHD is a rare disease making it challenging to conduct two AWC trials, and because historically FDA has accepted a single AWC study for the approval of hGH products with native GH sequence for the PGHD indication.

The lonapegsomatropin-tcgd clinical program for growth failure in patients with PGHD includes three phase 3 clinical studies. The primary objective of two phase 3 studies (Study CT-302 and Study CT-301EXT) was to evaluate safety of lonapegsomatropin-tcgd in subjects with PGHD previously treated with other hGH formulations (CT-302) or to evaluate the long-term safety of lonapegsomatropin-tcgd in subjects who completed studies CT-301 and CT-302 (CT-301EXT). Both studies were open label single arm studies without a comparator arm. There was no pre-specified hypothesis testing for the efficacy endpoints in both studies. However, these studies evaluated and provided the growth parameters (AGV and height) in descriptive manner, thus the information from these studies was considered as supportive. The information from these studies will be briefly summarized below as needed (for details refer to clinical review).

The primary study to support efficacy of lonapegsomatropin-tcgd is Study CT-301, a 52-week, randomized, open-label, study comparing the efficacy and safety of lonapegsomatropin-tcgd to Genotropin in pediatric subjects with short stature due to GHD. This study was the largest study and the only study using the control group in the intended population and included treatment-naïve subjects. The results of this study are briefly summarized below.

Study CT-301

Study CT-301 was a multi-center (54 centers across 14 countries), randomized, active-controlled, open-label, 52-week study that investigated the use of lonapegsomatropin-tcgd for the treatment of short stature in 161 prepubertal subjects with PGHD who were treatment-naïve to hGH. The trial design (randomized, active-controlled, non-inferiority trial) and the duration (52 weeks) have been used to support approval of other hGH formulations for the same indication.

The primary objective of the trial was to demonstrate the efficacy (AGV) of once-weekly dosing of lonapegsomatropin-tcgd compared to daily Genotropin after 52 weeks of treatment in prepubertal children with PGHD.

Study population

Consistent with the indication sought in this application (treatment of growth failure in prepubertal children with GHD), the study enrolled only boys 3-11 years old and girls 3-12 years with PGHD and height SDS ≤ -2 standardized for chronological age, or < 1.5 below mid-parental height. All subjects also had to have

Tanner stage 1 and bone age of at least 6 months less than chronological age. All subjects were hGH- and IGF-1-treatment naïve. The study had clear inclusion criteria to confirm the diagnosis of PGHD by provocative testing using peak GH level of ≤ 10 ng/ml. Although low IGF-1 levels are not generally required for the establishment of PGHD diagnosis, low IGF-1 levels are supportive of the diagnosis; thus, all subjects were required to have IGF-1 SDS ≤ -1. Overall, these inclusion criteria are consistent with current scientific society guidelines on the diagnosis of PGHD.[14] [15] The Applicant appropriately excluded subjects with closed epiphyses who would not benefit from the treatment with hGH, those who have delayed growth due to the other conditions (e.g., born small for gestational age, with idiopathic short stature), malnutrition, underlying chronic medical conditions (e.g., uncontrolled diabetes), use of medication that suppress growth (e.g., glucocorticoids, anabolic steroids) or would be at increased risk of adverse events associated with hGH treatment, including known active malignancy and intracranial tumors. The Applicant also prohibited use of systemic corticosteroids (except as replacement therapy for adrenal insufficiency), estrogens, anabolic steroids during the trial, since the effect of these treatments may confound overall efficacy (growth) of lonapegsomatropin-tcgd.

Study design

Study CT-301 included a 36-week screening period followed by a 52-week randomized, open-label, active-controlled treatment period. All subjects who completed this study were eligible to continue treatment with lonapegsomatropin-tcgd weekly injections in the extension trial CT-301EXT; no washout period was required between CT-301 and CT-301EXT. Eligible subjects were randomized in a 2:1 ratio to receive weekly injections of lonapegsomatropin-tcgd or daily injections of Genotropin, respectively. The randomization was stratified according to peak GH levels in stimulation tests (≤ 5 ng/ml and > 5 ng/ml), sex and age (> 3 to ≤ 6 and > 6 years).

In general, the growth rate is affected by age (children < 6 years old have higher AGV) and sex (boys grow on average slower and have delayed growth spur).[16] Very low peak GH levels on provocative testing (usually < 5 ng/ml) are consistent with severe PGHD, and patients with such results are expected to benefit greatly from hGH treatment and may have higher AGV during the first year of treatment compared to patients with less severe GHD and/or residual secretion of GH.[17] Thus, FDA has accepted a stratification by age, sex and peak GH levels for the studies evaluating hGH products with native GH sequence for the short stature due to PGHD indication. Lonapegsomatropin-tcgd and Genotropin were used in fixed doses throught the treatment period: 0.24 mg hGH/week and 0.034 mg hGH/kg/day, respectively. The Genotropin doses used during the trial are approved Genotropin doses for the treatment of short stature in pediatric patients with GHD.

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[14] GH Research Society: Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence: Summary Statement of the GH Research Society. 2000. JCEM, 85 (11), 3990–3993.
[15] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. 2016. Horm Res Paediatr;86:361-397

[16] https://www.cdc.gov/growthcharts/index.htm
[17] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. 2016. Horm Res Paediatr;86:361-397

The proposed-for-marketing autoinjector was not available in this study; rather, lonapegsomatropin-tcgd was available in two vial presentations during the trial. These vials provided final concentrations of 11 mg hGH/ml and 22 mg hGH/ml, thus the weight-based volumes to administer lonapegsomatropin-tcgd dose were used in the trial (**Table 2**). The dose per ml administered in the trial is consistent with the proposed cartridge dose per the same weight range in the label (e.g., 0.27 ml for weigh range 11.5-13.9 kg =3 mg, 0.33 ml for weight range 14-16.4 kg = 3.6 mg, etc.).

Table 2. Drug concentration, dosing brackets and volumes of lonapegsomatropin-tcgd 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 Review, table 4

Primary efficacy endpoint and analysis

The primary endpoint was AGV at week 52. The primary efficacy analysis was difference in AGV at 52-week time point for non-inferiority testing and then if successful, superiority testing was pre-specified (as a key secondary endpoint). The proposed non-inferiority margin of 2 cm/year was found to be acceptable by the Division (refer to Regulatory background section above). The primary efficacy analysis was conducted in the ITT population (all randomized subjects who received at least one dose of randomized drug) as recommended by FDA.

The selection of AGV as an endpoint to establish clinical benefit of lonapegsomatropin-tcgd therapy in patients with short stature due to GHD is briefly discussed below:

- As summarized in the **Error! Reference source not found.** section above, all currently marketed hGH were approved for the treatment of short stature in PGHD based on their effects on AGV. hGH therapy in children with GHD is a replacement therapy that leads to improvement in height. Thus, normalization of GH (and IGF-1) levels improves growth that ultimately translates into improvement of final adult height.
- Early long-term clinical trials, including those that supported the approval of Humatrope, evaluated final height in the subset of patients with PGHD. By doing so, there was confirmation that in pediatric patients with GHD, improvement in AGV persists over years of treatment and ultimately improves final adult height. Thus, FDA continues to accept hGH-induced improvement in AGV as evidence of effective treatment in pediatric patients with GHD.

- Current treatment guidelines for PGHD recommend "the use of GH to normalize adult height and avoid extreme shortness in children and adolescents with GHD".[18] Thus, FDA's approach is consistent with expert opinions described in the current treatment guidelines for PGHD management.
- Lastly, the selection of AGV as the primary endpoint to be used in phase 3 pivotal trial is in agreement with prior recommendations made by the Division (refer to EOP2 Meeting Minutes from 7/27/2016).

Lastly, the Applicant prespecified that a test for superiority of lonapegsomatropin-tcgd over Genotropin would be conducted if noninferiority for AGV at week 52 is confirmed. (b) (4) if the lower limit of the two-sided CI of the treatment difference is greater than or equal to 0 cm/year.

Secondary endpoints

The Applicant included the following secondary endpoints:
- AGV over 52 weeks at prespecified time points
- Changes in height SDS over 52 weeks from baseline in lonapegsomatropin-tcgd and in Genotropin groups.
- IGF-1 SDS, IGFBP-3 SDS, changes in these parameters over 52 week and the normalization of IGF-1 SDS over 52 weeks for the lonapegsomatropin-tcgd and the daily Genotropin treatment groups

No adjustments for multiple comparisons for these secondary endpoints to control the overall type 1 error or hierarchical testing were proposed by the Applicant.

Efficacy results

Subject disposition and completion rate

A total of 162 subjects with short stature due to PGHD were randomized to one of two treatment arms: 106 subjects were randomized to lonapegsomatropin-tcgd group and 56 subjects to Genotropin group. Of the 162 subjects, 161 subjects received treatment and were included in ITT population and one subject randomized to lonapegsomatropin-tcgd group did not receive any treatment. The completion rate of the study was high at 98% (159/161 subjects). Two subjects, one in the lonapegsomatropin-tcgd group (withdrew consent) and one in the Genotropin group (lost to follow-up) discontinued the study early. No subjects discontinued the study because of adverse events (**Table 3**).

