CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761177Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

BLA Number	761177
Link to EDR	\\CDSESUB1\evsprod\BLA761177\761177.enx
Submission Date	June 25, 2020; December 23, 2020
Submission Type	351(a)
Brand Name	Skytrofa
Generic Name	Lonapegsomatropin
Dosage Form and Strength	Injectable solution; 3.0, 3.6, 4.3, 5.2, 6.3, 7.6, 9.1, 11.0 or 13.3 mg powder in glass cartridge and diluent for auto-injector
Route of Administration	Subcutaneous, 0.24 mg human growth hormone/kg body weight, given once-weekly
Proposed Indication	(b) (4)
Applicant	Ascendis Pharma, Inc.
Associated IND	126053
OCP Review Team	Sang Chung, PhD, Justin Earp, PhD, Jayabharathi Vaidyanathan, PhD
OCP Final Signatory	Doanh Tran, PhD

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1. EXECUTIVE SUMMARY

Ascendis Pharma, Inc. (applicant) submitted the original Biologics License Application (BLA) under the 351(a) regulatory pathway (b) (4) Lonapegsomatropin is a long-acting prodrug of human GH (hGH), where hGH is conjugated with four methoxypolyethylene glycol (mPEG) moieties, each with approximately 10 kDa molecular weight as a carrier via a TransCon linker.

The drug product is supplied as a powder with diluent in a dual chamber cartridge (DCC) with an auto-injector for subcutaneous (SC) use.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Cardiometabolic and Endocrine Pharmacology (OCP/DCEP) has reviewed the clinical pharmacology data submitted under BLA 761177 and recommends approval. Key review issues with specific recommendations and comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness for the proposed weekly weight-based dosing regimen were obtained from the pivotal Study CT-301 in treatment-naïve pediatric patients, where the primary efficacy endpoint (i.e., annualized height velocity, AHV) was significantly greater following lonapegsomatropin compared to that of daily injection of Genotropin, active treatment. The estimated mean difference in AHV between treatments was 0.83 cm/year with 95% Confidence interval of [0.22, 1.50] (p=0.0088).
General dosing instructions	The proposed dosing of lonapegsomatropin is 0.24 mg hGH/kg body weight once weekly. This should be administered subcutaneously into the abdomen, buttock, or thigh with regular rotation of the injection sites.
Dosing in patient subgroups	There is no specific dosing for any patient subgroups.
Bridge between the "to-be-marketed" and clinical trial formulations	The to-be-marketed (TBM) drug product (i.e., an auto-injector with DCC) was bridged to the clinical product (i.e., prefilled syringe/needle with lyophilized powder in vial) using the pivotal pharmacokinetic (PK) comparability study. The hGH PK administered as lonapegsomatropin using the TBM product was shown to be comparable to that of the clinical product. Further, the safety of TBM product was evaluated in the open-label extension study (Study CT-301EXT).

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Lonapegsomatropin is a pro-drug of hGH, which consists of hGH conjugated with four mPEG moieties (mPEG40) through a TransCon linker. The hGH release from lonapegsomatropin is assumed to follow a first-order non-specific autocleavage kinetics. The slow release characteristics of hGH from lonapegsomatropin may contribute to the observed relatively long hGH terminal half-life ($t_{1/2}$; 20.5 hours, Study CT-102) in plasma following lonapegsomatropin subcutaneous (SC) injection compared to that of a daily injection hGH product [e.g., $t_{1/2}$ of 3.0 hours in adults with growth hormone deficiency (GHD), labeling of Genotropin]. This prolonged in vivo $t_{1/2}$ supports proposed once weekly injection regimen.

The following is a summary of the clinical pharmacokinetics of hGH, lonapegsomatropin, and mPEG following administration of lonapegsomatropin:

Absorption:	• The maximum plasma concentration (C_{max}) was reached 16, 36, and 240 hours post dose for hGH, lonapegsomatropin and mPEG40, respectively, following 0.24 mg hGH/kg SC injection in healthy adult subjects. There was no significant accumulation for hGH or lonapegsomatropin following weekly dosing. However, significant accumulation was observed for mPEG40 at steady-state and is consistent with its long half-life (i.e., 508 hours). • PK of hGH was greater than dose-proportional following single doses of 0.24, 0.3, and 0.42 mg hGH/kg.
Distribution:	• The estimated volume of distribution (V/F) of hGH and lonapegsomatropin is approximately 61.8 and 1.3 L for typical 19 kg pediatric patients with growth hormone deficiency (PGHD) according to the population PK analyses.
Elimination:	• The elimination half-life of hGH, lonapegsomatropin and mPEG40 in healthy adult subjects was 51.9, 25.4, and 508 hours, respectively, following administration of 0.24 hGH/kg SC. • The primary elimination of lonapegsomatropin occurs via auto-hydrolysis to mPEG40-TansCon and hGH • hGH elimination involves known protein catabolism in both liver and kidneys. • It is reported that mPEG is excreted into urine predominantly as intact mPEG and undergoes minor oxidative degradation in phagosomes.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended dosing is 0.24 mg hGH/kg body weight once weekly. The lonapegsomatropin drug product strength is described in weight of hGH (e.g., 0.24 mg hGH) to distinguish from a dose of lonapegsomatropin.

2.2.2 Therapeutic individualization

General dosing is individualized by body weight. No separate dose/dosing regimen is recommended in patient subgroups due to intrinsic (sex, race, body weight, renal impairment) and extrinsic factors. Lonapegsomatropin was not studied in specific populations including patients with organ impairment.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts be included in the final package insert:

Label Section	Recommendation
2 DOSAGE AND ADMINISTRATION	• The recommended dose is 0.24 mg hGH/kg for treatment naïve patients or for patients switching from daily GH (somatropin). The recommended starting dose was evaluated and supported by results of the pivotal Phase 3 study (Study CT-301). Maintenance dose can be reduced if IGF-1 SDS is elevated above +2.0. Dose adjustment data due to elevated IGF-1 SDS were sparse in the pivotal Phase 3 study. Therefore, the clinical relevance of IGF-1 elevation is inconclusive. • The proposed labeling for a missed dose is as follows; o (b) (4) o We recommend the following with sub-heading as 'a missed dose'; o *A dose can be taken ±2 days from the scheduled day if needed* o *If a dose is missed for more than 2 days, skip the scheduled dose and resume the next dose as scheduled.*
7 DRUG INTERACTIONS	• We recommend a tabular format for Section 7 drug-drug interactions.
12.2 Pharmacodynamics	• We recommend deleting (b) (4) in Section 12.2 as it is described in text.
12.3 Pharmacokinetics	• We recommend including clinically relevant covariates for hGH PK in Section 12.3 (e.g., age, sex, race and renal function).

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Lonapegsomatropin is a hGH prodrug, which is designed to slowly release hGH, the active moiety, through hydrolysis from mPEG conjugation and TransCon linker. The released hGH from lonapegsomatropin acts on the GH receptor in tissues and also stimulates the hepatic production of insulin-like growth factor 1 (IGF-1), which is considered as the primary pharmacodynamic (PD) marker for GH.

The applicant initially evaluated potential of a hGH conjugation with four molecules of (b) (4) kDa mPEG (described as (b) (4) kDa, ACP-001) and conducted a Phase 2 dose-ranging study in PGHD (Study CT-004) under IND (b) (4) with this product. However, it was determined that the formulation of ACP-001 was not supporting the TBM device due to its high viscosity and large injection volume. The applicant therefore selected mPEG with 10 kDa as an optimal candidate for lonapegsomatropin (also known as ACP-011) and used this formulation with a syringe/needle in Phase 3 studies under IND 126053 supporting this BLA. To bridge the clinical information obtained from ACP-001, the applicant conducted a Phase 1 study to evaluate PK and PD comparability between the two molecules (ACP-001 and ACP-011) (Study CT-101).

The applicant proposed an auto-injector as the TBM device. The proposed auto-injector was introduced in US sites of the Phase 3 extension study (Study CT-301EXT), and the comparability between clinical (syringe/needle) and TBM device was evaluated in a Phase 1 study (Study CT-102).

There were no significant pending clinical pharmacology issues from the regulatory communications and meetings during the development of lonapegsomatropin.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Growth hormone (GH) is secreted from the anterior pituitary gland through the stimulation by GH releasing hormone from the hypothalamus. Therefore, the known etiology of PGHD is associated with the congenital (e.g, pituitary aplasia or genetic) or acquired (e.g, tumors of the hypothalamic-pituitary region, head trauma or infection) conditions of pituitary gland or hypothalamus. However, the most common diagnosis of PGHD is known to be without clear etiology or idiopathic.

Lonapegsomatropin is a pegylated hGH with four molecules of mPEG and designed to slowly release hGH following SC injection (Figure 1). Molecular weight is an average of 63 kDa for lonapegsomatropin, approximately 22 kDa for hGH and average of approximately 41 kDa for mPEG-TransCon linker. The number of ethylene glycol units in each mPEG-chains is approximately (b) (4).

Figure 1 Structure of lonapegsomatropin
(Source: Module 2.3.S.1 CTD)

The clinical pharmacology information was evaluated in six studies: two studies in healthy adult subjects (CT-101 and CT-102), one study in PGHD patients using exploratory molecule (CT-004), and three Phase 3 studies in PGHD patients (CT-301, CT-301EXT and CT-302).

3.2.1 Mechanism of Action:

Lonapegsomatropin is a hGH pro-drug and slowly releases hGH, the active molecule, and mPEG-linker through hydrolysis after SC injection. The mechanism of action of hGH is the stimulation of GH-receptor in tissues and hepatic production of IGF-1, which mediates GH actions. The major effects of hGH are growth stimulation, body composition change (i.e., decreased body fat mass, increased lean body mass, increased bone mineral density) and stimulation of metabolic actions.

3.2.2 Pharmacokinetics:

3.2.2.1 Absorption

The single dose PK of lonapegsomatropin following SC administration was evaluated in healthy subjects (CT-101) at dose levels of 0.24, 0.30 or 0.42 mg hGH/kg.

The median (minimum, maximum) time to peak serum concentration (T_{max}) was 16.0 (8.00, 48.0), 36.0 (16.0, 4.0) or 240 (36.0, 670) hours post-dose for hGH, lonapegsomatropin or mPEG, respectively, following 0.24 mg hGH/kg (Figure 2, Table 1).

The PK (AUC and C_{max}) of hGH, lonapegsomatropin and mPEG was greater than dose-proportional; AUC_{0-168} increased 2.5-, 5.3-, and 3.3-fold for hGH, lonapegsomatropin and mPEG, respectively, with an 1.8-fold increase in dose (from 0.24 to 0.42 mg hGH/kg) (Figure 2, and Table 1). Results of a power model systematically assessing the PK-dose proportionality (PK parameter = $a*Dose^b$) indicate that PK was greater than proportional to dose as exponents of the model (b) were greater than 1 (proportional) for hGH, lonapegsomatropin and mPEG. Clinical relevance of the PK-dose proportionality may not be significant as there is no proposed dose adjustment with any intrinsic/extrinsic factors.

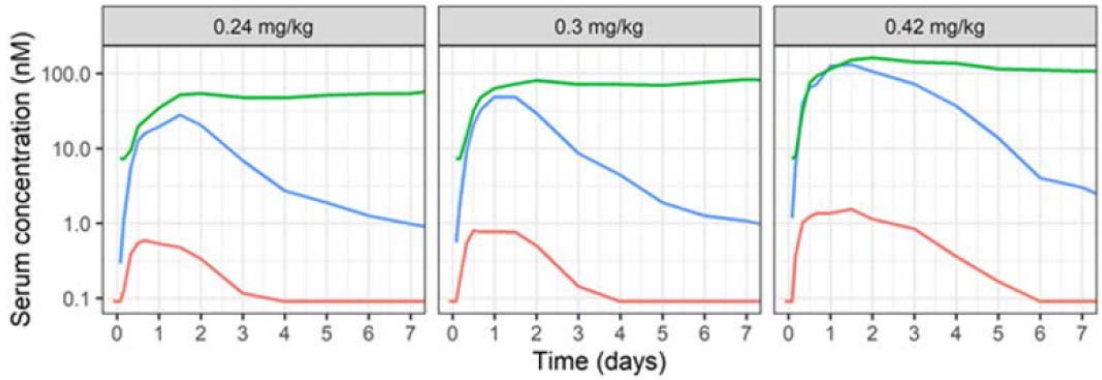


Figure 2 Mean lonapegsomatropin (blue), hGH (red) and mPEG (green) concentration-time profile (on log scale) following single dose administration in healthy subjects (Study CT-101)
(Source: Figure 3, Module 2.7.2 CTD)

Table 1 Descriptive summary of PK parameters (Study CT-101)
(Source; Table 3-5, Module 2.7.2, CTD)

Compound	Parameter (Unit)	0.24 mg hGH/kg (N=27)	0.30 mg hGH/kg (N=9)	0.42 mg hGH/kg (N=9)
hGH	AUC0-168 (h*ng/mL)	617 (49.8)	957 (25.8)	2050 (46.5)
	C_{max} (ng/mL)	13.4 (28.4)	19.4 (20.2)	32.9 (26.9)
	T_{max} (h)	16.0 (8.00, 48.0)	24.0 (12.0, 36.0)	36.0 (12.0, 36.0)
	$t_{½}$ (h)	25.4 (40.1)	21.8 (13.3)	25.0 (26.1)
Lonapegsomatropin	AUC0-168 (h*ng/mL)	30900 (114.7)	60300 (56.7)	164000 (118.0)
	C_{max} (ng/mL)	535 (112.4)	1280 (70.4)	2480 (133.4)
	T_{max} (h)	36.0 (16.0, 48.0)	24.0 (24.0, 36.0)	36.0 (36.0, 48.1)
	$t_{½}$ (h)	51.9 (35.4)	39.5 (29.0)	40.8 (32.1)
mPEG	AUC0-168 (h*ng/mL)	314,000 (50.4)	470,000 (23.2)	770,000 (57.4)
	C_{max} (ng/mL)	3,060 (32.9)	4,010 (15.8)	6,870 (30.6)
	T_{max} (h)	240 (36.0, 670)	168 (48.0, 336)	48.1 (36.0, 504)
	$t_{½}$ (h)	508 (18.0)	594 (16.1)	616 (14.1)

The steady state PK was evaluated in PGHD patients following multiple doses of lonapegsomatropin (Study CT-301) or ACP-001 (Study CT-004). PK assessments were done at Week 1, Week 13, and at later visits (trough concentrations) in both the studies (Study CT-301 and CT-004). It appears that hGH, lonapegsomatropin, and mPEG reached apparent steady-state by 13 weeks after multiple dosing in pediatric patients (Figure 3 from Study CT-004, Figure 18 in

Appendix from Study CT-301). There was no significant accumulation of hGH and lonapegsomatropin, while a significant accumulation of mPEG was observed.

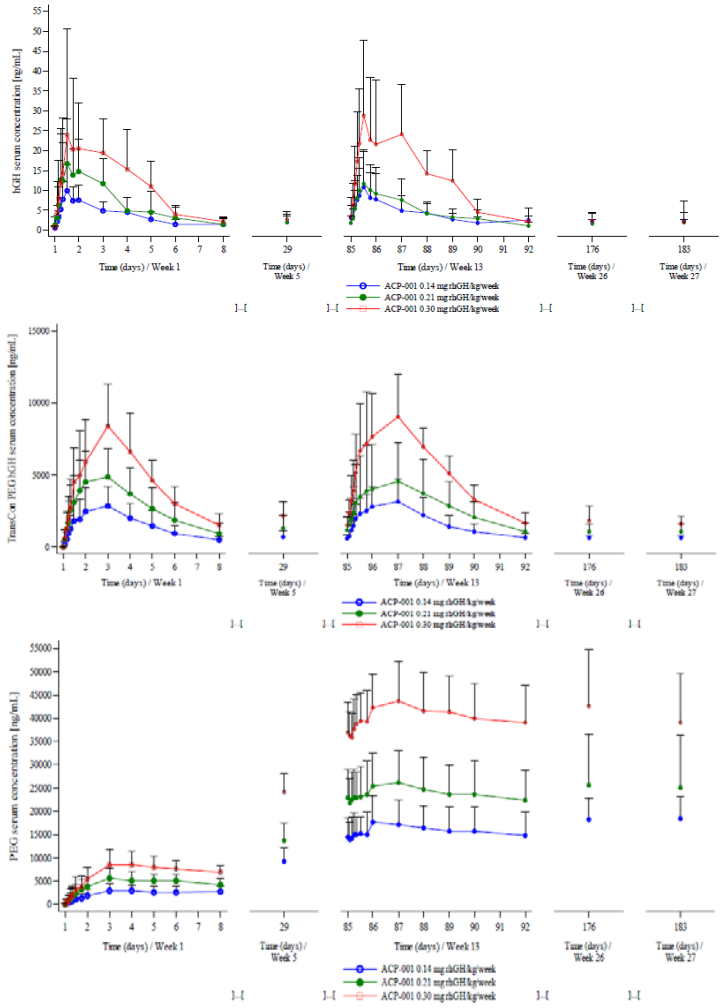


Figure 3 Mean (SD) hGH (upper), lonapegsomatropin (middle), and mPEG (b) (4) (lower) concentration-time profiles at Week 1 and 13 in PGHD patients (Study CT-004)
(Source: Figure 10, 8, 15, CSR, CT-004)

The impact of different injection sites on PK was not formally evaluated. Although injection sites were rotated among 6 sites (i.e., the left and right buttock, left and right thigh, and left and right abdomen) in Phase 3 studies, injection site information was not available as a covariate in the population PK analysis. There was no specific safety signal related to the injection sites in Phase 3 studies. Therefore, applicant's proposal to rotate injection sites is acceptable.

