Estimating the Weekly Average IGF-1 from a Single IGF-1 Sample in Children with Growth Hormone Deficiency (GHD) Treated with Lonapegsomatropin

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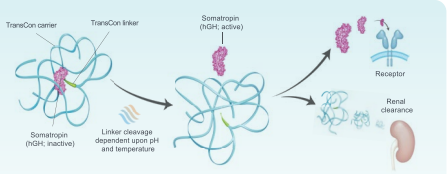
BACKGROUND

- Once-weekly lonapegsomatropin (TransConTM hGH) is an investigational prodrug for growth hormone deficiency (GHD) that consists of 3 components: unmodified somatropin, an inert carrier that protects it, and a linker that temporarily joins the two[1,2] (Figure 1)

Figure 1. TransCon hGH (lonapegsomatropin) Design



Once-weekly prodrug releases unmodified hGH designed to mimic daily hGH:

- Tissue Distribution
- Physiological levels
- Therapeutic effects: efficacy, safety and tolerability

- In 2015, the Growth Hormone Research Society recognized the need for a long-acting growth hormone (LAGH), and agreed that by decreasing injection frequency and offering different pharmacokinetic properties, a LAGH would potentially improve adherence and outcomes[3]
- Since the pharmacodynamic (PD) response of weekly growth hormone preparations, as measured by serum insulin-like growth factor 1 (IGF-1) levels, follows a weekly profile[4,5], it is important to develop tools that enable a single IGF-1 reading to be representative of the overall weekly IGF-1 exposure
- Here, we describe the IGF-1 response to once-weekly lonapegsomatropin in GHD children and provide a model that can predict the weekly average IGF-1 (Standard Deviation Score (SDS) or concentration) based on a single IGF-I sample, which may aid clinicians in assessing patient response to therapy

Phase 2 TransCon hGH Trial Design

- Randomized, open label, active-controlled study
- N = 53 prepubertal treatment-naïve subjects with pediatric GHD (ages 3–12 years)
- Three doses of weekly TransCon hGH1 compared to daily Genotropin, for 26 weeks

0.14 mg hGH/kg/week TransCon hGH

0.21 mg hGH/kg/week TransCon hGH

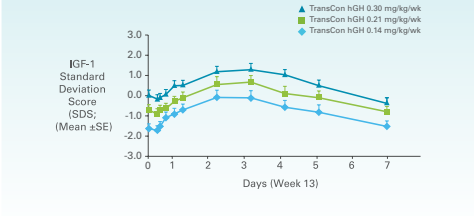
0.30 mg hGH/kg/week TransCon hGH

0.21 mg hGH/kg/week Genotropin

- PK/PD profile assessed at week 13 for TransCon hGH (n=27)

[1]Conducted with a bioequivalent predecessor of lonapegsomatropin

Figure 2. Dose Proportional IGF-1 Response in a Phase 2 Study



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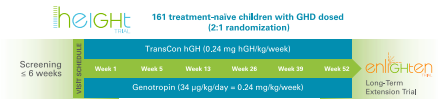
Phase 3 heiGHt Trial



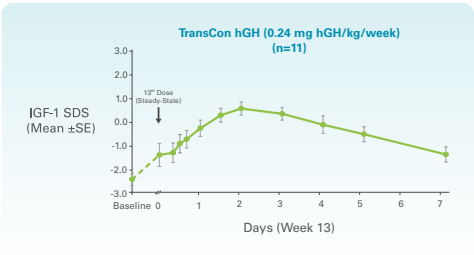
Key Inclusion Criteria

- Prepubertal children with GHD
- Height SDS ≤-2.0
- IGF-1 SDS ≤-1.0
- 2 GH stimulation tests (GH ≤10 ng/mL)
- Bone age ≥6 months behind chronological

Key Endpoints

- Annualized height velocity (AHV) at 52 weeks (primary endpoint)
- AHV at earlier time points
- Change in height SDS over 52 weeks
- Change in serum IGF-1/IGFBP-3 levels
- Change in IGF-1 SDS and IGFBP-3 SDS
- Normalization of IGF-1 SDS
- hGH and IGF-1 levels over 168 hours at Week 13 (PK/PD subset)