Table 3. Subject disposition

Disposition	**Lonapegsomatropin (N = 106) n (%)**	**Genotropin (N = 56) n (%)**	**Total (N = 162) n (%)**
Randomized	106	56	162
Randomized and dosed	105	56	161

[18] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. 2016. Horm Res Paediatr;86:361-397

Completed trial	104 (99)	55 (98)	159 (99)
Withdrawn from trial	1 (1)	1 (1.8)	2 (1.2)
Withdrawal of consent	1 (1)	0	1 (0.6)
Lost to follow up	0	1 (1.8)	1 (0.6)

Source: Clinical Study Report, Table 8.

Dr's. Vachhani review of protocol violators did not identify any significant deviations in the way the inclusion/exclusion criteria were applied in the clinical trial.

Baseline demographic and disease characteristics

The randomized groups were relatively well-balanced at baseline with respect to demographic and disease characteristics. The mean age at baseline was 8.5 years (range 3 to 13 years) in each group. Approximately 82% of all subjects in each group were male, consistent with male enrollment in other hGH pivotal trials and is seen in clinical practice. Approximately two-thirds of subjects in each group had idiopathic PGHD. Mean annualized growth velocity at baseline was 3.9 cm/year in each group and mean height SDS was approximately - 3 SDS in each group. The mean (SD) baseline IGF-1 SDS was similar across treatment groups (-2 (0.88) (lonapegsomatropin-tcgd), -1.96 (0.98) (Genotropin)). Approximately 26% of all subjects enrolled in the study were from the US; other subjects were from Europe (63%), Middle East/North Africa (6%) and Oceania (6%) regions. The predominance of ex-US subjects is acceptable. First, diagnostic criteria for PGHD in and outside the US are the same and patients generally have similar disease etiology. Manifestations of the disease are the same regardless of the region of enrollment, and comorbidities are also similar in these patients and are due to GH deficiency as well as to other pituitary hormonal deficiencies (i.e., hypothyroidism, hypocortisolism, hypogonadism). Consequently, common medications in patients worldwide include hormonal replacement therapies (e.g., levothyroxine, hydrocortisone). Thus, the efficacy and safety data on lonapegsomatropin-tcgd use obtained in subjects from other countries is applicable to US subjects.

Dr. Vachhani also indicated that the groups were well balanced at baseline with respect to other baseline comorbidities and concomitant medication.

Primary analysis

The primary endpoint, i.e., AGV at the end of 52 weeks, was compared between lonapegsomatropin-tcgd and Genotropin with a prespecified non-inferiority margin of 2 cm/year. Superiority was tested once non-inferiority was established.

Refer to Dr. Alexander Cambon's review for the primary statistical analysis methods used to support the establishment of efficacy. Refer to Dr. Vachhani's review for additional discussion of efficacy. This memorandum provides a summary of the main efficacy findings.

The Applicant conducted the primary efficacy analysis in 161 subjects who were randomized and received at least one dose of study drug (ITT population) using the FDA-recommended ANCOVA approach. Missing final assessments were multiply imputed using the missing at random assumption.

The mean treatment difference in AGV between lonapegsomatropin-tcgd and Genotropin groups was 0.8 cm/year (95% CI 0.13; 1.47), p=0.009 (**Table 4Table 4**). Dr. Cambon independently verified the Applicant's results for the primary analysis and confirmed that the pivotal study establishes efficacy of lonapegsomatropin-tcgd as demonstrated by non-inferiority of lonapegsomatropin-tcgd compared to Genotropin in terms of increase in AGV. Dr. Cambon also confirmed that the missing data and discontinuation rates were very low. Because of the unequal randomization ratio between lonapegsomatropin-tcgd and Genotropin, an ANCOVA allowing unequal variances between treatment groups was conducted. Results using this method were consistent with the other analyses. Dr. Cambon also repeated the primary efficacy analysis by using a single imputation ANCOVA with the fitted final assessment value from the ANCOVA model for the Genotropin subjects (who were still on treatment at Week 52, but final AGV was missing) and the not missing at random (NMAR) assumption for the subject on lonapegsomatropin-tcgd who discontinued treatment at week 34. In these subjects, Dr. Cambon used the baseline AGV value to impute the missing final AGV assessment. The difference between treatment arms remained similar and statistically significant (**Table 5**).

Table 4. Primary Endpoint--Applicant's Results

Endpoint	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val
Annualized Height Velocity (cm/year)	11.2	10.3	0.86	0.22	1.5	0.009

Abbreviations: cm/yr-centimeters per year; SDS- Standard Deviation Score; Exp.-Experimental Arm (lonapegsomatropin-tcgd); Ctr.-Control Arm (Genotropin); Diff.-Treatment Difference; LCL- Lower Confidence Limit; UCL -Upper Confidence Limit; P-Val-P-Value.
Source: Biostatistician's review, table 4, modified.

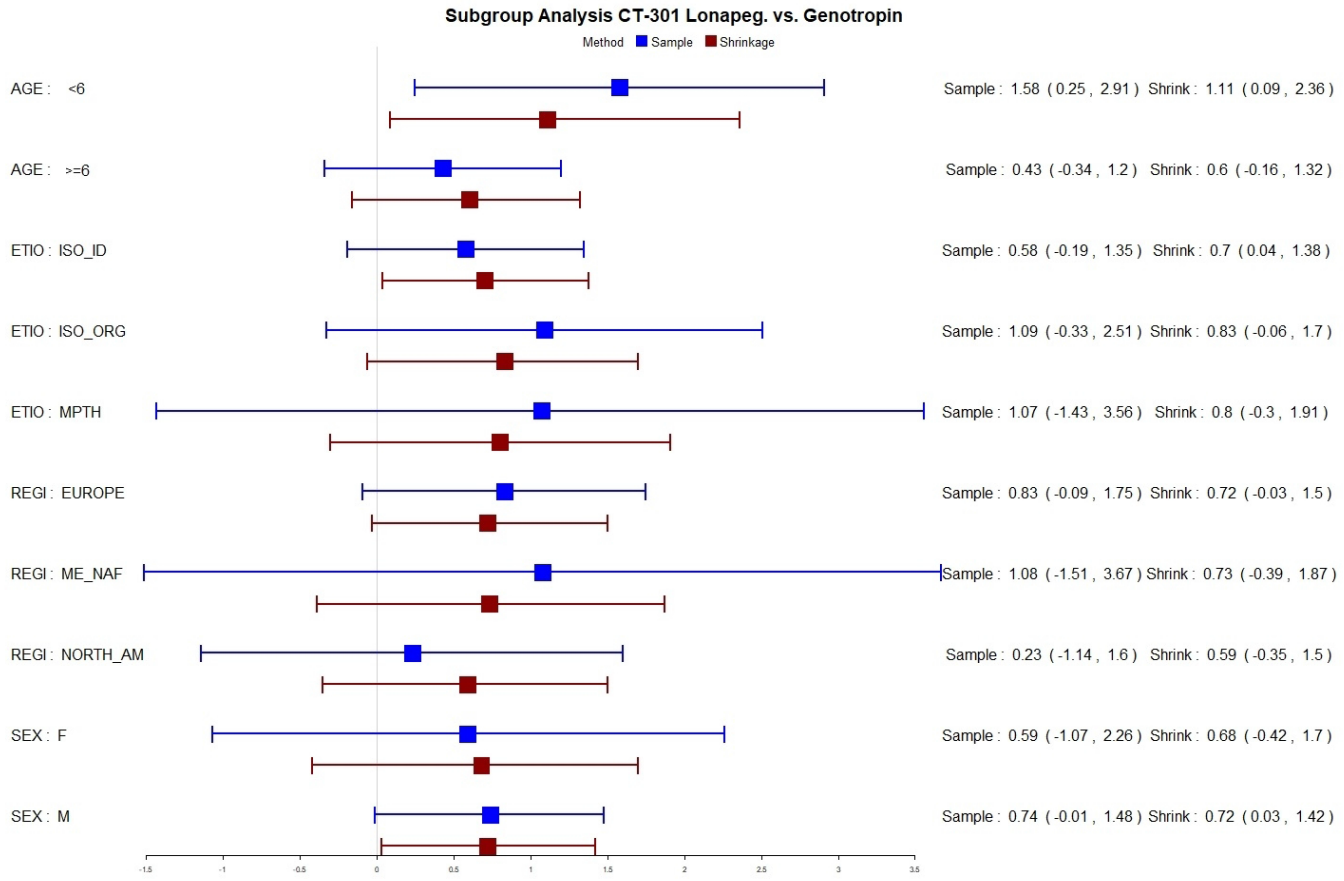
Table 5. Primary Endpoint—FDA Results

Endpoint	Exp.	Ctrl.	Diff.	LCL	UCL	P-Val
Annualized Height Velocity (cm/year)	11.1	10.3	0.80	0.13	1.47	0.02

*Results from the single imputation ANCOVA.
Abbreviations: cm/yr-centimeters per year; SDS- Standard Deviation Score; Exp.-Experimental Arm (lonapegsomatropin-tcgd); Ctr.-Control Arm (Genotropin); Diff.-Treatment Difference; LCL- Lower Confidence Limit; UCL -Upper Confidence Limit; P-Val-P-Value.
Source: Biostatistician's review, table 5.