The variability in PK was relatively high as CV of $AUC_{0\text{-}168h}$ was 82.3%, 67.0%, 34.0% for hGH, lonapegsomatropin and mPEG, respectively, in Phase 3 Study CT-301 (Table 2). There was apparent cross-reactivity in bioanalytical method measuring hGH from lonapegsomatropin. In general, the impact of cross reactivity in hGH PK assessment was not significant (Table 2, See further details of cross-reactivity in bioanalytical method in Appendix 4.1).

Due to the presence of endogenous hGH and IGF-1, its contribution was adjusted using the baseline as an average of pre-dose concentrations. In general, the contribution of endogenous level was low in the study with healthy adults [Study CT-102, mean (SD) and median hGH baseline were 0.18 (0.54) and 0 ng/mL, respectively] and in the PGHD population [Study CT-301 (n=19 with baseline reported), mean (SD) and median hGH baseline concentration =1.18 (1.35) and 0.66 ng/mL, respectively, or mean (SD) peak stimulated hGH =5.75 ng/mL (n=161)] .

Table 2 Descriptive summary of PK parameters at steady-state in PGHD (PK/PD subset, Study CT-301)
(source; Table 7, Module 2.7.2, CTD)

Parameter (Unit)	hGH (N=11)	hGH Corrected for Cross Reactivity (N=11)	Lonapegsomatropin (N=11)	mPEG (N=11)
AUC (h*ng/mL)[a]	678 (82.3)[b]	500 (83.8) [b]	74,000 (67.0)	1,740,000 (34.0)[c]
C_{max} (ng/mL) [a]	18.5 (81.5)	15.2 (83.4)	1,230 (86.3)	13,100 (28.1)
T_{max} (h)[d]	12 (8, 47.8)	12 (8, 47.8)	25.0 (8, 48.2)	36.0 (8, 96.0)
$t_{½}$ (h)	20.6 (33.7)[N=6]	16.2 (34.0)[N=4]	28.7 (38.5)[N=11]	435 (51.5)[N=9]

3.2.2.2 Distribution

There was no formal study for the distribution of lonapegsomatropin or mPEG. The estimated mean volume of distribution (Vd/F) for hGH, lonapegsomatropin, and mPEG in PGHD weighing approximately 20 kg was 61.8, 1.3, 3.5 L, respectively. The mean Vd/F of hGH following lonapegsomatropin seems to be significantly higher than that of estimated Vd/F from daily hGH (2.6 L or 1.3 L/kg, Genotropin labeling). The difference in bioavailability (F) values may result in the difference in Vd/F of hGH following ACP-011 compared to that of Genotropin. Further, the Vd/F of hGH following administration of lonapegsomatropin is confounded as its systemic availability is a hybrid of hGH release from lonapegsomatropin and subsequent absorption of hGH.

There is a concern of mPEG accumulation in tissues particularly in choroid plexus and its potential impact on the brain or central nervous system considering its long half-life and chronic dosing in children. It is known that certain PEGs may cause vacuolation leading to cell death in animal studies. The applicant addressed those concerns using 1) the relationship between estimated exposure in serum and choroid plexus from modeling and simulation and 2) extrapolating information using animal scale up related to 'No Observed Vacuolation' from non-clinical models, which utilizes similar approach of non-clinical risk assessment as that done with 'No-Observed-Adverse-Effect-Level' (Figure 4). The predicted mPEG levels in pediatric subjects was within the range of concentrations where there was no observed vacuolation in animal studies (Figure 4). See further details in Appendix 4.3.1. Overall, there was no adverse events related to the vacuolation in the clinically relevant lonapegsomatropin dosing groups in non-clinical studies. Further, there was no specific clinical safety signal in the Phase 3 program. No CNS or immune system associated safety events were detected in the Phase 3 program. Therefore, clinical concerns at the mPEG accumulation in choroid plexus and its adverse events appears to be minimal at the proposed dosing.

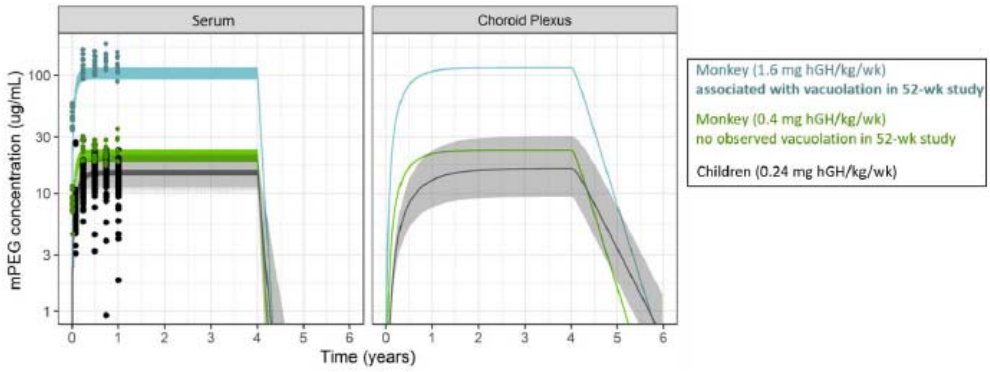


Figure 4 Predicted mPEG (lines) and individual observed mPEG (symbols) in serum (left) and choroid plexus (right) of children (BW = 22 kg, black) and cynomolgus monkey (BW = 3 kg, green and cyan) following 3 doses

[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; Figure 2, MODHGH001)

3.2.2.3 Metabolism and elimination

There was no formal in vivo study (e.g., mass balance or ADME study) for lonapegsomatropin.

Lonapegsomatropin is known to go through auto-hydrolysis and a few products were identified during auto-hydrolysis: lonapegsomatropin, hGH, mPEG linker [redacted] (b) (4), and a leaving group [redacted] (b) (4).

The hGH, when released from lonapegsomatropin, is considered to follow known catabolism of endogenous GH mainly in both the liver and kidney.

It is reported that the elimination of mPEG [redacted] (b) (4) is primarily via excretion in the urine as intact mPEG (Figure 5) and metabolism represents a minor route (Webster et al., Drug Metab Dispo, 35:9-16, 2007).

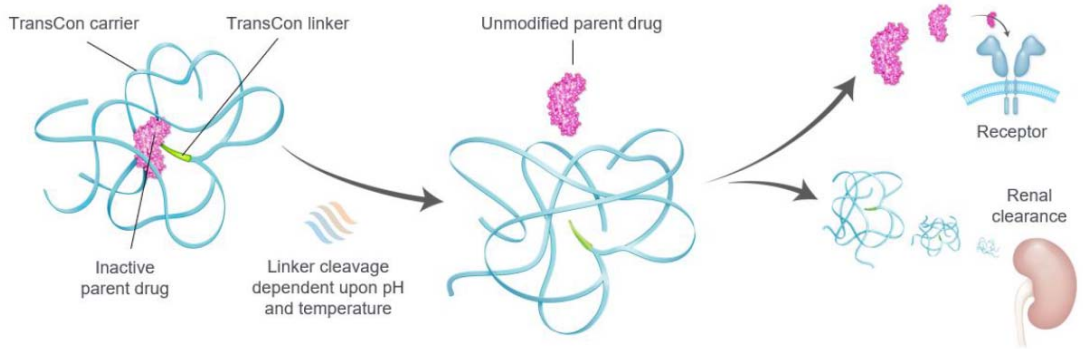


Figure 5 Schematic summary of release products of lonapegsomatropin and mPEG elimination.

(Source: Figure 2, Module 2.2, CTD)

The terminal half-life was 25.4, 51.9, and 508 hours for hGH, lonapegsomatropin and mPEG, respectively, following 0.24 hGH/kg in adults (Table 1). The mean clearance of hGH was

estimated as 125 L/day for PGHD with 19 kg body weight and it was similar to that of daily hGH in AGHD (0.3 L/hr/kg = 136.8 L/day in patient with 19 kg body weight, Genotropin labeling).

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes, the data presented in this BLA provides supportive evidence of effectiveness for SC lonapegsomatropin as (b) (4) . Refer to Section 3.3.2 for additional details.

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dosing regimen is appropriate for the PGHD from the clinical pharmacology perspective.

Although number of subjects was relatively small (N=12-14 per cohort), the results indicate that the efficacy was numerically increased with increasing dose in the exploratory dose-ranging study with a predecessor molecule (ACP-001) (Study CT-004, Table 3). Further, the efficacy of all doses of ACP-001 was numerically higher than that of active treatment, Genotropin 0.03 mg/kg daily injection (equivalent to 0.21 mg/kg/week) (Table 3). While exposure of hGH was comparable, IGF-1 was higher following 0.21 mg hGH/kg/week ACP-001 injection compared to those of active treatment (Figure 6). IGF-1 AUC was similar between 0.21 to 0.30 mg hGH/kg/week, and it indicates that IGF-1 response reached an apparent plateau from 0.21 mg hGH/kg/week.

Table 3 Least-Square Means (and 95% Confidence Intervals) for AHV [cm/year] at 6 Month

Statistics	Cohort 1 (N=12)	Cohort 2 (N=14)	Cohort 3 (N=14)	Cohort 4 (N=13)
LS Mean (AHV [cm/year])	12.56	13.29	13.91	12.27
95% CI	10.56 to 14.56	11.45 to 15.13	12.09 to 15.74	10.32 to 14.22

(Source; Table 23, CSR, 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)

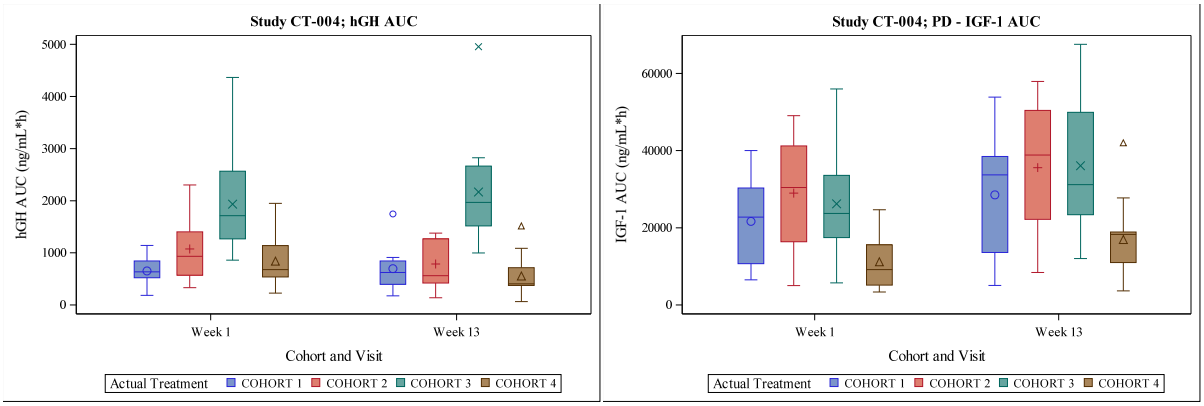


Figure 6 Box plot of AUC (hGH; left, IGF-1; right) by cohort and visit; $AUC_{0\text{-}168h}$ for cohort 1-3, $AUC_{0\text{-}24h}$ x 7 for cohort 4 (Study CT-004)
[Cohort 1; 0.14 mg hGH/kg/week, Cohort 2; 0.21 mg hGH/kg/week, Cohort 3; 0.30 mg hGH/kg/week Cohort 4; 0.03 mg hGH/kg/day (Genotropin once daily)]
(Source: Reviewer's analysis)

In the Phase 3 studies, the applicant selected 0.24 mg hGH/kg/week for both lonapegsomatropin and Genotropin. The dose selection for the Phase 3 studies seems reasonable based on results from the Study CT-004. In addition, the weekly lonapegsomatropin dosing is consistent with the weekly dose of active treatment, which is 0.16 to 0.24 mg/kg/week for the PGHD and the weekly dose should be divided into 6 (in case of 6 days administration for a week) or 7 (in case of 7 days administration for a week) injections as per the Genotropin labeling. Subjects were randomized 2:1 ratio to lonapegsomatropin and Genotropin (N=161 hGH-treatment naïve subjects in the ITT population).

Although according to the protocol, dose adjustment was allowed related to the elevated IGF-1 SDS, actual dose adjustment was extremely rare (see outlier observations for the dose adjustments from the pivotal Phase 3 study, Figure 19) (Figure 7). Therefore, there was no adequate data to support covariates for the different starting dose or dose adjustment during the treatment period in the pivotal Phase 3 study. There was a deviation (-11% to +9%) in the dosing from the designated 0.24 mg hGH/kg/week (Figure 7) mainly due to the body weight bracketing due to limited cartridge strengths (see Table 14 in Appendix). For example, dose is ranged 0.261-0.216 mg hGH/kg/week using 3 mg hGH cartridge for body weight bracket 11.5-13.9. However, this does not appear to be clinically meaningful.

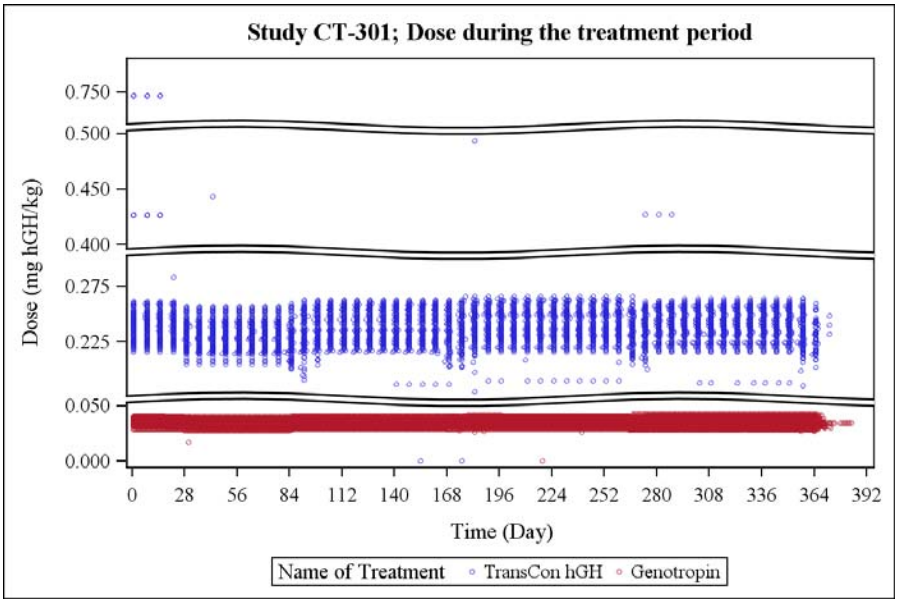


Figure 7 Individual dose during the treatment period (Study CT-301)
(note; TransCon hGH is for lonapegsomatropin)
(Source: Reviewer's analysis)

The primary efficacy endpoint was AHV at 52 weeks following weekly lonapegsomatropin and daily Genotropin treatments. The estimated treatment difference in AHV was statistically significant, for lonapegsomatropin over Genotropin (Table 4). Overall, it was concluded that once-weekly dose of lonapegsomatropin administered up to 52 weeks was well tolerated and no clinically significant safety issues were identified. Refer to the Clinical Review by Dr. Shivangi Vachhani and Statistics Review by Dr. Alex Cambon for additional details on efficacy and safety assessment of lonapegsomatropin in Phase 3 studies.