Figure 3. IGF-1 Profile at Week 13 (n=11)



Conducted with a bioequivalent predecessor of lonapegsomatropin

METHODS

An Easy-To-Use Average IGF-1 Predictor Based on a Single IGF-1 Sample Drawn at Steady State

- Objective: predict an average weekly IGF-1 at steady state from a single IGF-1 sample drawn at any day of the week

Sampling time since last dose TransCon hGH dose plus:

(A) IGF-1 SDS and/or
(B) IGF-1 concentration

→ Single formula →

Corresponding output:

(A) Average IGF-1 SDS and/or
(B) Average IGF-1 concentration

Note: IGF-1 conversion to Standard Deviation Score (SDS) depends on analytical platform

Population Nonlinear Mixed-effect PD Model for IGF-1

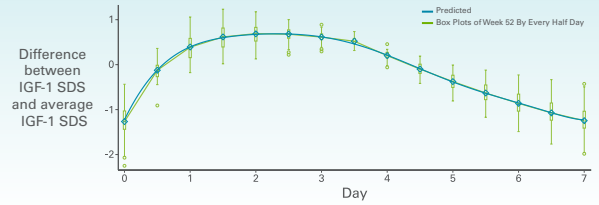
- A mathematical nonlinear model was developed utilizing IGF-1 data from the phase 2 trial and the heiGHt Trial to predict full IGF-1 profiles and support calculation of average weekly IGF-1 concentrations for the 105 lonapegsomatropin-treated subjects from the heiGHt trial
  - An endogenous 1-compartment model with simultaneous zero and first order stimulation of IGF-1 production, first order clearance, and proportional error was selected as the final model
  - Separate linear regressions were utilized to bridge baseline (pre-dose) IGF-1 data before and after steady state
  - Standard covariates were tested, e.g. age, weight, height, sex, and ethnicity. No significant covariates were identified as model parameters
- A nonparametric bootstrap approach was employed to verify that the final model adequately predicted both the central tendency and variability of the observed data

Statistical Analysis to Predict Average IGF-1 From a Single Sample of IGF-1

- Full weekly IGF-1 concentration profiles were simulated hourly for all 105 lonapegsomatropin-treated subjects of the heiGHt Trial from time 0.0 to 7.0 days based on sparse sampling concentration data collected at Weeks 13, 26, 39 and 52.
- A non-compartmental analysis (NCA) on the simulated profiles was used to calculate area under the effect curve of IGF-1 concentration from 0 to 7 days ($AUEC_{0\text{-}7\ days}$)
  - The average weekly IGF-1 concentration was calculated as $AUEC_{0\text{-}7\ days}/7$. This average IGF-1 concentration was then converted into an average IGF-1 SDS value using the age and gender specific reference intervals
- The simulated IGF-1 data for the phase 3 trial in pediatric GHD were statistically analyzed to predict average IGF-1 from a single sample of IGF-1 at any time during the weekly dose interval at Steady state
  - A linear mixed model with Taylor series expansion was established to describe the IGF-1 weekly profile of Δ(d), i.e. the difference between a single IGF-1 sample at "d" days after dosing and the weekly average IGF-1
  - This method was applied successfully for both IGF-1 SDS and IGF-1 concentration with log transformation
- Simple prediction of average weekly IGF-1 from a single sample was established for both the SDS and the concentration units

RESULTS

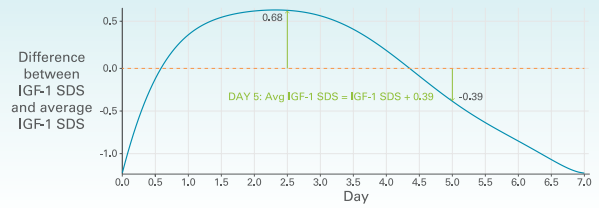
Figure 4. Comparing Δ(d) of IGF-1 SDS From The Mixed Model With Taylor Series, And From Boxplots of Simulation From The Population PD Model at Week 52