There was some variability in treatment differences between subgroups (e g., largest difference in age subgroup <6 years old subgroup and the smallest difference in the North American subgroup) (refer to Statistical review for the detailed subgroup differences). However, Dr. Cambon concluded that these variabilities were most likely due to small sample size and large variability in the sample estimates for some subgroups. To confirm this, Dr. Cambon conducted additional analysis and derived shrinkage estimates for subgroup treatment effects using a Bayesian hierarchal model. According to this analysis, the treatment difference in increase of AGV between lonapegsomatropin-tcgd and Genotropin was not affected by age, sex, etiology of GHD, or region (**Figure 4**).

Figure 4. Forest Plot Comparing Frequentist Subgroup Analysis to Bayesian Shrinkage Analysis



Abbreviations: ME_NAF-Middle East/North Africa region; Etio-etiology; II-Isolated Idiopathic; IO-Isolated Organic; MPHD-Multiple Pituitary Hormone Deficiencies
Source: Biostatistician's review, figure 3.

Analysis of change in AGV at 52 -week time point (b) (4) **that lonapegsomatropin-tcgd provides a significant improvement in AGV at Week 52 over Genotropin in pediatric patients with PGHD**

Following the demonstration of non-inferiority, the results also showed that AGV in the lonapegsomatropin-tcgd group was greater than that of the Genotropin group with statistical significance (refer to Table 4 and Table 5 in Primary Analysis Section above). (b) (4)

- The observed treatment difference was small and of unknown clinical significance (i.e., unknown how the observed difference of 0.86 cm/year in AGV will translate into improved final height with lonapegsomatropin-tcgd compared to Genotropin).
- Lastly, Dr. Cambon noted that superiority was demonstrated only in a single pivotal study and "it was not clear that statistical superiority would be replicated in another study and this study on its own may not provide sufficient evidence for a determination of superiority to another approved drug".

(b) (4)

Other analyses of growth parameters (secondary endpoints)

- *AGV at prespecified time points over 52 weeks*

The result of this analysis demonstrated that lonapegsomatropin-tcgd induced increase in AGV in children with short stature due to GHD at each pre-specified time point during the study (Table 6). As expected, the magnitude of increase in AHV in both groups was greater during the first 6 months of treatment; these early changes in AGV are due to well-known catch-up growth phenomenon seen in children when the cause of growth deficit is removed.[19] This phenomenon was also observed in pivotal trials for other hGH formulations. However, the conclusion regarding final height cannot be made based on this short-term exaggerated growth response, because growth rate usually decreases (but remains within target range) during the subsequent years of treatment. Therefore, AGV at 12 months is more predictive of the subsequent growth and improvement in final height.

Table 6: 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*

As expected with improvement in AGV and adequate replacement with missing GH in PGHD, the height SDS improved or normalized at 52 weeks in both treatment groups. Mean height SDS were approximately - 3 SDS in each group at baseline and normalized by the end of 52-week treatment (1.1 SDS in lonapegsomatropin-tcgd group and 0.96 SDS in Genotropin group). The difference in height SDS at the end of the treatment between the treatment groups was small and not statistically significant (p=0.02) (Table 7 Overall, the results of this analysis support the results of the primary endpoint.

[19] Catch-up growth: definition, mechanisms, and models. Jan-Maarten Wit [1], Bart Boersma J Pediatr Endocrinol Metab. 2002 Dec;15 Suppl 5:1229-41.

Height SDS is another growth parameter that widely used by health care providers for the assessment of adequate growth in children. Thus, I agree that improvement in height SDS during the treatment period should be included in the label. I recommend including in the label the baseline and height SDS at 52 week and changes in height SDS at 52 weeks from baseline (b) (4)

Table 7: 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

Analysis of change in mean IGF-1 SDS and IGFBP-3 at the end of 52-week treatment (secondary endpoint)

Mean IGF-1 SDS were low at baseline in both groups: -2.08 in lonapegsomatropin-tcgd group and -1.96 in Genotropin group, respectively. At the end of 52-week treatment, mean IGF-1 SDS normalized in both groups as would be expected with replacement of the inadequate hormone. Approximately 70% of subjects in lonapegsomatropin-tcgd group and 60% of subjects in Genotropin group had IGF-1 levels in 0 SDS - +2 SDS range. These results are overall supportive of the primary endpoint: the adequate replacement with missing GH normalizes GH levels, IGF-1 levels, and ultimately leads to the improvement in growth parameters in children whose short stature is due to GHD. Levels of IGFBP-3, a major IGF binding protein, also increased as expected with increase of IGF-1.

However, it should be noted that there is no correlation between levels of IGF-1 and final height. In addition, the ultimate goal of treatment is the improvement in growth and final height, and the target IGF-1 levels to

optimize the balance between height gain and potential risks are not established to date.[20] Thus, the clinical assessment of treatment efficacy should not be based on IGF-1 levels, but rather on AGV and height.

Other endpoints

Changes in bone age

Change in bone age was a safety endpoint to evaluate the risk of an undue acceleration in bone age. However, patients with GHD have a delay in bone age relative to chronological age and the bone age is expected to improve on treatment. Thus, change in bone age is considered as a supportive of efficacy and briefly discussed in this section.

At baseline, mean bone age was 5.8 years and 5.9 years in lonapegsomatropin-tcgd group and Genotropin group, respectively. The bone age was delayed by an average of 2.5 years relative to chronologic age in both groups. As expected, there was a trend in the improving of bone age with hGH treatment observed at week 52: mean (SD) change in bone age at Week 52 was 1.4 years for subjects treated with lonapegsomatropin and 1.4 years for subjects treated with Genotropin. The small changes from baseline are most likely due to the short duration of treatment.

Moreover, 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 and 0.8 (0.14) for the Genotropin group at week 52, suggesting that lonapegsomatropin-tcgd treatment does not advance bone age relative to chronological age.

Supportive evidence of effectiveness of lonapegsomatropin-tcgd in subjects with short stature due to PGHD from studies CT-301EXT and CT-302

Both studies were designed primarily as safety studies evaluating the safety profile of lonapegsomatropin-tcgd in subjects who were previously treated with hGH (CT-302) or who completed study CT-301 or CT-302 (CT-301EXT). The starting lonapegsomatropin-tcgd dose for both studies was the same as in the pivotal study. However, as opposed to the fixed-dose scheme I the pivotal study, up-titration was allowed by 20% based on IGF-1 levels with the goal to maintain IGF-1 SDS between 0 and +2. The dose per ml administered in both trials was the same as used in study CT-301 and consistent with the proposed cartridge dose per the same weight range in the label (**Table 2**, above).

CT-302

Study CT-302 was a 26-week, multicenter, single-arm, open-label study that evaluated the safety, tolerability, and efficacy of lonapegsomatropin-tcgd in children previously treated with short-acting hGH (3-17 years old) or in treatment-naïve children (1- 3 years old) with PGHD. Growth parameters were evaluated as secondary endpoints at the end of 26 weeks of treatment.

[20] Grimberg A, DiVall S.A, Polychronakos C, Allen D.B, Cohen L.E, Quintos J.B, Rossi W.C, Feudtner C, Murad M.H on behalf of the Drug and Therapeutics Committee and Ethics Committee of the Pediatric Endocrine Society. 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. 2016. Horm Res Paediatr;86:361-397

Enrollment criteria were similar to those in pivotal study CT-301 with exception for age at enrollment and use of hGH in past. The study enrolled younger children, including those > 6 months old. Subjects > 3 years old had to be on hGH treatment prior to the study enrollment for more than 13 weeks but fewer than 130; subjects 1 - 3 years old were allowed to be treatment-naïve.

One hundred forty-six subjects were enrolled in the trial, and 144 subjects completed. Two subjects withdrew informed consent after they have received 2 and 9 doses, respectively. The mean age at baseline was 10.6 years; of 146 subjects, 4 subjects were younger than 3 year. The majority of subjects were boys. Since subjects at enrollment had been already on treatment with hGH formulations, their baseline and height and IGF-1 levels were already improved: mean (SD) height SDS was -1.4 (0.8) and mean (SD) IGF-1 SDS was 0.85 (1.29), respectively.

Results of this study provides evidence that lonapegsomatropin-tcgd continues to induce growth in children with short stature due to PGHD who were previously treated with immediate-release hGH. The LS mean for AGV was 8.72 cm/year (95% CI: 8.55, 9.77) and LS mean (SE) for change in height SDS was 0.25 (00.2) (95% CI: 0.21, 0.29) at Week 26. The LS means (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.

This study also provides evidence on lonapegsomatropin-tcgd-induced improvement in growth in young children < 3 years old (all but one child was treatment-naïve). The subgroup analyses demonstrated improvement in all mean (SD) growth parameters and biomarkers at Week 26: AGV was 16.24 cm/year (2.32), height SDS -088 (1.08), change in height SDS from baseline was 0.96 (0.43), and IGF-1 SDS was 1.41 (0.43). The observed greater AGV response is expected in these patients due to the catch-up growth phenomenon during the first year of treatment of treatment-naïve patients and overall expected greater growth rate in this age group.