Table 4 Primary efficacy endpoints – AHV (cm/year) at Week 52 (Study CT-301)

Summary Statistic	Lonapegsomatropin (N=105)	Genotropin (N=56)	Estimate of Difference Lonapegsomatropin - Genotropin	P-value
Least square mean (SE) [95% CI]	11.17 (0.23) [10.71, 11.62]	10.31 (0.30) [9.73, 10.89]	0.86 (0.33) [0.22, 1.50]	0.0088

(Source, Table 19, CSR, CT-301)

In Phase 3 study, once-weekly lonapegsomatropin showed numerically higher average IGF-1 SDS levels at steady state compared to those of Genotropin (Figure 8).

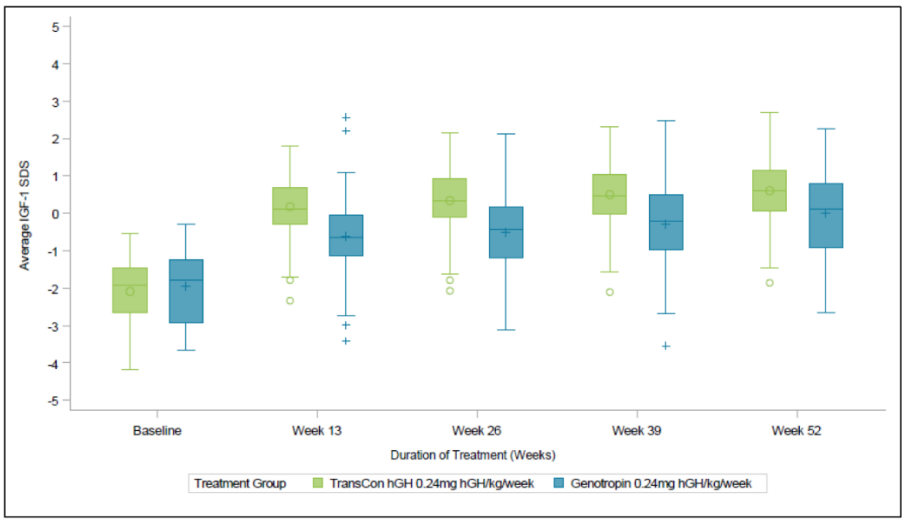


Figure 8 Box plot of average IGF-1 SDS over 52 weeks by treatment group (Study CT-301).
(Source: Figure 8, CSR, CT-301)

Missed dose:

To evaluate the impact of a missed or delayed dose of lonapegsomatropin, simulations of hGH and IGF-1 were performed for different scenarios - effect of shortened (7-5-9-7 days schedule) or extended dosing intervals (7-9-5-7 days schedule) compared to regular intervals (7-7-7-7 days schedule) starting at Week 13. There was no significant difference in simulated average IGF-1 SDS among scenarios tested (Figure 9). In addition, there was no significant change in simulated hGH levels as its accumulation was known to be minimal at steady-state.

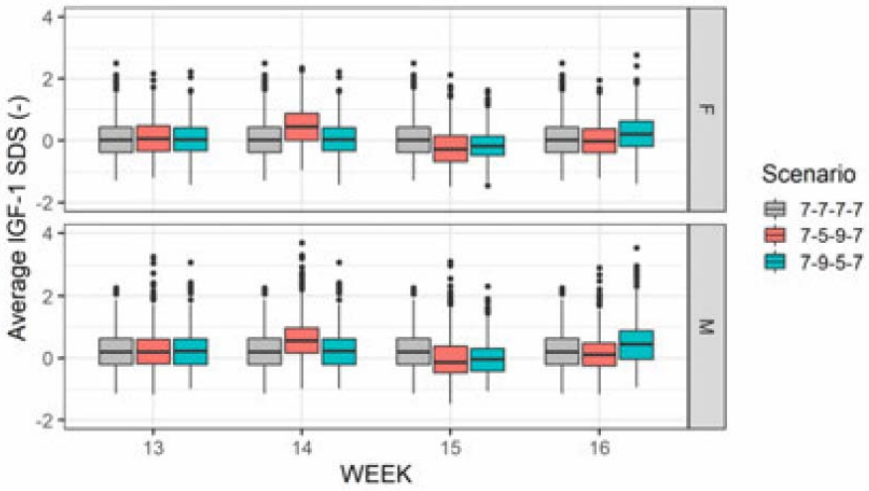


Figure 9 Predicted IGF-1 SDS among scenarios
(Source: Figure 97, MODHGH002)

The applicant proposed the dosing instruction based on the simulations as follows;

- (b) (4)

- (b) (4)

We recommend labeling as follows;

- a dose can be taken within ±2 days of the scheduled day
  - this is to ensure that there is a dosing interval of no less than 5 days between 2 consecutive doses
- if more than 3 days have passed, the dose should be skipped, and the next dose should be administered on the regular dosing day

Effect on QT/QTc interval:

The applicant did not conduct a dedicated QT/QTc trial. The potential effect of lonapegsomatropin on cardiac repolarization was assessed based on ECGs collected in the Phase 3 Study CT-301. The ECGs were collected at baseline and Week 26 from all subjects, and there was extensive ECG sampling matching to PK sampling including at the expected Tmax in a sub-set (n=11).

There was no meaningful signal from the qualitative data summary as follows;

- change in QTcF from baseline at Week 26 was 8.9 ms in the lonapegsomatropin group and 5.3 ms in the Genotropin group
- at the median hGH Tmax (12 h postdose) of the PK/PD subset, the mean QTcF change from Week 13 pre-dose was 2.9 ms

There was no apparent positive relationship observed between change in QTcF from pre-dose at Week 13 and hGH plasma concentrations (Figure 10).

According to non-clinical study results, there was no significant inhibition of the hERG channel from the intact PEGylated hGH, as well as the products of the hydrolysis, hGH and mPEG linker (b) (4)

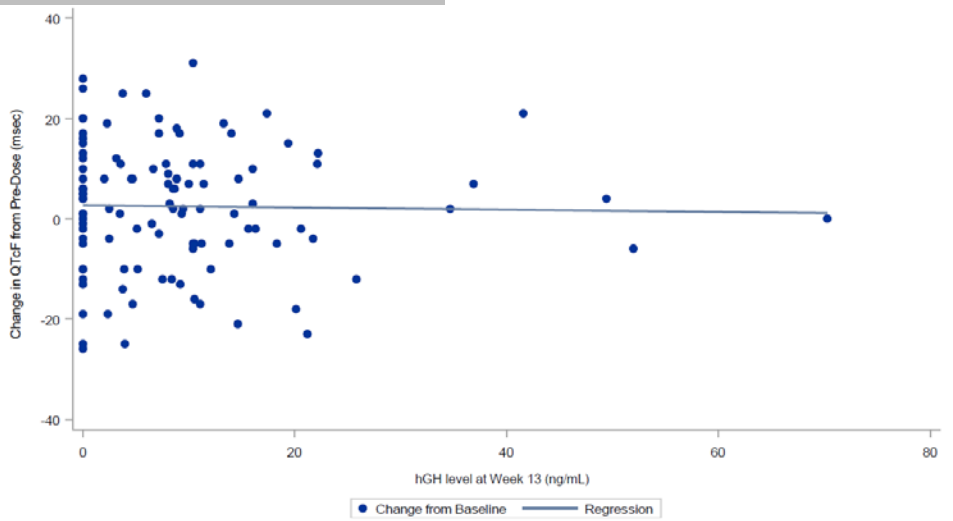


Figure 10 Relationship between change in QTcF from pre-dose and hGH concentration at Week 13 in a sub-set (n=11)
(source, Figure 15, CSR, CT-301)

Immunogenicity:

Overall, 11 subjects (10.5%) had detectable but transient antibodies after baseline for any of antibodies - anti-hGH (n=7, 6.7%), anti-mPEG (n=2, 1.9%) and anti-lonapegsomatropin (n=4, 3.8%) in lonapegsomatropin treatment arm compared to anti-hGH (n=2, 3.6%) in Genotropin arm (Source; Table 47, Module 2.7.4, CTD). There were no observed effects of immunogenicity on safety, efficacy, IGF-1 or PK. Refer to the Quality review in DARRTS for additional detail on the immunogenicity assay for lonapegsomatropin, hGH and mPEG.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Results from the clinical pharmacology trials and population PK analysis of data from Phase 3 studies indicate that dose adjustment is not required for patients based on intrinsic factors of sex, body weight, race, ethnicity or renal function. Although hGH exposure and IGF-1 SDS response were relatively lower in female patients, average IGF-1 SDS was not significantly different between males and females in PGHD (Figure 11). The proposed dosing is weight-based. Therefore, no further dose adjustment is needed for the known clinically relevant covariates such as sex and age since they are highly correlated with body weight.

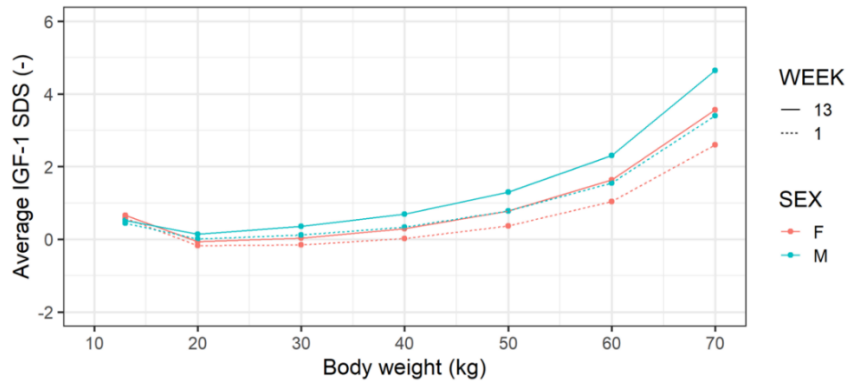


Figure 11 Relationship between average IGF-1 SDS and body weight at Week 1 or 13 by sex

(source, Figure 13, 2.7.2 CTD)

3.3.3.1 Race, Sex, Body weight, Age, and Renal Function

The effects of clinically relevant pre-specified covariates on exposure of lonapegsomatropin, hGH and mPEG and IGF-1 response were assessed using population PK and PK/PD analyses based on data from CT-101 in healthy adults (N=45) and CT-301 in PGHD (N=105).

Of all investigated covariates, body weight and sex were the major covariates (Figure 11, and Figure 12). Mean (SD) age of patients was 8.5 (2.7) years in Study CT-301. The age ranged from 3.3 to 13.1 years and approximately 24% (N=25) patients were less than 6 years of age in the lonapegsomatropin treatment arm. However, there was no apparent relationship between significant covariates (body weight and sex) and exposure in PGHD (Figure 13). Further, there was no clinically significant covariates supporting additional dose adjustment for the primary efficacy endpoint (Figure 14).

Therefore, no dose adjustment is necessary for those covariates in addition to the body weight-based dosing. See Appendix 4.3 for additional details of population analyses.

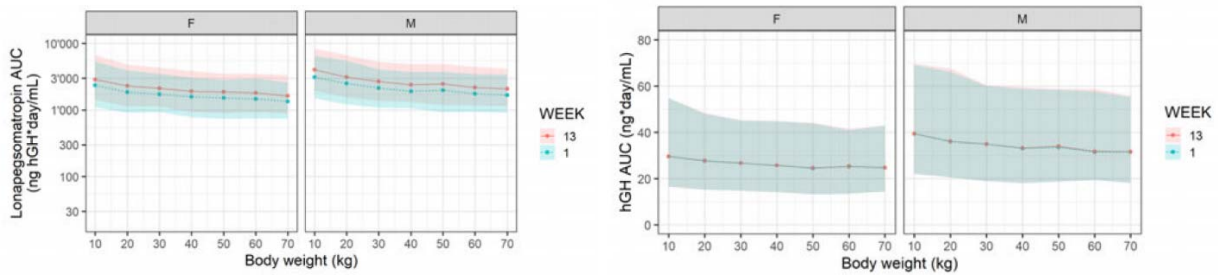


Figure 12 Effect of sex and body weight on AUCtau of lonapegsomatropin (left) or hGH (right); Median, 5th and 95th percentiles from 500 simulated profiles
(source, Figure 54,88, MODHGH002)

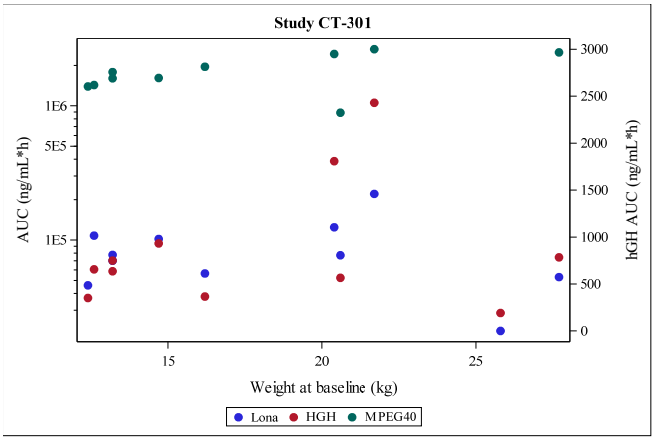


Figure 13 Scatter plot for AUCtau of lonapegsomatropin (Lona), hGH (HGH) and mPEG (MPEG40) versus body weight at baseline in PK/PD subset (N=11) of CT-301

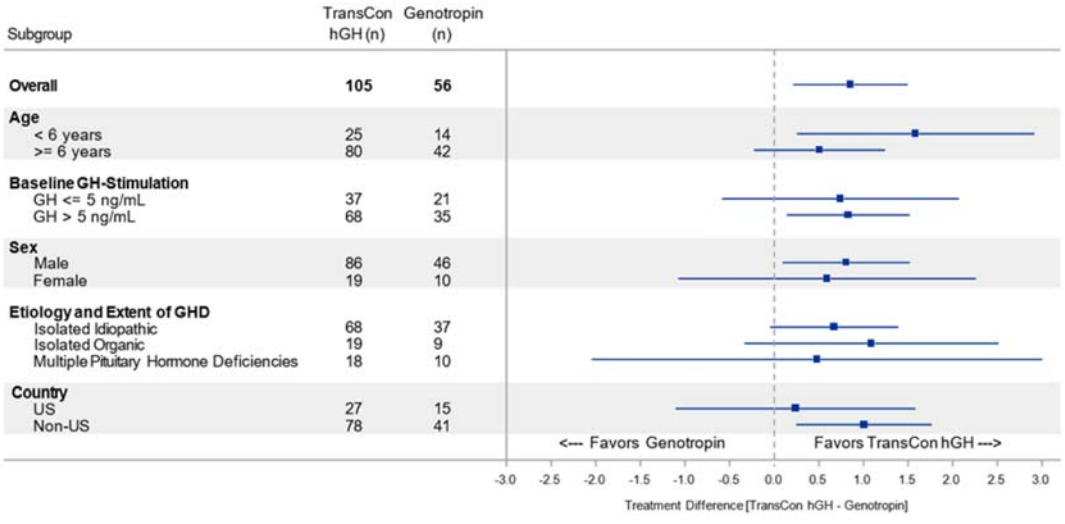


Figure 14 Forest Plot of AHV by subgroups
(Source; Figure 5, 2.5 CTD)

The impact of renal function on hGH, lonapegsomatropin and mPEG was evaluated using the relationship between estimated creatinine clearance (CRCL) and their observed concentrations in PGHD (Study CT-301). There were no apparent relationships between CRCL and hGH or lonapegsomatropin. The primary concern related to the renal function change was potential for increase in mPEG exposure as mPEG is known to primarily be excreted into urine. There was no apparent impact of renal function on mPEG exposure (Figure 15). The sponsor used Cockcroft-Gault (CG) method for CRCL estimation. In addition, they introduced lower conversion factor for female [CRCL=(140-age)*BW/(72*Scr)*0.385 (if female)] compared to that of CG method (i.e., 0.85 for female). Due to CG method with lower female factor, there were unusual numbers of subject classified with the severe renal impairment in the sponsor's analysis. However, it was found that there were no severe and limited moderate renal impairment sub-group following the original conversion factor of CG method or Schwartz methods (i.e., eGFR=k*height/Scr, k=0.419 if male aged >13 years, otherwise 0.373), which is known to provide better estimation of glomerular filtration rate for children compared to other methods. There was no apparent association between mPEG concentrations and CRCL estimated by the Schwartz method (Figure 15).