The mixed model with the Taylor series function fit the simulated profiles very well, illustrated by comparing the simulated IGF-1 SDS values (green boxplots) at week 52 with the model-predicted value (blue line)

- The Taylor series model provides a simple and smooth formula for the calculation of Δ(d) at any time during a 7-day dosing week

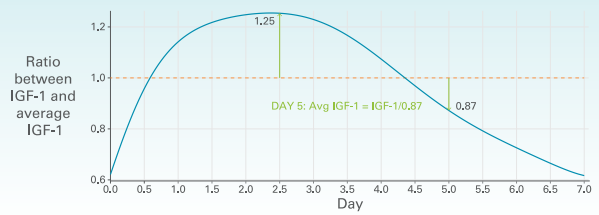
Figure 5. Average IGF-1 SDS From an IGF-1 Sample at Steady State: Results From a Linear Mixed Model With Taylor Series



To predict an average IGF-1 SDS using IGF-1 SDS reading at a time since last dose:

- For an IGF-1 sample drawn 2.5 days post-dose, subtract the measured value by 0.68
- For an IGF-1 sample drawn 5 days post-dose, add the measured value by 0.39

Figure 6. Average IGF-1 Concentration From an IGF-1 Sample at Steady State: Results From a Linear Mixed Model With Taylor Series



To predict the average IGF-1 concentration using IGF-1 reading at a time since last dose:

- For an IGF-1 sample drawn 2.5 days post-dose, divide the sample concentration by the ratio of 1.25
- For an IGF-1 sample drawn 5 days post-dose, divide the sample concentration by the ratio of 0.87

CONCLUSIONS

- A simple linear mixed model was established to predict weekly average IGF-1 for children with GHD on lonapegsomatropin based on a single sample at steady state using either IGF-1 SDS or concentration data
- This prediction has good accuracy from a single sample of IGF-1 anytime during the weekly dosing interval, with lowest estimation errors between days 2.5 and 5
- The sampling time coincident with weekly average IGF-1 is around 4.5 days after dosing
- This analysis creates a single linear function explaining the entire IGF-1 weekly profile of subjects treated with lonapegsomatropin at steady state, instead of relying on a unique formula at each timepoint

REFERENCES:

1. Sprogøe K et al. *Endocr Connect*, 2017;6(8):R171-R181. 2. Chatelain P et al. *J Clin Endocrinol Metab*, 2017;102(5):1673-1682. 3. Christiansen JS, Backeljauw PF, Bidlingmaier M, Biller BM, Boguszewski MC, Casanueva FF, Chanson P, Chatelain P, Choong CS, Clemmons DR, Cohen LE, Cohen P, Frystyk J, Grimberg A, Hasegawa Y, Haymond MW, Ho K, Hoffman AR, Holly JM, Horikawa R, Hoybye C, Jorgensen JO, Johannsson G, Juul A, Katznelson L, Kopchick JJ, Lee KO, Lee KW, Luo X, Melmed S, Miller BS, Misra M, Popovic V, Rosenfeld RG, Ross J, Ross RJ, Saenger P, Strasburger CJ, Thorner MO, Werner H, Yuen K. Growth Hormone Research Society perspective on the development of long-acting growth hormone preparations. *Eur J Endocrinol*. 2016;174(6):C1-8. 4. Fisher DM, Rosenfeld RG, Jaron-Mendelson M, Amitzi L, Koren R, Hart G. Pharmacokinetic and Pharmacodynamic Modeling of MOD-4023, a Long-Acting Human Growth Hormone, in Growth Hormone Deficiency Children. *Horm Res Paediatr*. 2017;87(5):324-332. 5. Juul Kildemoes R, Hojby Rasmussen M, Agersø H, Overgaard RV. Optimal Monitoring of Weekly IGF-I Levels During Growth Hormone Therapy With Once-Weekly Somapacitan. *J Clin Endocrinol Metab*. 2021;106(2):567-576.

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