CT-301EXT

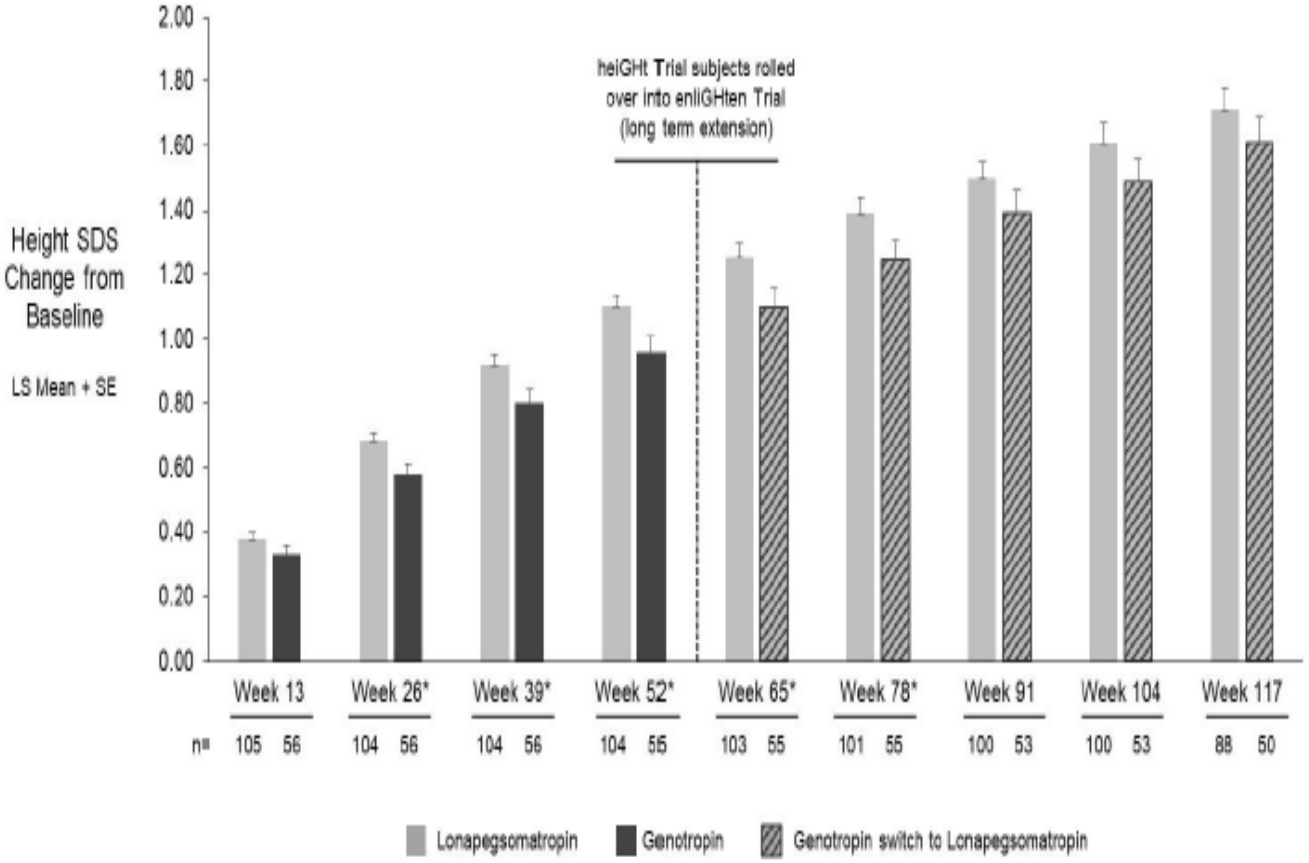
This was a multicenter, open-label, single arm trial evaluating the long-term safety of lonapegsomatropin-tcgd in children with GHD who completed the 52-week treatment period in study CT-301 or 26-week period in study CT-302. Subjects who were treated with Genotropin in study CT-301 were switched to lonapegsomatropin-tcgd 0.24 mg hGH/kg/week and all other subjects (from lonapegsomatropin-tcgd group in study CT-301 and from CT-302) were continued with lonapegsomatropin-tcgd.

Growth parameters were evaluated at each visit. A total of 296 subjects were enrolled in the study as of data cut-off of 9/30/19. Of these, 156 subjects were from study CT-301 (102 subjects originally randomized to lonapegsomatropin group and 54 subjects originally randomized to Genotropin group) and 140 subjects were from CT-302. The majority of subjects continued to use the drug via vial/syringe and 45/296 subjects received the drug via autoinjector in study CT301EXT. The mean treatment duration via autoinjector was 10 weeks (range 6-14 weeks).

At week 26 in CT-301EXT trial (78 weeks of total treatment for subjects from trial CT-301 and 52 weeks - for subjects from CT-302 trial), mean (SD) AGV was 8.8 (2.2) cm/year, mean change in height SDS from baseline was 0.27 (0.19) and IGF-1 SDS was 1.2 (1.34), respectively. Because the data were obtained from subjects with different exposure to lonapegsomatropin (from a total of 52 weeks in trial CT-302 to up to 78 weeks in subjects from trial CT-301), Dr. Cambon analyzed the long-term effect of the drug in subgroups of subjects who were originally randomized to Genotropin and who were originally randomized to lonapegsomatropin-tcgd in study CT-301. Results of this analysis demonstrate that both groups continued to show increases in change in height SDS at each time point (Figure 5). However, Dr. Cambon noted that

the analysis has limitations since only non-missing values were included; the assessment of subjects who already had discontinued treatment at each end point were not imputed in this analysis.

Figure 5. Change from baseline in height SDS by visit



Source: Statistical review, figure 2

The study also provided evidence benefit in subjects younger than 3 years old. All 4 subjects younger than 3 years old from Study CT-302 continued demonstrating improvement in growth in study CT-301EXT: after an additional 26 weeks of treatment with lonapegsomatropin (a total exposure of 52 weeks) mean AGV was 12.88 cm/year, mean height SDS was -0.18, mean change in height SDS was 0.71 and IGF-1 SDS was 2.11.

Lastly, two subjects reached final adult height while being treated with lonapegsomatropin in Study-30EXT. One subject achieved final height of 149.9 cm that was close to mid-parental height (150cm), and the other subject archived height of 168.8 cm (although the parental target was not reported). Although these data is limited and confounded by previous treatment with other hGH, it provides additional reassurance that treatment with lonapegsomatropin in children with short stature will translate in the improvement in final height.

This study also provides limited but reassuring safety data on use of drug via autoinjector: no new safety signals or increase in frequency of ARs were noted. The conclusion regarding efficacy of the drug delivered via the autoinjector is complicated because of the small number of subjects and short duration of treatment (i.e., 10 weeks are not sufficient to demonstrate effect on growth and the data is also confounded by previous

hGH treatment). However, based on results from the study CT-102 demonstrating comparability of PK characteristics of the drug administered via vial/syringe compared to autoinjector, it is expected that drug delivered via autoinjector will have the same effect on growth as drug administered via vial/syringe.

In conclusion, the findings from the supportive studies, CT-302 and CT301EXT, are consistent with results from Study CT-301 and provide additional evidence that lonapegsomatropin-tcgd is effective in the growth improvement in patients with PGHD. Although the growth was slower in these studies compared to pivotal study, the mean AGV remained at levels above those at baseline. Lower AGV observed in these studies reflects the normalization of growth after the initial accelerated growth due to catch-up phenomenon (see discussion above) in children previously exposed to hGH products. The similar growth pattern was observed in studies evaluating the efficacy of short-acting hGH formulations in children with short stature due to PGHD.

These studies also provided evidence of effectiveness of the drug in in children younger than 3 years old, despite few subjects enrolled in this age category. (b) (4)

Conclusions Regarding Efficacy

Trial CT-301 demonstrated that lonapegsomatropin-tcgd improves AGV at the end of 52-week treatment; the improvement in AGV was within prespecified non-inferiority margins compared to Genotropin with mean treatment difference in AGV between lonapegsomatropin-tcgd and Genotropin groups of 0.8 cm/year (95% CI 0.13; 1.47), p=0.009. Directional changes in other growth parameters (height SDS, change in height SDS from baseline) were consistent with expectations and suggest that lonapegsomatropin-tcgd use is associated with a net improvement in growth. The observed lonapegsomatropin-tcgd-induced improvements in growth are also overall consistent with improvements in growth parameters values observed with other hGH treatments in PGHD (7.5 cm/year-13.5 cm/year).[21]
Studies CT-302 and CT-301EXT CT-301 provide supportive evidence of effectiveness; the results were consistent with changes in growth parameters observed in the pivotal study. However, these results should be interpreted with caution because of multiple factors, including that the studies were not designed to evaluate efficacy, did not have a placebo arm, dose was titrated based on IGF-1, and all subjects had been exposed to other hGH therapies prior to the enrollment. (b) (4)

Studies CT-302 and 301EXT also provided important information on evidence of lonapegsomatropin-tcgd -induced growth in children > 1 year - < 3 years old (not enrolled in study CT-301). The lonapegsomatropin-tcgd-induced AGV, changes in height SDS and IGF-1 SDS in these younger subjects were overall consistent with growth parameters observed in older children in studies CT-301, CT-301 and CT-301EXT. However, children < 1 year old were not included in lonapegsomatropin-tcgd clinical program and the efficacy and safety of this drug remains unknown in very young children. Thus, I recommend approval of this product only for pediatric patients > 1 year old with open epiphysis.