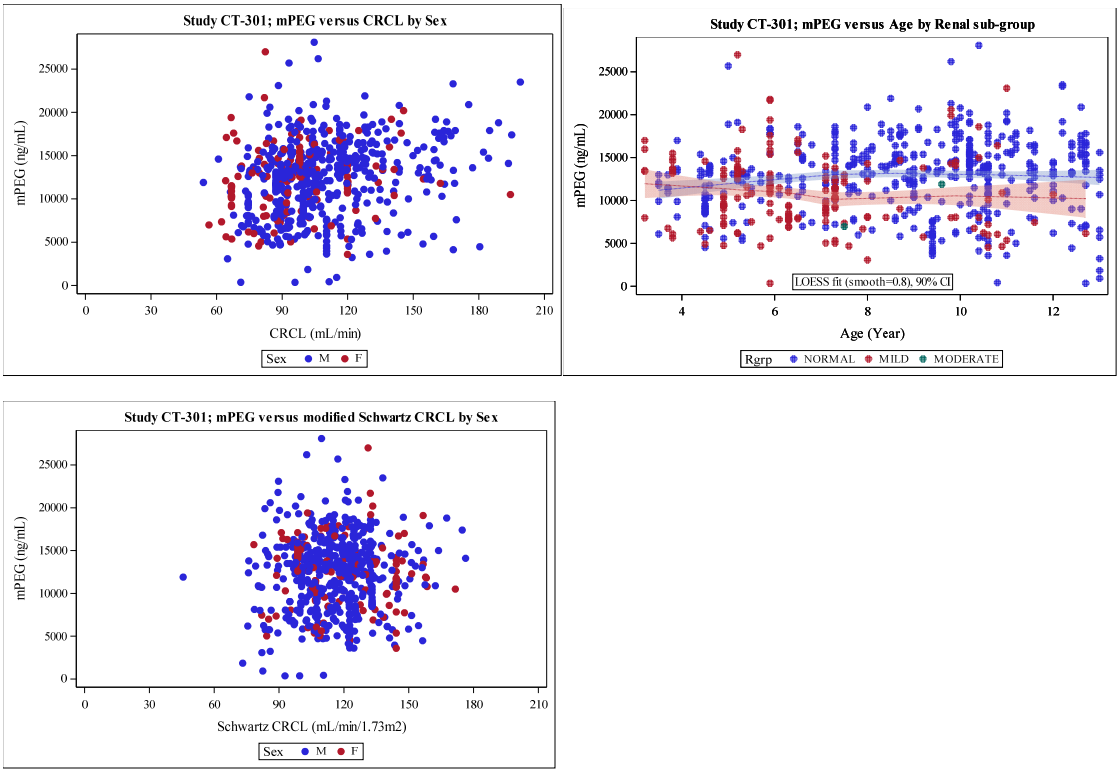


Figure 15 Relationships between 1) mPEG concentration versus CRCL by Cockcroft-Gault method (upper left) or Age by renal function sub-group (upper right) or 2) mPEG (lower) versus CRCL by modified Schwartz method (Study CT-301) (about 5 measures per subject)

3.3.4 Are there clinically relevant drug-drug interactions and what is the appropriate management strategy?

There was no formal study for the evaluation of potential of drug-drug interaction. It is known that mPEG is primarily excreted into urine through the glomerular filtration and metabolism is minor elimination pathway. Therefore, there is no significant metabolic potential for drug-drug interaction with lonapegsomatropin or mPEG.

Lonapegsomatropin releases hGH. hGH can induce changes in CYP450 activity in humans, and concomitant treatment with CYP450 substrates is addressed as per the class labeling of GH products.

3.3.5 Was there PK bridging between to-be-marketed product and clinical trial product?

Yes, the applicant conducted the pivotal PK comparability study (Study CT-102) to bridge the proposed to-be-marketed product (auto-injector and dual chamber cartridge) to the clinical product (pre-filled syringe and needle with lyophilized powder in vial).

The comparability of hGH was assessed in a Phase 1, randomized, open-label trial comparing lonapegsomatropin administered as a single dose of 13.3 mg hGH via syringe and needle versus auto-injector in healthy volunteers (Study CT-102). The primary endpoint was baseline corrected PK parameters (AUC and Cmax) of hGH, and the secondary endpoint was PD parameters (AUC and Cmax of IGF-1).

Results indicate that the comparability of hGH was demonstrated between the TBM and clinical products (Table 5).

Table 5 Statistical Comparisons of Baseline-Corrected Serum hGH PK (upper) and PD (lower) parameters (Study CT-102)
(Source; Table 14, CSR, CT-102)

	Geometric Least-Squares Means[a]		% Geometric Least Squares Mean Ratio (90% CI)		
Pharmacokinetic Parameter	TransCon hGH Syringe and Needle (N = 27)	TransCon hGH Auto-Injector (N = 27)	TransCon hGH Auto-Injector / Syringe and Needle	Intra-subject CV (%)	*P*-Value for Period Effect
C_{max} (ng/mL)	10.0	9.8	97.1 (86.8, 108.6)	24.5	0.742
$AUC_{0\text{-}168}$ (ng*hr./mL)	390.2	369.4	94.7 (85.4, 104.9)	22.3	0.684
$AUC_{0\text{-}t}$ (ng*hr./mL)	382.8	360.6	94.2 (85.5, 104.4)	22.3	0.632
$AUC_{0\text{-}inf}$ (ng*hr./mL)	410.3	383.5	93.5 (84.4, 103.5)	22.2	0.890

Pharmacodynamic Parameter	Geometric Least-Squares Means[a]		% Geometric Least Square Mean Ratio (90% CI)	Intra-subject CV (%)	*P* Value for Period Effect
	TransCon hGH Syringe and Needle (N = 27)	TransCon hGH Auto-Injector (N = 27)	TransCon hGH Auto-Injector / Syringe and Needle		
E_{max} (ng/mL)	509.1	518.4	101.8 (98.6, 105.2)	7.0	0.139
$AUEC_{0-168}$ (ng*hr./mL)	56536.2	56943.7	100.7 (97.8, 103.7)	6.3	0.117
$AUEC_{0-336}$ (ng*hr./mL)	73381.5	74670.6	101.8 (97.9, 105.7)	8.3	0.117

a Geometric least-squares means were obtained by the back-transformation of least-squares means of the parameters from an ANOVA using a mixed model based on log-transformed data. The model included treatment modality (Auto-Injector or Syringe and Needle), period, and sequence as fixed effects and subjects within sequence as a random effect.

- Abbreviations: ANOVA = analysis of variance; CI = confidence interval
- Baseline; average of two pre-dose concentrations
- In IGF-1 table, Cmax=Emax, AUC=AUEC

The applicant submitted responses to the clinical pharmacology Information Request (IR), which was communicated during the Mid-Cycle Communication dated December 7, 2020. The IR was to address potential impact of the cross-reactivity (0.29%) between lonapegsomatropin and hGH in the bioanalytical method. The applicant indicated that the cross-reactivity may not affect the comparability conclusions since it will introduce the same bias in the measurement of hGH from the two treatments. The division recommended that the applicant confirm the assumption using a worst-case scenario since lonapegsomatropin was not measured in Study CT-102. The applicant responded to the IR using the known cross-reactivity and concentration relationship between hGH and lonapegsomatropin from the previous relative bioavailability study (Study CT-101) as designs were comparable between the two studies. The observed hGH concentrations were adjusted in a time-dependent manner using ratios between hGH and lonapegsomatropin concentrations from Study CT-101; hGHcorr(t) = hGHobs(t) – hGHobs(t)*ratio(t)*cross-reactivity. The bioanalytical bias was expected to increase with higher lonapegsomatropin concentration compared to that of hGH in a given time (ratio) and the ratios ranged from 14 to 212. Results of this reanalysis indicate that the comparability assessment remains unchanged. The impact of cross-reactivity on the comparability assessment is not significant according to a worst-case scenario (Table 6). Therefore, the conclusion of comparability between the TBM and clinical products is acceptable.

Table 6 **Statistical analyses of PK parameters following a worst-case scenario**
Source; Table 4, Responses to IR dated 12/23/2020 (\\CDSESUB1\evsprod\BLA761177\0022)

PK Parameter	Lonapegsomatropin (N=27)			
	Geometric LS Mean			
	Syringe and Needle (Reference)	Auto-Injector (Test)	Geo LS Mean Ratio (Test/Reference) (%)	90% CI of Geometric LS Mean Ratio Test/Reference (%)
Baseline-Corrected hGH[a]				
C_{max} (ng/mL)	10.04	9.75	97.1	(86.8, 108.6)
AUC_{0-t} (hr*ng/mL)	382.75	360.58	94.2	(85.0, 104.4)
AUC_{inf} (hr*ng/mL)	410.30	383.46	93.5	(84.4, 103.5)
Baseline-Corrected hGH and Cross-reactivity Adjusted[b]				
C_{max} (ng/mL)	9.07	8.72	96.2	(85.9, 107.6)
AUC_{0-t} (hr*ng/mL)	315.32	294.32	93.3	(83.3, 104.6)
AUC_{inf} (hr*ng/mL)	330.38	318.43	96.4	(87.4, 106.3)
Absolute hGH[c]				
C_{max} (ng/mL)	10.10	10.08	99.8	(90.0, 110.6)
AUC_{0-t}(hr*ng/mL)	388.12	389.60	100.4	(94.2, 107.0)
AUC_{inf} (hr*ng/mL)	417.71	416.03	99.6	(93.8, 105.8)
Absolute hGH and Cross-reactivity Adjusted[d]				
C_{max} (ng/mL)	9.13	9.06	99.2	(89.6, 109.8)
AUC_{0-t} (hr*ng/mL)	321.09	323.50	100.8	(94.6, 107.3)
AUC_{inf} (hr*ng/mL)	336.66	340.16	101.0	(95.2, 107.3)

a and c; data from CT-102 CSR
b and d; new results following cross-reactivity adjustment

The on-site inspection for the bioanalytical and clinical study (CT-102) was requested to the Office of Study Integrity and Surveillance (OSIS). The OSIS determined that the inspection was not warranted for the sites as the Office of Regulatory Affairs and OSIS inspected the clinical and bioanalytical sites recently.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation

Lonapegsomatropin, hGH and mPEG in human serum were quantified by bioanalytical methods of enzyme-linked immunosorbent assay (ELISA).

Methods of ELISA followed standard assay methods. To minimize cross-reactivity between hGH and lonapegsomatropin, lonapegsomatropin was removed from the serum sample prior to assaying with immunoprecipitation step with biotinylated rabbit anti-mPEG polyclonal antibody coupled to streptavidin coated agarose beads. The capture antibody and detection antibody were as follows:

- hGH; a biotinylated rabbit anti-hGH antibody, a rabbit anti-hGH polyclonal antibody
- lonapegsomatropin; a sheep anti-hGH polyclonal antibody, a biotinylated rabbit anti-mPEG monoclonal antibody
- mPEG; a rabbit anti-mPEG monoclonal antibody, a biotinylated anti-PEG mouse monoclonal antibody

In general, the bioanalytical methods (Table 7) were acceptable refering guidelines in the guidance (https://www.fda.gov/media/70858/download).

Table 7 Summary of bioanalytical method validation

	hGH	**Lonapegsomatropin**	**mPEG**
Matrix	Normal and GHD children serum	Human serum	Human serum
Analytical method/detection	Sandwich ELISA	Sandwich ELISA	Sandwich ELISA
Calibration Range	2.00 – 50.0 ng/mL 0.500 ng/mL – 15.0 ng/mL	15.0 – 500 ng/mL corresponding to: 5.00 – 167 ng hGH/mL	300 – 8000 ng/mL
Cumulative accuracy (% bias) in standard calibrators from LLOQ to ULOQ	-1.6 to 2.9% -5.8 to 6.5%	-0.9 to 2.0%	-2.3 to 3.8%
Cumulative precision (% CV) from LLOQ to ULOQ	≤ 3.0% ≤ 7.9%	≤ 8.1%	≤ 9.1%
Cumulative accuracy (%bias) in QCs	-2.4 to 9.8% -11.8 to 2.2%	-14.2 to -8.0%	-5.8 to 7.1%
Dilution Linearity & Hook Effect	Dilution QC: 500 ng /mL (dilution factor: 25, 30, 50) Accuracy: 92.6 – 99.6% Precision: 4.0 – 9.8% Dilution QC: 100 ng /mL (dilution factor: 8, 50, 100) Accuracy range: 89.9 - 109% Precision: ≤ 7.2%	Dilution QC: 10,000 ng/mL (dilution factor: 200) Accuracy: 85.0% Precision: 4.96% Dilution QC: 60,000 ng/mL (dilution factor: 500) Accuracy: 102.3% Precision: 7.20% Dilution QC: 60,000 ng/mL (dilution factor: 1000) Accuracy: 102.7% Precision: 5.11%	Dilution QC: 50,000 ng/mL (dilution factor: 8, 10 and 15) Accuracy: 101.4 to 103.2% Precision: 1.7 to 4.7%
Freeze-Thaw Stability	hGH: 6 freeze (-80 C)-thaw (ambient temperature) cycles in polypropylene tubes under white light	6 freeze (-80 C)-thaw (ambient temperature) cycles in polypropylene tubes under white light	6 freeze (-80 C)-thaw (ambient temperature) cycles in polypropylene tubes under white light
Long-Term Storage	hGH: 406 days in polypropylene tubes at -80 C 476 days in polypropylene tubes at -20 C	259 days in polypropylene tubes at -80 C 92 days in polypropylene tubes at -20 C	456 days in polypropylene tubes at -80 C (low and dilution QCs), 329 days in polypropylene tubes at -80 C (low and high QCs), 87 days (low QC) and 71 days (dilution QC) in polypropylene tubes at -20 C, 179 days in polypropylene tubes at - 20 C (low and dilution QCs)

4.2 Summary of Individual Clinical Pharmacology Studies

4.2.1. Study CT-102 – Pivotal PK bridging study for the TBM product compared to clinical product

Title: A Phase 1, randomized, open-label bioequivalence trial in healthy volunteers comparing TransCon hgH administered as a single dose via syringe and needle vs. auto-injector

Objective:

Primary objective:

- To establish pharmacokinetic (PK) bioequivalence between TransCon hGH administered by syringe/needle and auto-injector, measured as human growth hormone (hGH) maximum concentration (Cmax) and area under the concentration-time curve (AUC).

Secondary objectives:

- To establish pharmacodynamic (PD) bioequivalence of TransCon hGH administered by syringe/needle and auto-injector, measured as insulin-like growth factor-1 (IGF-1) maximum observed response (E_{max}) and area under the effect-time curve (AUEC).
- To characterize the safety and tolerability profile of TransCon hGH administered by syringe and needle or an auto-injector.
- To characterize the immunogenicity of TransCon hGH after two single doses.

Study design:

This was a single center, Phase 1, randomized, open-label, single dose, crossover study in healthy male adult subjects (N=26) designed to compare the PK and PD of two injection modalities of TransCon hGH to confirm bioequivalence (BE). PK (hGH) was to be evaluated by C_{max} and AUC, and PD (IGF-1) was to be evaluated by E_{max} and AUEC.

TransCon hGH was to be administered at a fixed nominal dose of 13.3 mg hGH (corresponding to approximately 0.20 mg hGH/kg) subcutaneously (SC) to normal healthy volunteers via syringe and needle versus the auto-injector during 2 separate periods separated by a washout period.

Major study results:

- PK of hGH was comparable between TBM and clinical products
- The impact of potential bioanalytical bias due to cross-reactivity between hGH and lonapegsomatropin on the comparability assessment was not significant (see in section 3.3.5).