Based on study 301, (b) (4)
lonapegsomatropin-tcgd provides a significant improvement in growth over Genotropin in pediatric patients with GHD. However, the observed difference of 0.86 cm/year in AGV at 12 months is small and of unknown clinical significance (b) (4) and it remains unknown whether this

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

difference will ultimately translate in difference in final adult height. In addition, increase in height SDS at 52 weeks over baseline was similar in both groups (1.01 vs 0.9, respectively). The conclusion regarding the superiority of lonapegsomatropin-tcgd over Genotropin in increasing AGV is further complicated by the fact that the superiority was demonstrated in a single trial only and the difference was not consistent between all subgroups, e.g., lonapegsomatropin-tcgd was not superior to Genotropin in subjects > 6 years old, in female subjects, in subjects from US. In conclusion, I agree with clinical and statistical reviewers (b) (4) based on limitations discussed above.

Lastly, based on the result of Study CT-301, I recommend a starting dose for lonapegsomatropin-tcgd 0.24 mg hGH/kg/week for all patients regardless of age, severity of PGHD at baseline, or etiology of PGHD. I also agree with the proposed in the label cartridge doses: these doses are consistent with the weight-based volumes used in the pivotal trial (**Table 2. Drug concentration, dosing brackets and volumes of lonapegsomatropin-tcgd in CT-301**

). However, because the lowest available dosage strength is for patients with weight 11.5 kg, the indication should be restricted to children with body weight > 11.5 kg. Lastly, the assessment of treatment efficacy should be based on growth rate; IGF-1 levels should be monitored for safety reasons only.

7. Safety

The primary safety data in support of the proposed indication of lonapegsomatropin-tcgd in pediatric patients with growth failure due to GHD is derived from the pivotal Study CT-301. Supportive safety data in these subjects come from two phase 3 studies in subjects with PGHD (CT-302 and CT-301EXT). However, it should be noted that the results from supportive studies are confounded by the previous exposure to hGH; the absence of the control group in these studies further complicates the safety assessment. Thus, the data from these studies should be interpreted with caution.

Overall, 305 subjects with PGHD were exposed to lonapegsomatropin-tcgd in three phase 3 studies. Based on data obtained to date (cutoff date 3/31/2019) from three phase 3 studies, 301 subjects received drug for > 6 months, and 104 subjects for > 12 months. This level of exposure is acceptable for this drug to support chronic dosing.

The Applicant also included the results of two phase 1 study conducted in healthy volunteers (CT-102 and CT-101) and one phase 2 study in pediatric subjects with GHD using ACP-001, predecessor molecule containing an (b) (4) kDa mPEG carrier (CT-004). The results from these studies will not be discussed in this memorandum, since these studies have been conducted in the different populations (CT-102 and CT-101), were of short duration and/or used different drug (ACP-001; CT-004 and CT-101). Refer to Dr.'s Vachhani review for the details.

This CDTL review will further focus on the safety observations made in the pivotal Study CT-301. This study provides the most informative data on common product-related safety issues because the study allows side by side comparison of lonapegsomatropin-tcgd to Genotropin (with well-established safety profile in the proposed indication), were obtained in randomized groups with frequent assessment and had an approximately 12-month duration of controlled observation. The safety data from the studies CT-302 and CT-301EXT will be summarized only briefly and as needed. The additional sources will be mentioned only when relevant.

In study CT-301, 105 subjects were treated with lonapegsomatropin-tcgd for > 6 months, and 104 subjects for > 12 months.

Deaths, Adverse Events (AE) that led to the study discontinuation, and Serious Adverse Events (SAE)

There were no deaths reported in any of the studies. No subjects treated with lonapegsomatropin-tcgd in any of three phase 3 studies study discontinued the study due to the AEs.

A total of 9 SAEs were reported in 6 subjects treated with lonapegsomatropin-tcgd in three phase 3 studies.

In study CT-301, 1 subject developed SAE of appendicitis.

In study CT-301EXT, a total of 7 SAEs occurred in 5 subjects: adenoid hypertrophy, gastrointestinal viral infection and vomiting, pyrexia, generalized tonic-clonic seizures and epilepsy, rash. All SAEs were most likely due to the underlying medical conditions (e.g., seizures and epilepsy in subject with previous history of seizures, vomiting in subject with cyclic vomiting syndrome) or concomitant medications (e.g., rash in subject treated with amoxicillin). In addition, subject who developed rash had negative antibody titers. All subjects recovered and continued treatment with lonapegsomatropin-tcgd. Overall, no new safety signals or increase in frequency of SAEs were identified with longer exposure to the study drug.

In study CT-302, one subject developed two SAEs that were most likely related to the underlying medical condition and/or induced by trauma: chest pain (related to chest trauma) and atrioventricular block (that was most likely related to the underlying congenital cardiac conditions).

Overall, no new safety signals were identified. All SAEs were reported in one subject each and resolved without treatment interruption. I also agree with Dr. Vachhani's conclusion that the SAEs were unlikely to be related to study drug.

Common Adverse Events

Seventy seven percent (81/105) of subjects treated with lonapegsomatropin-tcgd and 70% (39/56) of subjects treated with Genotropin experienced at least one AE during Study CT-301. Overall, the AE profile observed in Study CT-301 was consistent with the known AE profile of hGH in patients with PGHD.

The review team conducted their own analysis of adverse reactions (ARs) occurring during the 52-week treatment with lonapegsomatropin-tcgd or Genotropin using FDA Medical Queries (FMQ). FMQs were developed by FDA to improve the capture of synonymous adverse event terms and to improve overall safety signal detection. The results of this analysis revealed additional ARs that occurred more frequently in lonapegsomatropin-tcgd arm compared to the Genotropin arm or rendered different results than reported and proposed in Section 6 of the label by the Applicant. The ARs that are new or rendered different results than the original table in Section 6 of the label are marked in **bold** in **Error! Reference source not found.** (refer to the Clinical Review in DARRTS for the original table). The relative (RR) and absolute (D) risks are presented in the table below highlighting FDA's rationale and are not meant to be displayed in the prescribing information.

Table 8. Adverse reactions with > 5% overall incidence in subjects with PGHD treated with lonapegsomatropin-tcgd compared to Genotropin during Study CT-301.

	Lonapegsomatropin-tcgd (N = 105) n (%)	Genotropin (N =56) n (%)	D risk (%)	RR; 95% CI
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)
Diarrhea	6 (5.7%)	3 (5.4%)	0.4	1.1 (0.3, 4.1)

N= number of subjects having the event, (%) = proportion of subjects having the event
Pyrexia includes preferred terms (PT): pyrexia, fever
Hemorrhage includes PT: epistaxis, contusion, petechia, eye hemorrhage
Infection, viral includes PT: viral upper respiratory tract infection, viral infection, varicella, rotavirus infection, respiratory tract infection viral, molluscum contagiosum, laryngitis viral, influenza, gastroenteritis viral, croup infectious.
Arthralgia and arthritis include PT: arthritis reactive, arthralgia
Cough includes PT: cough and allergic cough
Abdominal pain includes PT: abdominal discomfort, abdominal pain and abdominal pain upper
Source: Clinical Review, table 41.

Overall, since the use of FMQ captures synonymous adverse event terms and improves the overall safety information in the label, the reporting of ARs in Section 6 of the label should be based on the results of the FDA analysis. The criteria used for the selection of the ARs to be included in Section 6 Adverse Reaction table of the Prescribing Information, include event rate for lonapegsomatropin-tcgd > 5% and RR > 1.

Dr. Vachhani analyzed further all AEs that have not been previously reported (with hGH (cough, pyrexia, hemorrhage, viral infection, nausea and vomiting) and/or were observed more frequently with lonapegsomatropin-tcgd compared to Genotropin (arthralgia). She concluded that such AEs as cough, viral infection, pyrexia, nausea and vomiting or events of hemorrhage that occurred during the study (due to epistaxis or trauma) are common and overall expected events in this age group and are most likely not drug-related. Arthralgia is a known AE associated with hGH use and is due to fluid accumulation associated with GH. I agree with her conclusion: the observed imbalance in these events is most likely attributed to factors other than the interventional agent (e.g., uneven randomization) and to the play of chance. Importantly, none of these events were severe, they resolved during the study and did not require dose adjustment or treatment discontinuation. These risks can be mitigated through the labeling.