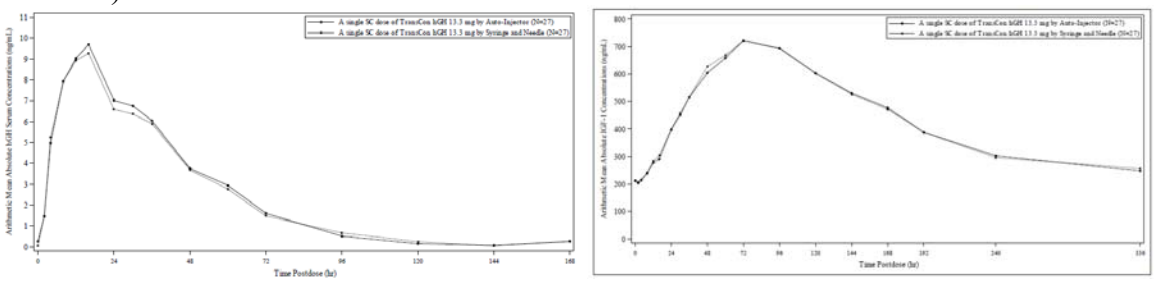


Figure 16 **Mean hGH (left) or IGF-1 (right) serum concentration-time profiles (Study CT-102)**
(Source, Figure 2 and 3, CSR)

Table 8 Summary of hGH PK and statistical analysis for the comparability (Study CT-102)

(Source; Table 12 and 14, CSR)

PK Parameter	Statistics	TransCon hGH Syringe and Needle (N=27)	TransCon hGH Auto-Injector (N=27)
C_{max} (ng/mL)	Mean (SD)	10.5 (3.9)	10.0 (2.3)
	SEM	0.7	0.4
	Median	9.8	10.2
	Min, Max	6.6, 28.1	5.9, 17.1
	Geometric Mean	10.1	10.1
	Geometric CV (%)	26.8	21.5
T_{max} (hr.)	Mean (SD)	12.6 (3.9)	14.2 (4.2)
	SEM	0.7	0.8
	Median	12.0	16.0
	Min, Max	4.0, 16.2	4.0, 24.0
$AUC_{(0-t)}$ (hr.*ng/mL)	Mean (SD)	401.7 (103.6)	405.8 (115.6)
	SEM	19.9	22.2
	Median	389.9	417.9
	Min, Max	232.8, 584.2	193.7, 675.9
	Geometric Mean	388.5	389.1
	Geometric CV (%)	27.2	31.1
$AUC_{(0-168)}$ (hr.*ng/mL)	Mean (SD)	410.0 (104.5)	416.2 (115.2)
	SEM	20.1	22.2
	Median	398.7	425.3
	Min, Max	242.2, 618.6	212.6, 688.8
	Geometric Mean	397.0	400.0
	Geometric CV (%)	26.7	30.0
$AUC_{(0-inf)}$ (hr.*ng/mL)	Mean (SD)	430.6 (105.0)	430.8 (113.4)
	SEM	20.2	21.8
	Median	433.0	444.7
	Min, Max	253.3, 624.7	212.6, 697.2
	Geometric Mean	418.0	415.6
	Geometric CV (%)	25.6	28.6
AUC_{extrap} (%)	Mean (SD)	6.9 (5.0)	6.3 (3.8)
	SEM	1.0	0.7
	Median	4.8	5.4
	Min, Max	2.0, 18.7	1.7, 17.0
	Geometric Mean	5.6	5.3
	Geometric CV (%)	71.7	64.9
K_{el} (1/hr.)	Mean (SD)	0.034 (0.015)	0.039 (0.012)
	SEM	0.003	0.002
	Median	0.037	0.039
	Min, Max	0.01, 0.07	0.02, 0.06
$t_{1/2}$ (h)	Mean (SD)	27.3 (19.3)	20.5 (9.1)
	SEM	3.7	1.8
	Median	18.6	17.6
	Min, Max	9.6, 82.8	11.0, 42.6

Comparability assessment using baseline-corrected PK parameters

Pharmacokinetic Parameter	Geometric Least-Squares Means[a]		% Geometric Least Squares Mean Ratio (90% CI)	Intra-subject CV (%)	*P*-Value for Period Effect
	TransCon hGH Syringe and Needle (N = 27)	TransCon hGH Auto-Injector (N = 27)	TransCon hGH Auto-Injector / Syringe and Needle		
C_{max} (ng/mL)	10.0	9.8	97.1 (86.8, 108.6)	24.5	0.742
AUC_{0-168} (ng*hr./mL)	390.2	369.4	94.7 (85.4, 104.9)	22.3	0.684
AUC_{0-t} (ng*hr./mL)	382.8	360.6	94.2 (85.5, 104.4)	22.3	0.632
AUC_{0-inf} (ng*hr./mL)	410.3	383.5	93.5 (84.4, 103.5)	22.2	0.890

Table 9 Summary of IGF-1 parameters and statistical analysis for the comparability (Study CT-102)

(Source; Table 15 and 17, CSR)

		TransCon hGH	
PD Parameter	**Statistics**	**Syringe and Needle (N=27)**	**Auto-Injector (N=27)**
E_{max} (ng/mL)	Mean (SD)	730.5 (97.3)	735.7 (103.5)
	SE	18.7	19.9
	Median	744.2	745.0
	Min, Max	500.6, 898.7	482.6, 1025.3
	Geometric Mean	723.9	728.5
	Geometric CV (%)	14.0	14.6
TE_{max} (hr.)	Mean (SD)	77.8 (11.2)	77.8 (12.6)
	SE	2.2	2.4
	Median	72.0	72.0
	Min, Max	60.0, 96.0	60.0, 96.0
$AUEC_{(0-168)}$ (hr.*ng/mL)	Mean (SD)	93247.5 (13156.6)	92932.5 (12915.1)
	SE	2532.0	2485.5
	Median	93386.0	92926.0
	Min, Max	69332.8, 123487.6	67304.2, 133208.8
	Geometric Mean	92340.5	92090.4
	Geometric CV (%)	14.4	13.8
$AUEC_{(0-336)}$ (hr.*ng/mL)	Mean (SD)	146415.5 (23442.7)	146478.5 (25053.0)
	SE	4511.6	4821.5
	Median	141420.0	144438.4
	Min, Max	106879.6, 211085.4	109295.9, 232372.8
	Geometric Mean	144663.3	144612.1
	Geometric CV (%)	15.9	16.1

Comparability assessment using baseline-corrected PD parameters

	Geometric Least-Squares Means[a]		**% Geometric Least Square Mean Ratio (90% CI)**		
Pharmacodynamic Parameter	**TransCon hGH Syringe and Needle (N = 27)**	**TransCon hGH Auto-Injector (N = 27)**	**TransCon hGH Auto-Injector / Syringe and Needle**	**Intra-subject CV (%)**	***P* Value for Period Effect**
E_{max} (ng/mL)	509.1	518.4	101.8 (98.6, 105.2)	7.0	0.139
$AUEC_{0-168}$ (ng*hr./mL)	56536.2	56943.7	100.7 (97.8, 103.7)	6.3	0.117
$AUEC_{0-336}$ (ng*hr./mL)	73381.5	74670.6	101.8 (97.9, 105.7)	8.3	0.117

4.2.2. Study CT-101 – Relative bioavailability and PK-dose proportionality

Title: A Phase 1, Randomized, Open-Label Study in Healthy Volunteers, Investigating the Safety and Tolerability of a Single Dose of ACP-011 at Three Different Dose Levels and Comparing Exposures of a Single Dose of ACP-011 to ACP-001 in a Cross-Over Design

Objectives:

Primary objective:

- To evaluate the safety and tolerability of a single dose of ACP-011 at 3 different dose levels

Secondary objectives:

- To evaluate the pharmacodynamic (PD) response parameters of ACP-011 compared to ACP-001 at a single dose level.
- To evaluate the pharmacokinetic (PK) and PD parameters of ACP-011 at 3 different dose levels

Study design:

This was a single-center, randomized, open-label study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of ACP-011 at doses of 0.24, 0.30, and 0.42 mg human growth hormone (hGH)/kg administered subcutaneously as a single dose to healthy subjects. There was a crossover portion in the study to compare ACP-011 and ACP-001 in terms of PK and PD parameters.

Group 1:

Twenty-eight healthy subjects were randomly assigned to the comparative crossover portion of the study to receive 1 of 2 treatment sequences (AB or BA) in a 1:1 ratio. Treatment A was a single subcutaneous (SC) dose of ACP-001 0.24 mg hGH/kg. Treatment B was a single SC dose of ACP-011 0.24 mg hGH/kg.

Group 2:

Eighteen subjects (9 subjects in each dose cohort) were enrolled in Group 2. Subjects were assigned to a dose cohort based on the order in which they were enrolled. Subjects in Cohort 1 received a single SC dose of ACP-011 0.30 mg hGH/kg (Treatment C) and subjects in Cohort 2 received a single SC dose of ACP-011 0.42 mg hGH/kg (Treatment D). There was only 1 treatment period for subjects in Group 2; subjects in Cohort 1 were enrolled and dosed before subjects in Cohort 2.

Major study results:

- PK of hGH was comparable between ACP-011 and ACP-001.
- PK proportionality of hGH, lonapegsomatropin and mPEG was greater than dose following single doses. Numbers of subject were small (N=9) for 0.3 and 0.42 mg hGH/kg compared to that of 0.24 mg hGH/kg (N=27). Therefore, variability in PK was heterogenous among doses.

Table 10 Summary of PK (top) and PD (middle) parameters, and statistical assessment of comparability (bottom)

hGH (geometric mean and % CV) (source; Table 11-2)

Parameter (unit)	Treatment A (ACP-001 0.24 mg hGH/kg) (N=28)	Treatment B (ACP-011 0.24 mg hGH/kg) (N=27)
$AUC_{0\text{-}inf}$ (h*ng/mL)	755 (48.9)[b]	734 (52.6)[c]
$AUC_{0\text{-}168}$ (h*ng/mL)	595 (52.7)	617 (49.8)
C_{max} (ng/mL)	11.7 (29.5)	13.4 (28.4)
T_{max} (h)[a]	16.0 (8.00, 48.0)	16.0 (8.00, 48.0)
$t_{1/2}$ (h)	34.9 (48.0)[b]	25.4 (40.1)[c]

Abbreviations: CV, coefficient of variation; N, number of non-missing observations.

[a] For T_{max}, the median (minimum, maximum) values are presented.

[b] N=23.

[c] N=17.

IGF-1 (Baseline-Adjusted) (geometric mean and % CV) (source; Table 11-3)

Parameter (unit)	Treatment A (ACP-001 0.24 mg hGH/kg) (N=28)	Treatment B (ACP-011 0.24 mg hGH/kg) (N=27)
$AUEC_{0\text{-}168}$ (h*ng/mL)	54400 (29.2)	54500 (28.1)
$AUEC_{0\text{-}336}$ (h*ng/mL)	75900 (35.6)	71000 (35.1)
E_{max} (ng/mL)	475 (26.9)	498 (25.2)
TE_{max} (h)[a]	72.0 (48.0, 144)	72.0 (48.0, 144)

Statistical Assessment of PK and PD parameters Between ACP-011 (Treatment B) and ACP-001 (Treatment A) (Source; Table 11-4)

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	$AUC_{0\text{-}168}$ (h*ng/mL)	28	595	27	623	104.64	(94.91, 115.37)	21.25
		$AUC_{0\text{-}336}$ (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	$AUEC_{0\text{-}168}$ (h*ng/mL)	28	88400	26	87600	99.07	(96.84, 101.35)	4.81
		$AUEC_{0\text{-}336}$ (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	$AUEC_{0\text{-}168}$ (h*ng/mL)	28	54400	27	54000	99.17	(94.57, 103.99)	10.24
		$AUEC_{0\text{-}336}$ (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.

Table 11 Summary of pegylated prodrug PK (TransCon PEG (b) (4) hGH and TransCon PEG40 hGH) [GM (%CV)] (Study CT-101, Group 1)

(Source; Table 11-6)

Parameter (unit)	TransCon PEG (b) (4) hGH Treatment A (ACP-001 0.24 mg hGH/kg) (N= 28)	TransCon PEG40 hGH Treatment B (ACP-011 0.24 mg hGH/kg) (N=27)
$AUC_{0\text{-}inf}$ (h*ng hGH eq/mL)	82500 (66.6)	33900 (104.6)
$AUC_{0\text{-}168}$ (h*ng hGH eq/mL)	65400 (82.8)	30900 (114.7)
C_{max} (ng hGH eq/mL)	731 (90.9)	535 (112.4)
T_{max} (h)[a]	48.0 (24.0, 96.0)	36.0 (16.0, 48.0)
$t_{1/2}$ (h)	66.0 (32.4)	51.9 (35.4)

Table 12 Summary of PK-dose proportionality (Study CT-101, Group 2)

hGH [GM (%CV)] (source; Table 11-9, CSR)

Parameter (unit)	Treatment B (ACP-011 0.24 mg hGH/kg) (N=27)	Treatment C (ACP-011 0.30 mg hGH/kg) (N=9)	Treatment D (ACP-011 0.42 mg hGH/kg) (N=9)
$AUC_{0\text{-}inf}$ (h*ng/mL)	734 (52.6)[b]	897 (36.8)[c]	2320 (26.3)[d]
$AUC_{0\text{-}168}$ (h*ng/mL)	617 (49.8)	957 (25.8)	2050 (46.5)
C_{max} (ng/mL)	13.4 (28.4)	19.4 (20.2)	32.9 (26.9)
T_{max} (h)[a]	16.0 (8.00, 48.0)	24.0 (12.0, 36.0)	36.0 (12.0, 36.0)
$t_{1/2}$ (h)	25.4 (40.1)[b]	21.8 (13.3)[c]	25.0 (26.1)[d]

Abbreviations: CV, coefficient of variation; N, number of non-missing observations.

[a] For T_{max}, the median (minimum, maximum) values are presented.

[b] N=17.

[c] N=3.

[d] N=7.

Lonapegsomatropin [GM (%CV)] (Source; Table 11-10)

Parameter (unit)	Treatment B (ACP-011 0.24 mg hGH/kg) (N=27)	Treatment C (ACP-011 0.30 mg hGH/kg) (N=9)	Treatment D (ACP-011 0.42 mg hGH/kg) (N=9)
$AUC_{0\text{-}inf}$ (h*ng/mL)	33900 (104.6)	62600 (54.3)	171000 (108.8)
$AUC_{0\text{-}168}$ (h*ng/mL)	30900 (114.7)	60300 (56.7)	164000 (118.0)
C_{max} (ng/mL)	535 (112.4)	1280 (70.4)	2480 (133.4)
T_{max} (h)[a]	36.0 (16.0, 48.0)	24.0 (24.0, 36.0)	36.0 (36.0, 48.1)
$t_{1/2}$ (h)	51.9 (35.4)	39.5 (29.0)	40.8 (32.1)

mPEG [GM (%CV)] (Source; Table 11-11)

Parameter (unit)	Treatment B (ACP-011 0.24 mg hGH/kg) (N=14)	Treatment C (ACP-011 0.30 mg hGH/kg) (N=9)	Treatment D (ACP-011 0.42 mg hGH/kg) (N=9)
$AUC_{0\text{-}inf}$ (h*ng/mL)	3020000 (10.5)[b]	4130000 (19.7)[c]	5910000 (8.2)[c]
$AUC_{0\text{-}168}$ (h*ng/mL)	314000 (50.4)	470000 (23.2)	770000 (57.4)
$AUC_{0\text{-}672}$ (h*ng/mL)	1810000 (5.7)[b]	2040000 (11.8)	2950000 (17.4)
$AUC_{0\text{-}1344}$ (h*ng/mL)	NA	3220000 (15.3)	4530000 (9.6)
C_{max} (ng/mL)	3060 (32.9)	4010 (15.8)	6870 (30.6)
T_{max} (h)[a]	240 (36.0, 670)	168 (48.0, 336)	48.1 (36.0, 504)
$t_{1/2}$ (h)	508 (18.0)[b]	594 (16.1)[c]	616 (14.1)[c]

Abbreviations: CV, coefficient of variation; N, number of non-missing observations; mPEG40, methoxypolyethylene glycol 40 kDa; NA, not applicable.
[a] For T_{max}, the median (minimum, maximum) values are presented.
[b] N=3.
[c] N=8.