Adverse events of special interest (AESI)

AESI included injections site reactions, neoplasms, glucose intolerance, intracranial hypertension, fluid retention, hypoadrenalism, hypothyroidism, slipped capital femoral epiphyses, progression of pre-existing scoliosis, pancreatitis, and lipoatrophy. Dr. Vachhani analyzed all class-specific adverse reactions that are included in approved hGH labels and adverse reactions that may be associated with safety concerns identified in non-clinical program (mPEG-related; refer to Nonclinical section above).

No increase in incidence or in severity of AESIs, including headache, hypothyroidism, or adrenal insufficiency, was observed during treatment with lonapegsomatropin-tcgd compared to Genotropin. No AEs of intracranial hypertension, pancreatitis or slipped capital femoral epiphyses were reported in lonapegsomatropin-tcgd-treated subjects. The frequency of the injection site reactions was low in subjects treated with lonapegsomatropin in the clinical development program: lipoatrophy (2 subjects), urticaria (1 subject), and pain (1 subject).

Allergic reactions were mild and occurred in 6% of subjects in lonapegsomatropin-tcgd group compared to 7% of subjects in Genotropin group, respectively. Lastly, as discussed in *Clinical/Statistical*- Efficacy section above, treatment with lonapegsomatropin-tcgd was not associated with an acceleration in bone age relative to chronologic age.

Neoplasms benign/malignant

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

The overall incidence of neoplasms reported was low in the clinical program. A total of five subjects treated with lonapegsomatropin-tcgd in clinical program developed benign tumors: 4 subjects developed skin papilloma (2- in CT-301, 1- in CT-302 and 1- in CT-301EXT) and one subject developed osteoma (in study CT-301; with previous history of osteochondroma). There was no imbalance in events of skin papilloma in study CT-301: one subject treated with Genotropin in study CT-301 developed skin papilloma. A

In conclusion, no increased risk of malignant or benign tumors with lonapegsomatropin-tcgd use was observed in the clinical program. The proposed labeling for lonapegsomatropin-tcgd appropriately contraindicates the drug in patients with active malignancies and includes these SAEs in Warnings and Precautions of the label. In addition, the risk of tumorogenesis is mitigated by the proper titration of the drug based on IGF-1 levels and avoiding chronically elevated IGF-1 levels above normal range.

Risk of toxicities related to mPEG (refer to Nonclinical Pharmacology Toxicology and Clinical Pharmacology sections above)

As described in the Nonclinical section, cellular vacuolation of epithelial cells of choroid plexus was noted and thought to be associated with mPEG in animal studies. Notably, minimal vacuolation of the choroid plexus epithelium was observed histologically in cynomolgus monkeys after 52 weeks dosing at an exposure of 9-10-fold higher than the clinical dose.

Accumulation of mPEG and vacuolation were not associated with any distortion of the intracellular compartments, degeneration, necrosis or inflammation. There were no signs of neurotoxicity in these animals, such as tremors, convulsions, or unusual behavior. Overall, the results of the three pivotal chronic

toxicity studies provide compelling evidence that the accumulation of mPEG in the choroid plexus and other brain regions was not adverse at the doses evaluated, which, in the monkey, provided large exposure margins relative to the proposed clinical dose of 0.24 mg hGH/kg/week.

Importantly, clinical pharmacology reviewers also concluded that based on the results of the analysis modeling the predicted median steady state level of mPEG in the choroid plexus of humans at the proposed dose of 0.24 mg hGH/kg/week, the level of mPEG at this dose is 2-fold lower that the predicted steady state levels in choroid plexus of monkeys at the NOEL 0.4 mg/hGH/kg/week for the drug-related microscopic findings in the brain observed at doses 1.6 mg hGH/kg/week in animals. Thus, no accumulation of mPEG is expected at the proposed clinical doses.

However, to more completely understand whether the mPEG accumulation at higher than proposed doses poses a clinical risk and to characterize this hypothetical risk, DGE consulted the Division of Neurology (DNP) and the Division of Pediatric and Maternal Health (DPMH) (refer to DNP reviews by Drs. David Hawer (non-clinical) from 1/19/21 and David Hosford (clinical) from 1/12/2021 in DARRTS and DPMH review by Dr. Ethan Hausman from 3/3/2021). Dr. Hawer agreed with Dr.'s Quinn conclusion that, based on the available non-clinical information, including large exposure margins and the lack of evidence that observed accumulation of mPEG is associated with abnormalities, the proposed human dose carries a minimal risk of adverse neurological effects at the clinical therapeutic dose of 0.24 mg/kg/week in children with GHD. Therefore, no additional nonclinical studies are needed at this time.

Dr. Hosford indicated that the data accumulated with use of 6 approved pegylated products to date for different indications in adults and children do not reveal any potential neurological safety signals. In addition, Drs. Vachhani and Hosford analyzed AEs reported in the SOC of Nervous system disorder and Psychiatric disorder and concluded the following:

- Two neurologic SAEs (generalized tonic-clonic seizure and epilepsy) reported in one subject in study CT-301EXT were most likely not drug-related and in this subject with a history of seizures. No neurologic SAEs were reported in studies CT-301 or CT-302.
- The most frequently reported AEs in Study CT-301 were headache (12.4% in lonapegsomatropin-tcgd group vs. 14.3% in Genotropin group) and dizziness (1.9% in lonapegsomatropin-tcgd group vs. 1.8 % in Genotropin group). All other AEs (attention deficit disorder, affect lability, depressive symptom, tremor, enuresis) occurred in one subject each. Headaches are not unexpected in this age group and are also a known effect of hGH therapy.

The safety findings from studies CT-302 and CT-301EXT were consistent with findings from the pivotal study.

The clinical team concluded that that there were no relevant mPEG-related safety signals in subjects treated with lonapegsomatropin-tcgd. The DPMH reviewer agreed with other reviewers' conclusions.

Overall, the review team agree that the nonclinical, clinical pharmacology and clinical data for lonapegsomatropin-tcgd in total support a minimal mPEG-related risk. (b) (4)

Laboratory parameters

Parameters of glucose control (fasting blood glucose, HbA1C and insulin levels)

There is a known risk of hyperglycemia associated with use of hGH due to direct insulin antagonistic effects of GH. The risk of hyperglycemia is included in all hGH labels. Thus, the Clinical Reviewer paid special attention to the occurrence of out-of-range values and adverse events related to these biochemical changes.

The mean fasting glucose ranged from 87.1- 94.3 mg/dL across two treatment groups during the trial CT-301. Mean HbA1C ranged from 5.0 % to 5.2 %. The mean insulin levels were within reference range in all groups up to week 52.

Three subjects experienced HBA1C > 6.1% (up to 6.7%) during the study, of these two subjects had elevated HbA1C at baseline and one subject had elevated HbA1C due to the laboratory error. All subjects were asymptomatic, and no SAEs were reported; the events resolved with or without appropriate treatment.
No subjects treated with lonapegsomatropin-tcgd in the Study CT-301 had a new diagnosis of diabetes mellitus (DM).

No clinically meaningful changes in glucose parameters were observed in trials CT-302 and CT-301EXT.

IGF-1

There is a concern with all hGH formulations that chronically elevated IGF-1 levels above the normal range may be associated with various AEs characteristic of acromegaly, including headache, intracranial hypertension, edema, and tumors. However, the levels of IGF-1 that are clearly associated with adverse reactions are not established to date. The Applicant proposed to monitor IGF-1 levels in the clinical studies not to exceed +2 SDS - +3 SDS.

In Study CT-301, approximately 35% of subjects treated with lonapegsomatropin-tcgd had at least one IGF-1 value > +2SDS but < +3SDS compared to 2% of subjects treated with Genotropin. The difference in the proportion of patients with elevated IGF-1 levels between groups may be due to uneven randomization and measurements of IGF-1 levels at different time points in lonapegsomatropin-tcgd group (IGF-1 levels were measured as trough levels at week 52 and as peak levels at Weeks 13, 26, and 39) and Genotropin group (at any time during the pre-specified weeks). Importantly, the elevation in IGF-1 levels were transient and the majority of subjects had a single elevation in IGF-1 levels that normalized at the next visit with or without a dose adjustment. There was no imbalance in the proportion of patients who had had elevated IGF-1 SDS at 2 consecutive visits (2 subjects in lonapegsomatropin-tcgd group and 1 subject in Genotropin group), the levels normalized in all 3 subjects. No adverse reactions were reported at the time of the recorded IGF-1 elevations.

Approximately 23% of subjects in study CT-302 and 15.5% in study 301-EXT had elevated IGF-1 > +2SDS from baseline at the last assessment. It should be noted that both studies used IGF-1 based titration schedule with goal to normalize IGF-1 levels, thus it is not unexpected to see higher proportion of subjects with elevated IGF-1 levels. All subjects were asymptomatic, and IGF-1 levels decreased at the next visit. As discussed in *Clinical/Statistical- Efficacy* Section above, the assessment of treatment efficacy are not be based on IGF-1 levels, but rather on growth parameters. Since the levels of IGF-1 that are associated with adverse events are also not well understood today, IGF-1 are not routinely monitored, but rather obtained when the potential IGF-1-associated adverse events occurr.