Statistical Assessment of Dose Proportionality for Pharmacokinetic Parameters of ACP-011 (Treatments B, C, and D) (Pharmacokinetic Analysis Set) (Source; Table 11-12)

Analyte	Dependent Variable	N	Intercept Estimate	Slope Estimate	90% CI of Slope	Correlation Coefficient
TransCon PEG40 hGH	C_{max} (ng/mL)	45	10.34	2.81	(1.81, 3.81)	0.5837
	$AUC_{0\text{-}336}$ (h*ng/mL)	45	14.56	2.91	(1.98, 3.84)	0.6259
	$AUC_{0\text{-}inf}$ (h*ng/mL)	45	14.54	2.88	(1.97, 3.80)	0.6288
hGH	C_{max} (units)	45	4.90	1.61	(1.32, 1.91)	0.8127
	$AUC_{0\text{-}336}$ (h*ng/mL)	45	9.52	2.14	(1.63, 2.65)	0.7333
	$AUC_{0\text{-}inf}$ (h*ng/mL)	27	9.47	2.03	(1.43, 2.62)	0.7589
mPEG40	C_{max} (ng/mL)	32	10.07	1.45	(1.09, 1.80)	0.7825
	$AUC_{0\text{-}336}$ (h*ng/mL)	32	15.47	1.37	(1.01, 1.73)	0.7616
	$AUC_{0\text{-}672}$ (h*ng/mL)	21	15.71	0.96	(0.70, 1.21)	0.8284
	$AUC_{0\text{-}inf}$ (h*ng/mL)	19	16.60	1.15	(0.89, 1.42)	0.8752

Abbreviations: CI, confidence interval; N, number of subjects; mPEG40, methoxypolyethylene glycol 40 kDa; PEG, polyethylene glycol.
Treatment B: A single SC dose of ACP-011 0.24 mg hGH/kg.
Treatment C: A single SC dose of ACP-011 0.30 mg hGH/kg.
Treatment D: A single SC dose of ACP-011 0.42 mg hGH/kg.
Note: Natural log-transformed pharmacokinetic parameters were analyzed using a power model. Dose proportionality is concluded when the 90% CI lies entirely within the range (0.60, 1.40).

4.2.3. Study CT-004 – dose ranging with ACP-001 (pegylated with (b) (4) kDa) vs Genotropin® in pediatric patients

Title: A multicenter, Phase 2, randomized, open label, active-controlled, parallel-group study investigating the safety, tolerability, and efficacy of different dose levels of ACP-001 administered once weekly versus standard daily rhGH replacement therapy in pre-pubertal children with Growth Hormone Deficiency (GHD)

Objectives:

Primary objective:

- To compare the safety and pharmacokinetic and pharmacodynamic (PK/PD) profile of three different ACP-001 doses to that of a commercially available standard daily recombinant human growth hormone (rhGH) formulation (Genotropin®) in pre-pubertal children with growth failure due to GHD

Secondary objectives:

- To evaluate the 6-month growth pattern (height velocity)
- To select a safe and efficacious dose for pivotal development

Study design:

This was a Phase 2, randomized, open label, active-controlled trial of 3 different dose levels of ACP-001 administered weekly, compared with a currently available growth hormone (GH) replacement therapy (Genotropin) administered daily over a period of 26 weeks (6 calendar months).

A total of 34 AGHD patients were exposed in the trial (25 male and 9 female patients). A total of 33 patients were White and 1 patient was reported as 'other' (White/African). The age range was 21−69 years. The medical history and concomitant illnesses were consistent with a diagnosis of AGHD. The patients were all to be in stable GH replacement therapy for at least 3 months at inclusion and a GH wash-out period of 14 days was required prior to randomization.

Treatments were as follows;

- Cohort 1: ACP-001 once weekly at a dose equivalent to 0.14 mg rhGH/kg/week
- Cohort 2: ACP-001 once weekly at a dose equivalent to 0.21 mg rhGH/kg/week
- Cohort 3: ACP-001 once weekly at a dose equivalent to 0.30 mg rhGH/kg/week
- Cohort 4: Genotropin once daily at a dose of 0.03 mg rhGH/kg/day (equivalent to 0.21 mg rhGH/kg/week)

PK/PD samplings were as follows;

- Cohorts 1-3: predose, 2*, 4*, 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours post-dose (*: PK only)
- Cohort 4: predose, 1*, 2*, 4*, 6, 8, 12, 24, and 168** hours post-dose (*: PK only, **: PD only)

Study endpoints:

- PK endpoints: $AUC_{0\text{-}168h}$, $AUC_{0\text{-}24h}$ (Genotropin®), C_{max}, T_{max}, $t_{1/2}$ and others

- PD endpoints: $AUEC_{0\text{-}168h}$, C_{max}, T_{max} for both IGF-1 and IGFBP-3, change from baseline at 168 hours for IGF-1 and IGFBP-3, IGF-1 SDS, and IGFBP-3 SDS at 168 hour and C_{max} SDS at 168 hours
- Annualized HV [cm/year] at Visit 3 =
  Delta HT * 365 / (Visit 3 visit date – Visit 1 visit date) [days]), where Delta HT is (Mean body HT at Visit 3 [cm]) - (Mean body HT at Visit 1 [cm])
  - Annualized HV [cm/year] at Visit 5 =
    Delta HT * 365 / (Visit 5 visit date – Visit 1 visit date) [days]), where Delta HT is (Mean body HT at Visit 5 [cm]) - (Mean body HT at Visit 1 [cm])
  - The HV SDS ranges were determined according to Prader et al., 1989 Helv Paediatr Acta Suppl. 52:1-125.

Major study results:

- The study was considered as exploratory since drug was predecessor version (ACP-001).
- There was no significant accumulation of hGH or ACP-001, while a significant accumulation of mPEG in Week 13 compared to those in Week 1.
- There was trend towards a dose related AHV increase though it was not statistically significant due to small numbers of subject per dose.
- There were no apparent relationships between 1) PK (e.g., AUC of hGH) and PD (e.g., AUC of IGF-1) or 2) PD (e.g., AUC of IGF-1) and AHV. It should be cautious at comparison in those relationship between ACP-001 and Genotropin as PK and PD parameters were within corresponding dosing intervals, weekly vs. daily.

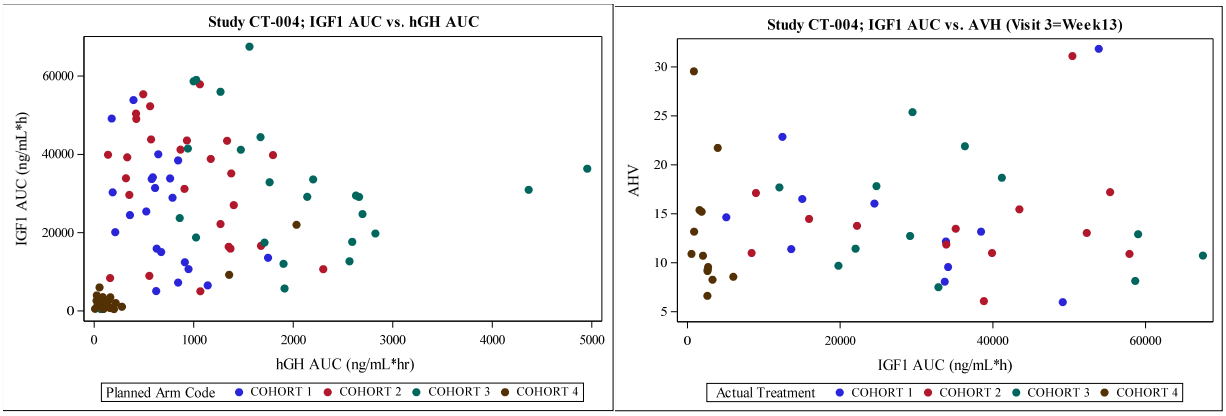


Figure 17 Relationship between PK (hGH AUC) and PD (IGF-1 AUC) (Study CT-004)
[note; there was dosing interval difference between Genotropin (Cohort 4, daily) and ACP-001 (other cohorts, weekly)]

4.2.3. Study CT-301 – Phase 3

Title: A Multicenter, Phase 3, Randomized, Open-Label, Active-Controlled, Parallel-Group Trial Investigating the Safety, Tolerability and Efficacy of Lonapegsomatropin Administered Once a Week Versus Standard Daily hGH Replacement Therapy Over 52 Weeks in Prepubertal Children with Growth Hormone Deficiency

Objectives:

Primary objective:

- To evaluate and compare the AHV of prepubertal children with GHD treated with weekly lonapegsomatropin to that of a commercially available daily hGH formulation at 52 weeks.

Secondary objectives:

- To evaluate the safety of weekly lonapegsomatropin compared to daily hGH over 52 weeks
- To evaluate and compare the AHV of weekly lonapegsomatropin to daily hGH over 52 weeks
- To evaluate and compare the change in HT SDS of weekly lonapegsomatropin to daily hGH over 52 weeks
- To evaluate serum IGF-1, IGFBP-3, IGF-1 SDS and IGFBP-3 SDS; and the normalization of IGF-1 SDS of weekly lonapegsomatropin or daily hGH over 52 weeks
- To describe the PK/PD profile of lonapegsomatropin, hGH, IGF-1, IGF-1 SDS, IGFBP-3, IGFBP-3 SDS and mPEG administered as a weekly injection (PK/PD subset; lonapegsomatropin group only)
- To compare the Cmax for hGH of lonapegsomatropin to the anticipated Cmax of daily hGH
- To determine the incidence of anti-hGH antibodies for both treatments, and treatment-emergent anti-mPEG antibodies for lonapegsomatropin over 52 weeks

Study design:

Treatments were as follows;

- Lonapegsomatropin 0.24 mg hGH/kg/week (administered once-weekly), or
- Genotropin 0.034 mg hGH/kg/day, a dose equivalent to 0.24 mg hGH/kg/week (administered daily)

PK/PD samplings were as follows;

- Blood samples were processed to serum for quantification of hGH, lonapegsomatropin (ie, TransCon mPEG40 hGH) and mPEG (40 kDa [mPEG40]), at screening and Visits 1 through 6.
- Blood samples for PK assessment in the lonapegsomatropin group PK/PD population (n=11) were collected at Visit 3 (Week 13) at following time points: Pre-dose (defined as time zero), 8, 12, 16, 24, 36, 48, 72, 96, 120, and 168 h post-dose.

Major study results related to clinical pharmacology information:

- The primary endpoint, AHV at Week 52, was compared between lonapegsomatropin and daily Genotropin by a non-inferiority comparison with a non-inferiority margin of 2.0 cm/year, followed by a test of superiority if non-inferiority was established (see details in review Section 3.3.2).
- It was reported that the site 748 had potential dosing error (e.g., administering the reconstituted product up to one week after reconstitution). To investigate the issue, subject

level concentrations of hGH, lonapegsomatropin and mPEG were identified from the site (N=3) and compared those with population level. There were no apparent trends in concentrations from the site compared to the population levels (Figure 18).

- There were no starting dose adjustment or dose adjustment during the treatment period using covariates.
- There was no significant covariate identified warranting a dose adjustment in addition to the proposed dosing based on body weight.

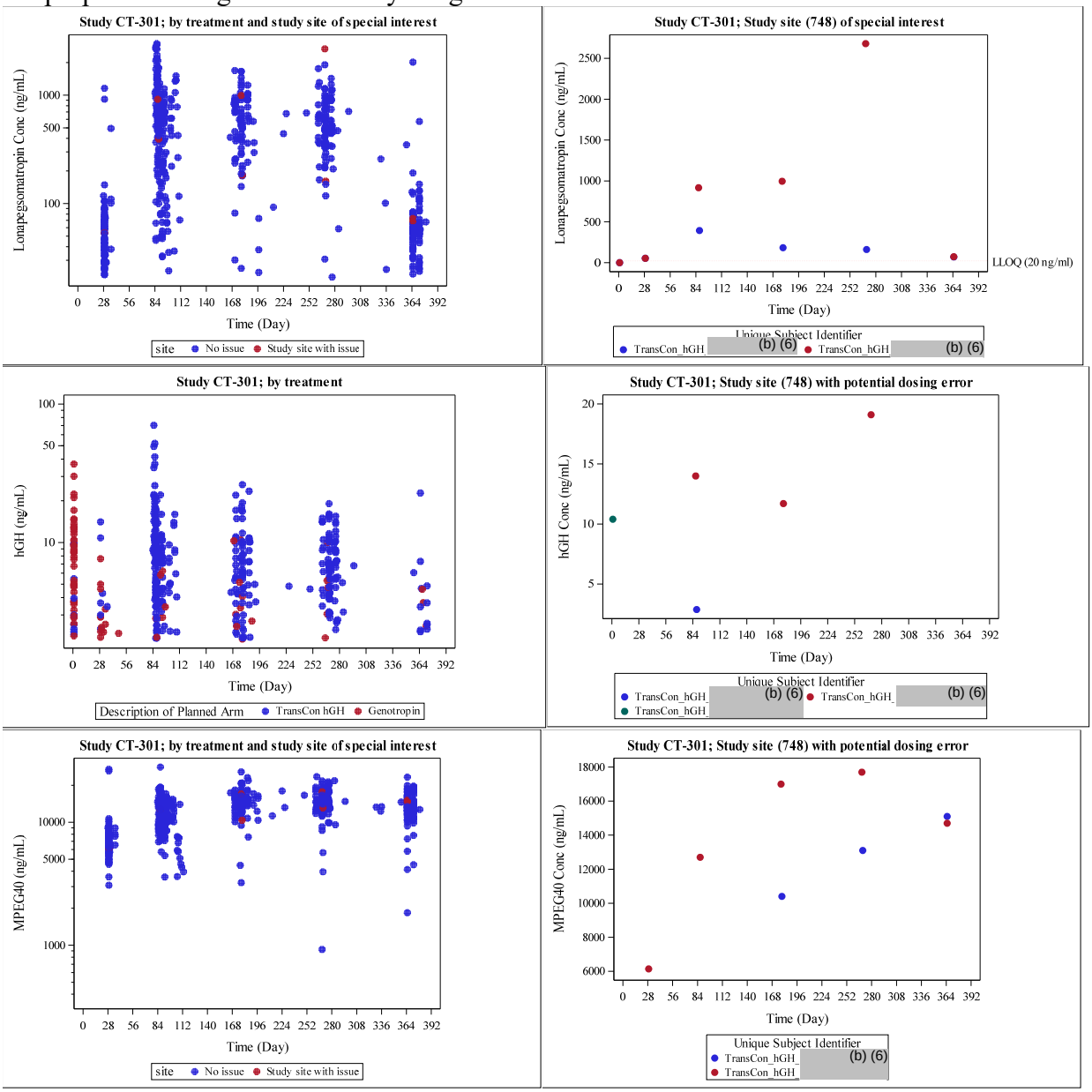


Figure 18 Observed concentrations of lonapegsomatropin (upper), hGH (middle) and mPEG (lower) and corresponding concentrations from the site (Site ID=748, right column) with potential dosing deviation (Study CT-301)

(note: observed concentrations were pooled from extensive PK sampling, which included Cmax, and Ctrough)

Table 13 PK Analysis at Week 13 (Visit 3) PK Parameters (PK/PD Subset)

(Source; Table 37, CSR)

Characteristic	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	AUC_{0-t} (h*ng/mL)	AUC_{0-168} (h*ng/mL)	$t_{½}$ (h)
hGH (as measured)						
n	11	11	11	11	6	6
Mean	24.0	19.4	75.3	861	1230	21.6
SD	20.2	13.9	22.8	672	826	7.53
95% CI	10.4, 37.6	10.0, 28.7	60.0, 90.6	409, 1,310	364, 2,100	13.7, 29.5
% CV	84.4	71.7	30.3	78.1	67.1	34.8
Geo mean	18.5	15.8	71.9	678	1,030	20.6
Geo % CV	81.5	72.1	33.6	82.3	74.0	33.7
Minimum	8.06	8.00	36.0	191	451	13.7
Median	14.6	12.0	72.0	656	916	20.7
Maximum	70.3	47.8	120	2,430	2,550	35.0
hGH (corrected for lonapegsomatropin cross-reactivity)						
n	11	11	11	11	4	4
Mean	20.0	17.6	75.3	647	1,140	16.8
SD	17.8	12.7	22.8	535	716	4.93
95% CI	8.08, 32.0	9.00, 26.1	60.0, 90.6	287, 1,010	3.60, 2,280	8.97, 24.7
% CV	88.8	72.6	30.3	82.7	62.6	29.3
Geo mean	15.2	14.7	71.9	500	955	16.2
Geo % CV	83.4	64.1	33.6	83.8	83.0	34.0
Minimum	7.29	8.00	36.0	168	410	10.2
Median	11.6	12.0	72.0	479	1,130	17.6
Maximum	62.5	47.8	120	1,850	1,910	21.9
lonapegsomatropin (hGH equivalents)						
n	11	11	11	11	11	11
Mean	1,530	27.7	157	86,600	86,900	30.7
SD	960	11.8	19.9	53,500	53,400	12.7
95% CI	886, 2,180	19.8, 35.7	144, 171	50,600, 123,000	51,000, 123,000	22.1, 39.2
% CV	62.7	42.5	12.6	61.8	61.4	41.5
Geo mean	1,230	25.0	156	73,500	74,000	28.7
Geo % CV	86.3	55.2	13.9	68.4	67.0	38.5
Minimum	245	8.00	120	19,940	21,000	18.0
Median	1,390	25.0	168	75,400	77,000	28.1
Maximum	2,990	48.2	171	221,000	221,000	57.4
mPEG						
n	11	11	11	11	10	9
Mean	13,600	40.0	166	1,810,000	1,820,000	485
SD	3,600	29.9	7.37	537,000	560,000	251
95% CI	11200, 16000	19.9, 60.1	161, 171	1,450,000, 2,180,000	1,420,000, 2,220,000	293, 678
% CV	26.5	74.8	4.40	29.6	30.7	51.7
Geo mean	13,100	30.7	166	1,740,000	1,740,000	435
Geo % CV	28.1	94.0	4.70	32.3	34.0	51.5
Minimum	7,650	8.00	144	888,000	888,000	244
Median	13,100	36.0	168	1,700,000	1,700,000	406
Maximum	19,000	96.0	171	2,640,000	2,640,000	985

- **Observations with unusual dose changes**

Dose adjustment (i.e., 20% reduction) for both lonapegsomatropin and Genotropin was allowed mainly if IGF-1 SDS was elevated > +2.0 with clinical concerns. In general, dose adjustment rarely occurred during the treatment for Study CT-301 (Figure 7). There were two subjects with starting dose higher than an average; 0.746 and 0.427 mg hGH/kg/week for initial 2 weeks to Subject ID TransCon_hGH_(b) (6) and TransCon_hGH_(b) (6), respectively (Figure 19). It was not clear for the reason of unusual high starting dose in two subjects. In addition, three subjects had sporadic and erratic doses higher than starting dose (e.g., 0.427 or 0.494 mg hGH/kg/week) (Figure 19).

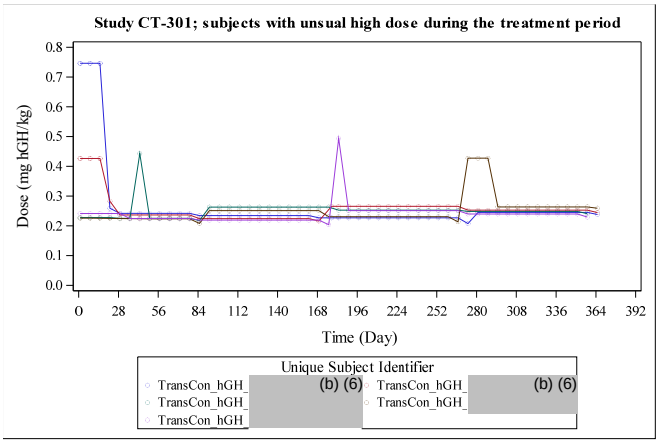


Figure 19 Subjects (n=5) with unusual high dose (right) during the treatment period (Study CT-301)
(Source: Reviewer's analysis)

Table 14 Dual Chamber cartridge dose strengths and body weight bracket to use
(Source; Table 2, Module 2.5)

Subject Weight (kg)	Cartridge(s) mg hGH
11.5 - 13.9	3.0
14.0 – 16.4	3.6
16.5 – 19.9	4.3
20.0 – 23.9	5.2
24.0 – 28.9	6.3
29.0 – 34.9	7.6
35.0 – 41.9	9.1
42.0 – 50.9	11.0
51.0 – 60.4	13.3
60.5 – 69.9	Two cartridges of 7.6 each
70.0 – 84.9	Two cartridges of 9.1 each
85.0 – 100.0	Two cartridges of 11.0 each

4.3. Pharmacometrics Review

4.3.1 Synopsis: Prediction of mPEG concentration in choroid plexus of children

The aim of study was 1) to characterize population PK of mPEG in healthy adult volunteers and PGHD, 2) to predict the choroid plexus concentration of mPEG in children after 0.24 mg hGH/kg, and 3) to compare them to those of predicted the prediction in cynomolgus monkeys, where dose related vacuole formation was investigated.

PK of mPEG was best characterized using a two-compartment model (Figure 20) for data from studies in rat, monkey, healthy volunteers and PGHD (Table 15). Clinically relevant covariates (sex, age, body weight and dose) were investigated. The models were evaluated by standard goodness of fit diagnostics.

Table 15 Summary of studies used for the serum mPEG PK analysis
(Source; Table 3, MODHGH001)

Study number	Species	Dosing	Observation period after last dose (weeks)	Doses [mg hGH/kg] (number of individuals)	Doses [mg mPEG/kg]	Body weights (kg)
1704-037	Rat	SC q1wk for 26 weeks	26	1.2 (22)	2.2	0.2-0.8
				2.4 (22)	4.5	
				4.8 (22)	9.0	
1704-035	Cynomolgus monkey	SC q1wk for 52 weeks	52	0.4 (12)	0.7	2-4
				1.6 (12)	3.0	
				4.8 (12)	9.0	
CT-101	Healthy volunteers	SC single dose	2	0.24 (14)	0.45	70 (assumed)
			8	0.3 (9)	0.6	
			8	0.42 (9)	0.78	
CT-301	Children with GHD	SC q1wk for 52 weeks	1	0.24 (105)	0.45	12.1-47.5

Estimated PK parameters are summarized in Table 16. Clearance and volume were scaled well with body weight in humans; coefficients were 0.84 (β_{CL}) and 0.86 (β_V) for clearance and volume, respectively. Corresponding inter-species scaling parameters were characterized as 0.83 and 0.69. Biodistribution coefficient into choroid plexus was available from rat model of nonacog beta pegol (N9-GP), which is another approved PEGylated biologics and has the same molecular weight as the PEG-moiety contained in lonapegsomatropin. The coefficient was scaled to human based on the allometric scaling coefficients and the overall scaling approach was informed using available data from N9-GP.

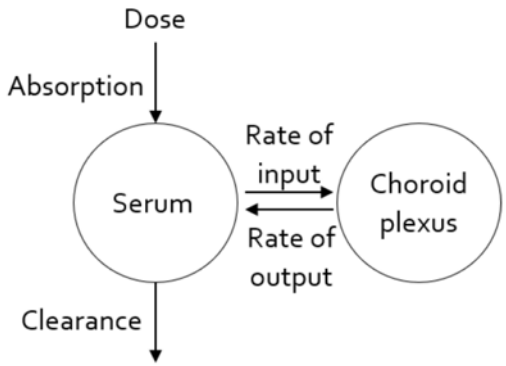


Figure 20 Schematic summary of mPEG compartment model

Table 16 Summary of estimated PK parameters (MODHGH001)
(source; Table 2, MODHGH001)

Parameter	Tissue	Rat		Cynomolgus monkey	Human	
		Female	Male		70 kg	22 kg
Volume of distribution *V/F* (L)	Serum	0.185	0.062	0.382	9.36	3.46
Clearance *Cl/F* (L/day)		0.0068	0.0068	0.0153	0.247	0.093
Terminal half-life $T_{1/2}$ (days)		19	7	17	26	26
Time to SS (months)		2.1	0.8	1.9	2.9	2.9
Terminal half-life $T_{1/2}$ (days)	Choroid plexus	49		87	192	143
Time to SS (months)		5.4		9.6	21	16

Parameterization of human mPEG serum-choroid plexus model in adults (BW = 70 kg) and children with GHD (BW = 22 kg). (Source; Table 13, MODHGH001)

Parameter	Source	Adult (70 kg)	Child (22 kg)
Central volume of distribution *Vc/F* (L)	Estimated from CT-101 and CT-301	9.36	3.46
Clearance *Cl/F* (L/day)		0.247	0.093
Absorption rate *ka* (1/day)		0.733	
Choroid plexus volume of distribution *Vcp* (L)	Physiological value	0.0035	0.003
Serum-to-choroid plexus exchange rate *k12* (1/day)	Preserved tissue partitioning between serum and choroid plexus	$1.49 \cdot 10^{-6}$	$4.61 \cdot 10^{-6}$
Choroid plexus-to-serum exchange rate *k21* (1/day)	Allometric scaling of rat PEG40(N9-GP) choroid plexus half-life	$3.62 \cdot 10^{-3}$	$4.83 \cdot 10^{-3}$

Predicted mPEG concentrations in choroid plexus of pediatric subjects following 0.24 mg hGH/kg/week were comparable to those of monkey following a dose of 0.4 mg hGH/kg/week, which did not result in vacuolation and was significantly below following a dose of 1.6 mg hGH/kg/week, associated with vacuolation (Figure 4). The predicted serum concentration threshold of mPEG for vacuolation was 100 mcg/mL, and the predicted threshold reasonably explained the relationship between observed vacuolation in choroid plexus epithelial cell and serum concentrations (Figure 21) for lonapegsomatropin and other biologics containing similar mPEG in literature.

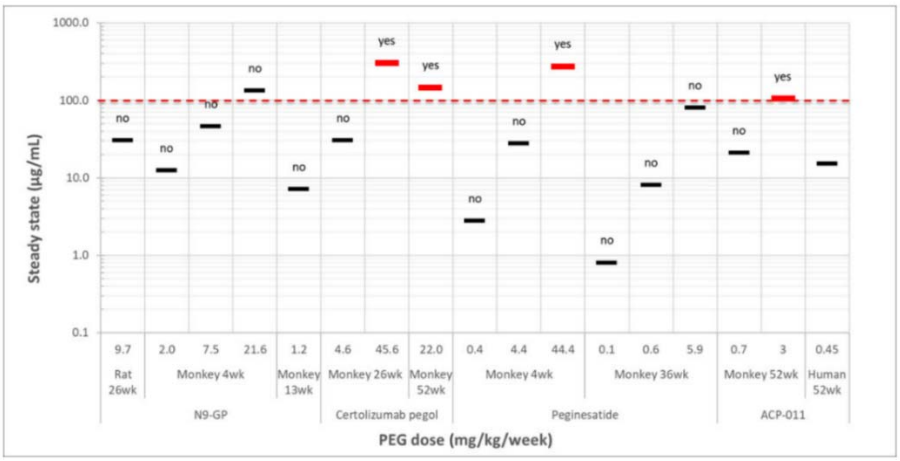


Figure 21 Relationship between predicted steady state concentrations among pegylated compounds and observed vacuolation in choroid plexus epithelial cells non-clinical models
(Yes-observed vacuolation, No-no vacuolation, Source; Figure 3, MODHGH001)

Reviewer's comment: *The modeling and simulation were acceptable for supportive information. However, it should be used with caution for interpreting clinical relevance of results as the results of modeling and simulation is largely based on theoretical considerations and cross-study comparisons (e.g., using mPEG safety experience in other adult and pediatric indications). There was no safety signal related to the vacuolation in the clinically relevant doses groups in lonapegsomatropin non-clinical studies. Further, there was no specific clinical safety signal in the Phase 3 program (See the clinical review by Dr. Shivangi Vachhani). No CNS or immune system associated safety signs were detected in the Phase 3 program. Therefore, clinical concerns at the mPEG accumulation in choroid plexus and its adverse events appears to be minimal at the proposed dosing.*

4.3.2 Synopsis: Population PK and PK/PD modeling of hGH

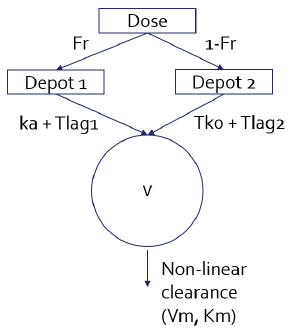
The aim of study was 1) to characterize population PK of lonapegsomatropin, 2) to characterize the population PK/PD between hGH and IGF-1, and 3) to evaluate covariates of PK or PK/PD for data obtained from Study CT-101 and CT-301 (Table 17).

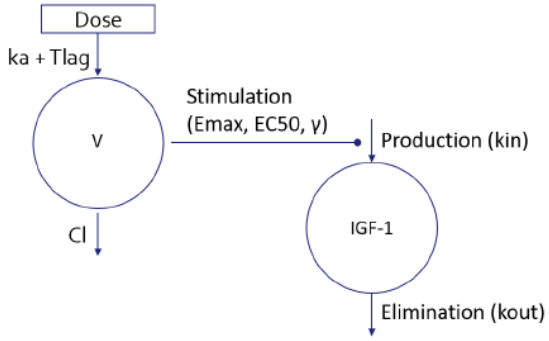
Table 17 Overview of trials and covariates included in the population PK and PK/PD evaluation
(Source; Table 9, MODHGH002)

Patient factor	Unit	CT-101				CT-301	
		Overall	0.24 mg/kg	0.3 mg/kg	0.42 mg/kg	Overall	PK/PD subset
N	-	45	27	9	9	105	11
Age	years	29 (20-45)	32 (20-45)	27 (22-43)	28 (21-44)	8.6 (3.2-13)	7.3 (4.5-11)
Body weight							
Baseline	kg	74 (52-98)	77 (55-98)	72 (62-81)	72 (52-80)	21 (12-40)	16 (12-28)
EOS	kg	-	-	-	-	26 (15-48)	19 (16-37)
Creatinine clearance	mL/min	126 (81.9-206)	130 (82.9-206)	126 (96.0-148)	124 (81.9-168)	87.3 (43.2 - 142)	90.3 (55.9-121)
IGF-1 baseline	ng/mL	199 (102-289)	199 (102-289)	222 (137-260)	185 (160-282)	75.5 (20.0-213)	49.1 (20.0-139.7)
Race	White	31 (68%)	18 (67%)	7 (78%)	6 (67%)	100 (95%)	11 (100%)
	Asian	1 (2%)	1 (4%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)
	Black or African American	12 (27%)	7 (26%)	2 (22%)	3 (33%)	2 (2%)	0 (0%)
	Multiple or Other	1 (2%)	1 (4%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)
Sex	Female	19 (42%)	10 (37%)	7 (78%)	2 (22%)	19 (18%)	3 (27%)
	Male	26 (58%)	17 (63%)	2 (22%)	7 (78%)	86 (82%)	8 (73%)

Models describing data (Figure 22) were as follows;

- Lonapegsomatropin; a one-compartment model with parallel first- and zero-order absorption. Serum clearance was described with a nonlinear elimination process.
- hGH: a one-compartmental model with first-order absorption and linear clearance.
- PK/PD: effect of hGH on IGF-1 with an Emax model with hGH stimulating the IGF-1 production.





Lonapegsomatropin (Source; Figure 3) PK/PD (Source; Figure 4)

Figure 22 Schematic summary of modeling

Clinically relevant covariates (sex, age, body weight, renal function) were investigated. The models were evaluated by the typical measures of goodness-of-fit and model diagnostics.

Table 18 Summary of estimated parameters

Lonapegsomatropin (Source; Table 2, MODHGH002)

Parameter	70 kg		19 kg	
	female	male	female	male
Volume of distribution, *V/F* (L)	7.2		1.3	
Maximal clearance, *Vm* (ng/day)	7'500'000	6'300'000	1'800'000	1'500'000

hGH (Source; Table 3, MODHGH002)

Parameter	70 kg		19 kg	
	female	male	female	male
Volume of distribution, *V/F* (L)	374		61.8	
Clearance, *Cl/F* (L/day)	690	525	164	125
Maximal effect, *Emax* (ng/mL/day)	361		206	
IGF-1 elimination rate, *kout* (1/day)	0.265		0.503	

Table 19 Covariate effects in the final PK model

Lonapegsomatropin (Source; Table 14, MODHGH002)

Parameter (unit)	Covariate effect
V/F (L)	$(BW/70)^{1.34}$
	$(DOSE/0.24)^{-1.46}$
Vm (ng/day)	$(BW/70)^{1.11}$
	1 (if female)
	0.85 (if male)

hGH (Source; Table 19, MODHGH002)

Parameter (unit)	Covariate effect
V/F (L)	$(BW/70)^{1.38}$
Cl/F (L/day)	$(BW/70)^{1.1}$
	$(DOSE/0.24)^{-0.767}$
	1 (if female)
	0.76 (if male)

PK/PD (Source; Table 20, MODHGH002)

Parameter (unit)	Covariate effect
kout (1/day)	$(BW/70)^{-0.492}$
Emax (ng/mL/day)	$(BW/70)^{0.432}$

Results

- PK and PK/PD models described reasonably well for observed data, and characterized the effects of covariates (Figure 23)
- Simulation provided reasonable supporting information for a missed dose scenario (Figure 24).