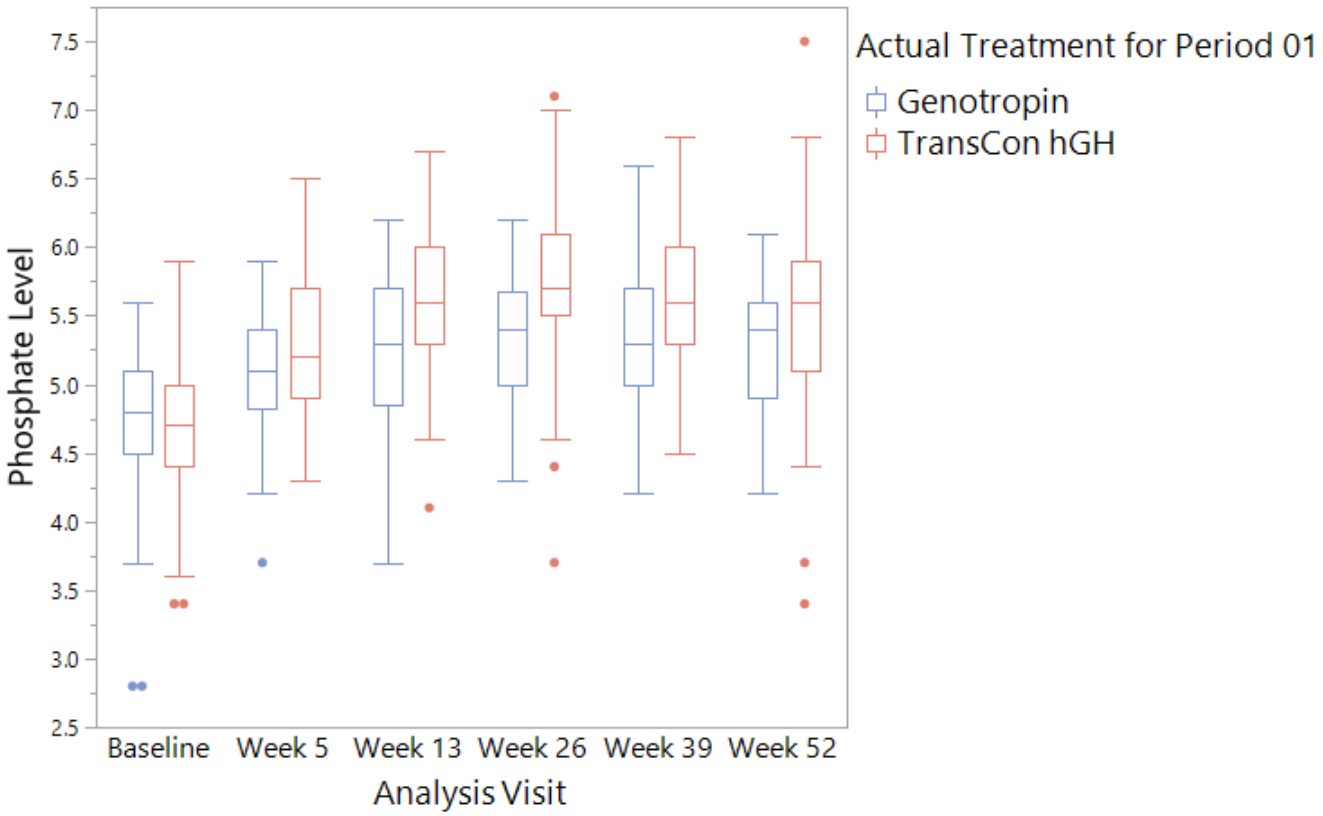
Elevated serum phosphate levels

Mean serum phosphate level at the end of 52-week treatment increased in subjects treated with lonapegsomatropin-tcgd or Genotropin compared to baseline levels but remained within normal pediatric

range (Figure 1). This is an expected action of growth hormone on renal tubular reabsorption of phosphate and the risk of elevated serum phosphorus levels is included in Warnings and Precautions section of all hGH labels.

The number of subjects with at least one elevated phosphate value above upper reference range during Study CT-301 was higher in lonapegsomatropin-tcgd group (86%), compared to Genotropin (60%). All elevations were intermittent, and levels returned to baseline levels in all subjects without treatment or dose adjustment. All subjects were asymptomatic, and calcium levels were normal. No phosphate-related AEs were reported.

Figure 6. Mean phosphate (mmol/L) by visit



Source, Clinical Review, Fig. 14

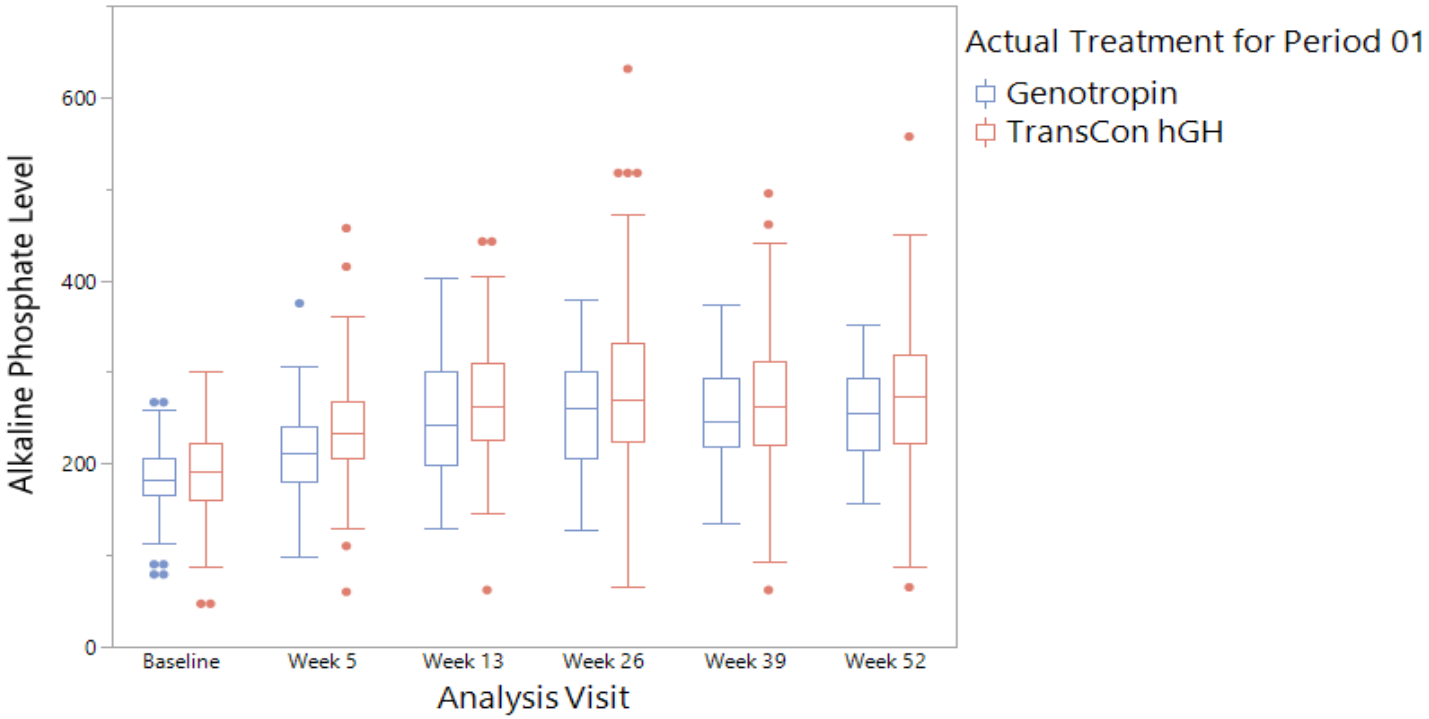
A similar trend in phosphate levels was noted in studies CT-302 and CT-301EXT.

Elevated alkaline phosphatase levels

Growth hormone promotes bone growth, and elevation in alkaline phosphatase (AlkPhos; primarily in bone alkaline phosphatase isomer) is expected with hGH treatment. Thus, the risk of elevated AlkPhos levels is included in Warnings and Precautions section of all hGH labels.

Mean AlkPhos levels at the end of the 52-week treatment period increased in subjects treated with either lonapegsomatropin-tcgd or Genotropin compared to baseline levels but remained within the normal range for children (**Error! Reference source not found.**). All elevations in AlkPhos levels were intermittent and all subjects were asymptomatic.

Figure 7. Mean AlkPhos levels (U/L) by visit



Source: Clinical Review, figure 15.

The results from studies CT-302 and CT-301EXT were consistent with findings from the pivotal study.

Other laboratory parameters
Analyses of other laboratory values do not identify any new safety signals.

Vital signs

There were no significant changes in vital signs between the treatment groups.

Immunogenicity

The immunogenicity data were reviewed by Dr. Zhong Zhao from the Division of Biotechnology Research and Review II, Office of Biotechnology Products (OBP) (refer to review from 4/6/2021). The OBP reviewer concludes that the immunogenicity assay is properly validated and suitable for the evaluation of the presence of anti-drug antibodies. The immunogenicity data were also reviewed by Clinical Pharmacology reviewers and by the Clinical reviewer. During the pivotal trial, 6.7% of subjects treated with lonapegsomatropin and 3.6% of subjects with Genotropin developed anti-hGH antibodies; 1.9% (2 subjects) of subjects developed anti-mPEG antibodies. The titers of antibodies were low in all subjects and all antibodies were transient (defined as < 16 weeks between the first and last positive antibody results). No increase in antibody rates were observed with longer duration treatment: of 305 pediatric subjects in included in 120-Day Safety

update (as of 6/ 1/ 2020), 6.9% of subjects had positive binding antibodies. No anti-hGH neutralizing antibodies were reported in the trials. The frequency of allergic reaction was similar in lonapegsomatropin-tcgd group compared to Genotropin group, all reactions were mild, not related to the study drug and resolved without treatment interruption. No severe hypersensitivity reactions were reported in lonapegsomatropin-tcgd clinical program. Overall, the reviewers concluded that there was no impact of antibodies on efficacy, safety, IGF-1, or PK parameters.

Conclusions Regarding Safety

The safety observations made during the lonapegsomatropin-tcgd clinical program in subjects with PGHD are consistent with the known hGH class specific side effects (e.g., headache, arthralgia, AI, lipoatrophy, injection site reactions). Lonapegsomatropin-tcgd was not associated with increased tumorogenesis and no severe hypersensitivity reactions was reported in the trial. Small and intermittent elevations in phosphate and AlkPhos levels were observed more frequently in lonapegsomatropin-tcgd -treated subjects compared to Genotropin-treated subjects during the trials, most likely due to the prolonged action of lonapegsomatropin-tcgd. The abnormal laboratory parameters resolved without dose adjustment or treatment. All subjects were asymptomatic. Lastly, potential risk of mPEG accumulation in choroid plexus identified in nonclinical studies is considered to be low in humans at the proposed doses based on nonclinical data (large exposure margins and the lack of evidence of neurotoxicity), clinical pharmacology analysis (low predicted mPEG levels at the proposed doses) and absence of mPEG-safety signals in clinical program. (b) (4)

Overall, no new safety issues were identified in subjects with PGHD treated with lonapegsomatropin-tcgd. All safety issues will be mitigated through labeling.

Lastly, findings from studies CT-302 and CT-301EXT were supportive of safety findings obtained from pivotal study CT-301 and no new safety signals were identified in these studies. (b) (4)

8. Advisory Committee Meeting

No AC meeting was held, as this was not the first drug in class, the application did not raise significant public health questions on the role of the biologic, and there were no controversial issues that would benefit from advisory committee discussion.

9. Pediatrics

The intended indication is (b) (4). In addition, lonapegsomatropin-tcgd has received orphan-drug designation in April 2020. Therefore, the requirements of the Pediatric research Equity Act are not applicable.

10. Other Relevant Regulatory Issues

Office of Scientific Investigation (OSI)

A clinical inspection summary was completed by Dr. Cynthia F. Kleppinger on 5/4/2021.

The inspection for this BLA consisted of one domestic site (Site 731) and the sponsor. At time of the BLA submission, OSI planned to conduct an inspection of three sites, the applicant and the contract research organization. However, due to COVID-19 pandemic and abiding by guidelines to protect the health, safety, and welfare of FDA employees and study staff, and with repeated evaluations of the current situation and mission-critical priorities, the planned inspections of Site 741, Site 748 and AmeRuss Clinical Trials, LLC were not able to be conducted. The decision was made to investigate only one domestic site and the Applicant. Based on these inspections, Dr. Kleppinger concluded that the inspectional findings support validity of data as reported by the Applicant under this BLA.

Financial Disclosure and compliance with Good Clinical Practice standards
Financial disclosure documentation was reviewed by Dr. Vachhani. She did not identify any issues that could influence the outcome of the trials. She also confirms that all studies were conducted in accordance with the principles of Good Clinical Practice governing clinical study conduct.

Proprietary name
The proposed proprietary name, SKYTROFA, was found to be acceptable by the Office of Medication Error Prevention and Risk Management. A letter stating this was issued to the Applicant on 12/11/2020.

Nonproprietary name
The proposed nonproprietary name that includes four-letter suffix -tcgd, i.e., lonapegsomatropin-tcgd, was found to be acceptable by the Office of Medication Error Prevention and Risk Management on 1/15/2021.

Division of Pediatric and Maternal Health (DPMH) Consult
DGE had consulted DPMH to provide an input on the proper format and content of the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections of lonapegsomatropin-tcgd labeling to follow the Pregnancy and Lactation Labeling Rule (PLLR). DPMH revised relevant sections of labeling for compliance with the PLLR and recommended to describe the lack of available human data with lonapegsomatropin-tcgd and lack of adverse developmental effects in animals. The reviewers also recommend including the clinical hGH product class information in section 8.1 and 8.2. Lastly, DPMH also concluded that published data with short acting hGH over several decades of use in pregnant and lactating women were useful in evaluating safety of lonapegsomatropin-tcgd in these specific populations. Therefore, DPMH agreed that postmarketing pregnancy safety and lactation studies are not required at this time for lonapegsomatropin-tcgd. Refer to the DPMH review from 4/1/2021 in DARRTS.

11. Labeling

Prescribing Information

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

- INDICATIONS AND USAGE:
  - The Applicant's proposed indication, i.e., [redacted] (b) (4) is appropriate.
  - I recommend approving lonapegsomatropin-tcgd only for the treatment of pediatric patients > 1 years old. The Applicant did not evaluate the use of lonapegsomatropin-tcgd in pediatric subjects with short stature due to GHD < 1 year old. In addition, the indication should be

also restricted to children with body weight > 11.5 kg based on the currently on the currently available lowest dosage strength of cartridge (3 mg) and on the weight-based dosing recommendations.

- DOSAGE AND ADMINISTRATION:
  - The recommended dose is 0.24 mg/kg/week in all patients regardless of the severity of the disease and previous treatments with hGH. The efficacy and safety of this dose is provided from well-controlled trial in subjects with PGHD.
  - Dose should be individualized and titrated based on the response.
  - If the dose is missed, the missing dose should be administered as soon as possible and not more than 2 days after the missed dose. If more than 2 days have passed, the dose should be skipped, and the next dose should be administered on the regular dosing day.
- Safety information in the BOXED WARNING, CONTRAINDICATIONS, or WARNINGS AND PRECAUTIONS:
  - Consistent with class rhGH contraindications, lonapegsomatropin-tcgd is contraindicated in patients with acute critical illness, active malignancies and with hypersensitivity to the drug.
  - WARNINGS AND PRECAUTIONS section appropriately describes class specific adverse reactions associated with rhGH use including increased risk of mortality in patients with acute critical illness, increased risk of malignancy progression, impaired glucose tolerance, intracranial hypertension, hypersensitivity, fluid retention, slipped capital femoral epiphysis, progression of scoliosis, hypoadrenalism and hypothyroidism, pancreatitis and lipoatrophy.
  - WARNING AND PRECAUTION section also appropriately describes the risk of laboratory abnormalities associated with all rhGH formulations, including increase in alkaline phosphatase and parathyroid hormone.
- ADVERSE REACTIONS:
  - I recommend reporting ARs in this section based on the results of the FDA analysis using FMQ, since the use of grouped terms (FMQ) captures synonymous adverse event terms and improves the overall safety information in the label.
  - I recommend (b) (4)
- CLINICAL STUDIES:
  - I recommend including the efficacy results from the adequate and well controlled Study CT-301 only in this section. (b) (4)
  - I agree with clinical and statistical recommendations to describe the observed changes in height SDS to make health care providers aware of the changes that are expected.
  - (b) (4)

12. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS)

A Risk Evaluation and Management Strategy (REMS) is not needed for lonapegsomatropin-tcgd for the proposed indication. All risks are appropriately labeled in the label to inform patients and prescribers and mitigate risks associated with use of this drug (refer to the Division of Risk Management review in DARRTS from 7/22/2021).

Postmarketing Requirements (PMRs) and Commitments (PMCs)

No safety findings prompt the need for Postmarketing Requirements.

Postmarketing Commitments:

- A post-approval submission of shipping validation report of the bulk drug product in dual-chamber cartridges shipped from (b) (4) performed during winter and summer conditions is required. before December 31, 2023. The report should be submitted before December 31, 2023.
- To provide testing that shows the device alarms to be complaint to IEC 60601-1-8:2006 and A1:2012 is required. Refer to the detailed information on PMC requirements in CDRH review from 6/22/2021.
- To provide testing of the device that shows the Applicant's implemented CAPA changes are effective to prevent the (b) (4) assembly problem. Refer to the detailed information on PMC requirements in CDRH review from 6/22/2021.

13. Recommended Comments to the Applicant

The above listed clinical PMCs should be added to the Action Letter.

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/

MARINA ZEMSKOVA
08/02/2021 12:53:40 PM

NAOMI N LOWY
08/02/2021 12:54:46 PM

LISA B YANOFF
08/02/2021 01:20:42 PM