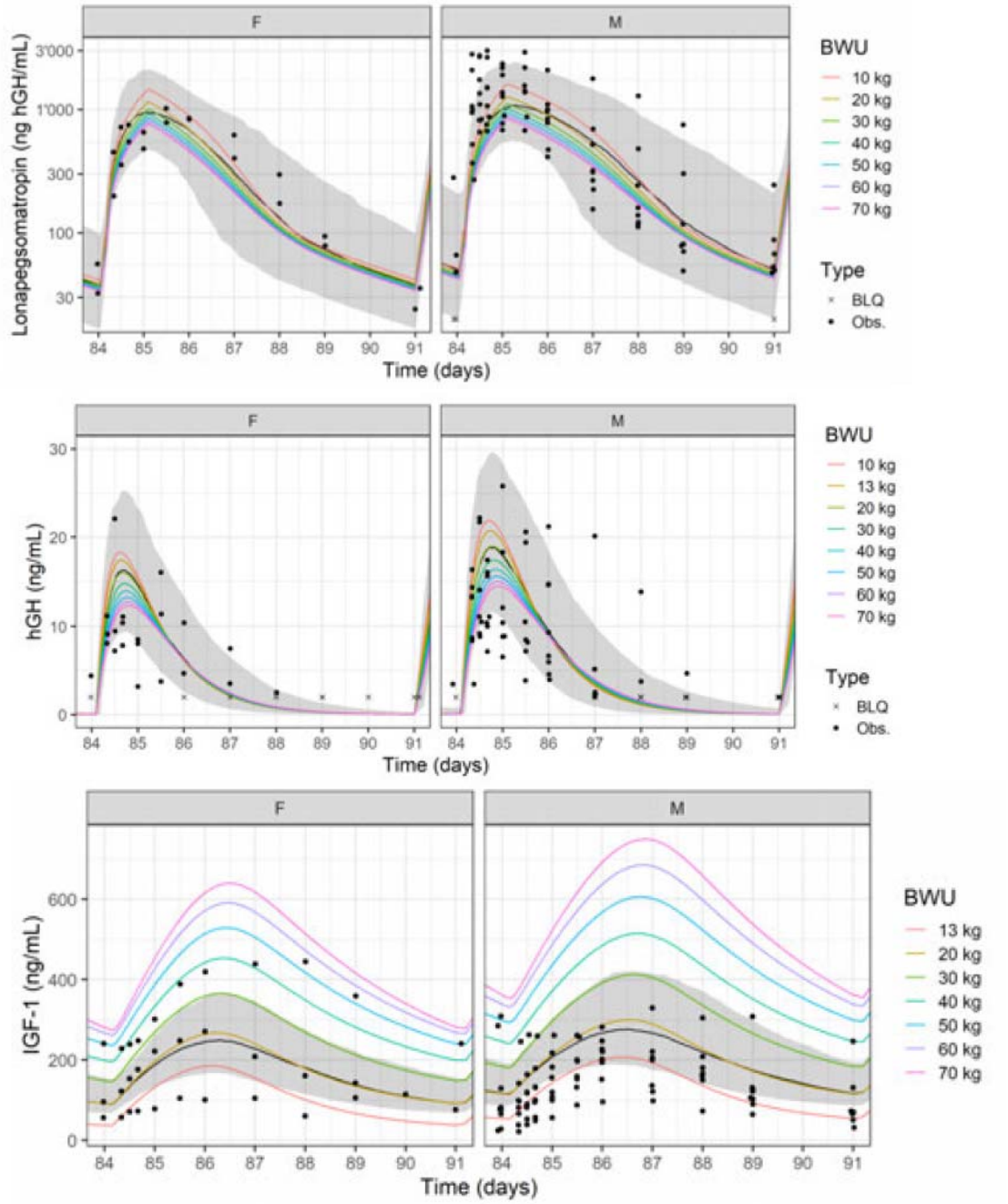


Figure 23 Effect of sex and body weight on week-13 lonapegsomatropin (upper), rGH (middle) and IGF-1 (lower) concentrations following 0.24 mg hGH/kg/week. Median, 5th and 95th percentiles from 500 simulated profiles.
(Source: Figure 53, 87 and 91 for lonapegsomatropin, hGH and mPEG, respectively, MODHGH002)

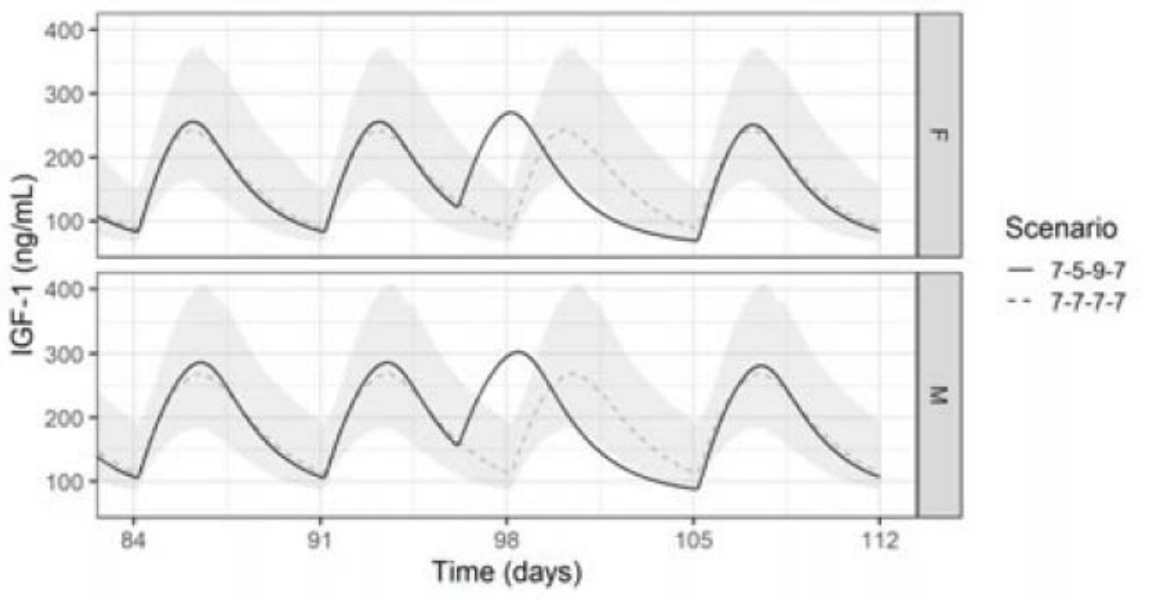


Figure 24 Simulation for the effect of a missed dosing scenario on PD; Predicted IGF-1 concentration profiles at steady state with missed dosing scenario; weekly (7-7-7-7) versus 7 days-5 days-9 days-7 days (7-5-9-7) for a dose of 0.24 mg hGH/kg.
(Black lines: Predictions for typical individuals. Grey: Median (dashed) and 5th to 95th percentile (area) from 500 simulated profiles. BW = 19 kg for all simulated individuals.)
(Source; Figure 95)

Reviewer's Comment: *The applicant's population PK, and PK/PD models generally appear acceptable for characterizing covariate effects and PD (IGF-1). However, the absorption kinetics of hGH and mPEG was confounded by lonapegsomatropin absorption and release kinetics of hGH and mPEG from lonapegsomatropin. Therefore, it should be interpreted and applied with caution.*

- **Final parameter estimates for PK and PK/PD models**

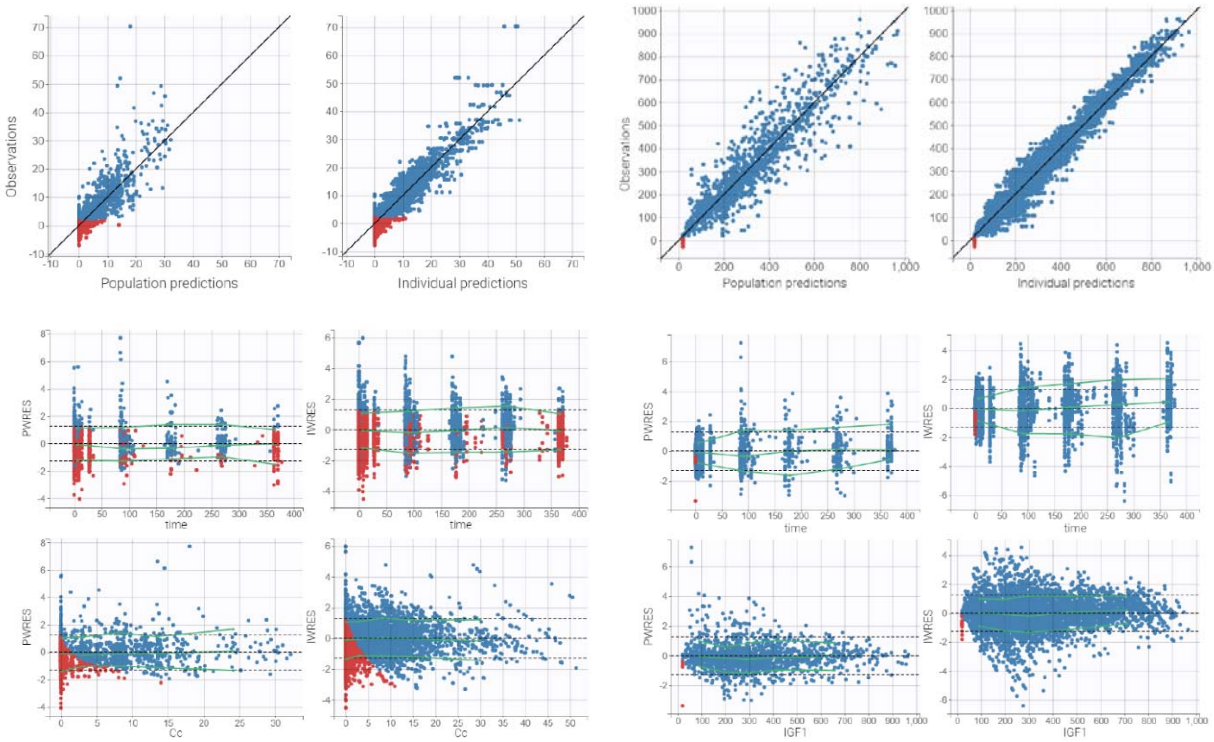


Figure 25 Standard goodness of fit diagnostics; DV vs PRED or iPRED for hGH (upper, left) and IGF-1 (top, right), PWRES or IWRES vs TIME for hGH (lower, left) and IGF-1 (lower, right).

Green lines: empirical 10th, 50th and 90th percentiles. Dashed lines: predicted percentiles.
DV; observation, PRED; population predicted, iPRED; individual predicted, PWRES; population weight residual, IWRES; individual weight
(Source; Figure 60, 62, 64, and 65 MODHGH002)

Table 20 Parameter estimates from the full and final model

lonapegsomatropin (Source; Table 13, MODHGH002)

Description	Parameter (Units)	Estimation (%CV)	RSE (%)	p- value
Fixed effects				
First-order absorption rate	ka (day^{-1})	0.243 (15)	2.9	
Lag-time before first-order absorption	Tlag1 (days)	0.0551 (59)	9.4	
Zero-order absorption duration	Tk0 (days)	0.933 (54)	7.7	
Lag-time before zero-order absorption	Tlag2 (days)	0.175 (17)	3.7	
Fraction of first-order absorption	Fr (-)	0.631 (19*)	3.5	
Apparent volume of distribution	V/F (L)	7.2 (40)	6	
Maximal elimination	Vm (ng/day)	7'500'000 (22)	fixed	
Michaelis-Menten constant	Km (ng/mL)	359 (26)	4.5	
Standard deviations				
First-order absorption rate	ω_{ka}	0.148	15	
Lag-time before first-order absorption	ω_{Tlag1}	0.549	15	
Zero-order absorption duration	ω_{Tk0}	0.503	12	
Lag-time before zero-order absorption	ω_{Tlag2}	0.167	21	
Fraction of first-order absorption	ω_{Fr}	0.58	12	
Apparent volume of distribution	$\omega_{V/F}$	0.387	9	
Maximal elimination	ω_{Vm}	0.216	9.6	
Michaelis-Menten constant	ω_{Km}	0.254	15	
Covariate coefficients				
Dose on V/F	$\beta_{V,tDOSE}$	-1.46	19	7.3e-08
Sex on Vm	$\beta_{Vm,SEX=M}$	-0.167	18	1.7e-08
Body weight on V/F	$\beta_{V,BWT}$	1.34	0.29	<1e-12
Body weight on Vm	$\beta_{Vm,BWT}$	1.11	0.34	<1e-12
Observational error				
Proportional error	b (-)	0.267	2.7	

PK (hGH)/PD (IGF-1) (Source; Table 18, MODHGH002)

Description	Parameter (Units)	Estimation (%CV)	RSE (%)	p-value
Fixed effects				
Absorption rate	ka (day^{-1})	1.08 (27)	6.7	
Apparent volume of distribution	V/F (L)	374 (30)	7.2	
Apparent clearance	Cl/F (L/day)	690 (36)	5.8	
Lag-time before the absorption	Tlag (days)	0.1 (42)	8.5	
Maximal effect	Emax (ng/mL/day)	361 (19)	3.2	
hGH concentration at half-maximal effect	EC50 (ng hGH/mL)	4.52 (0)	0.097	
Hill coefficient	γ (-)	2.5 (125)	23	
IGF-1 elimination rate	kout (day^{-1})	0.265 (26)	3.4	
Standard deviations				
Absorption rate	ω_{ka}	0.268	28	
Apparent volume of distribution	$\omega_{V/F}$	0.292	20	
Apparent clearance	$\omega_{Cl/F}$	0.347	7.8	
Lag-time before the absorption	ω_{Tlag}	0.399	35	
Maximal effect	ω_{Emax}	0.193	9.7	
hGH concentration at half-maximal effect	ω_{EC50}	0.00148	22	
Hill coefficient	ω_{γ}	0.968	20	
IGF-1 elimination rate	ω_{kout}	0.253	10	
Correlations				
Cl-kout correlation	$\omega_{kout,Cl}$	-0.612	14	
Covariate coefficients				
Sex on Cl/F	$\beta_{Cl,SEX=M}$	-0.274	23	1.7e-05
Dose on Cl/F	$\beta_{Cl,tDOSE}$	-0.767	23	2e-05
Body weight on Cl/F	$\beta_{Cl,BWT}$	1.1	3.05*	<1e-12
Body weight on V/F	$\beta_{V,BWT}$	1.38	0.18	<1e-12
Body weight on kout	$\beta_{kout,BWT}$	-0.492	8.34*	<1e-12
Body weight on Emax	$\beta_{Emax,BWT}$	0.432	0.19	<1e-12
Observational error				
Constant PK error	a (ng hGH/mL)	1.72	3.7	
Proportional PK error	b (-)	0.113	8.8	
Constant PD error	a2 (ng IGF-1/mL)	26.3	8.5	
Proportional PD error	b2 (-)	0.027	31	

4.3. Formulation composition of [redacted] solution

Table 21 Composition of drug products in vials and dual chamber cartridge

Description		Phase 2 and Phase 1 Bridging Trial	Phase 1 Bridging Trial	Phase 3 and Phase 1 Bioequivalence Trial[a]	Phase 3, Phase 1 Bioequivalence Trial[b] and Commercial
Clinical Trial No.		CT-004 CT-101	CT-101	CT-102 CT-301 CT-302 CT-301EXT	CT-301EXT CT-101
Active Pharmaceutical Ingredient		ACP-001	Lonapeg-somatropin	Lonapegsomatropin	Lonapegsomatropin
Primary packaging, lyophilized powder		Vial	Vial	Vial	DCC
Strength		[redacted]			
Diluent		Water for Injection			
Primary packaging, diluent		Prefilled syringe	Prefilled syringe	Prefilled syringe	DCC
Composition of [redacted] of the reconstituted solution	Active Pharmaceutical Ingredient (mg hGH)	[redacted]			
	Trehalose dihydrate (mg)				
	Succinic acid (mg)	1.18			
	Tromethamine (mg)	q.s. to pH 5.0			
	Water for Injection	Up to [redacted]			

Source: Table 1, Module 2.7.1, CTD

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