Design and Rationale for the heiGHt Trial, a Phase 3 TransCon hGH Study in Children with Growth Hormone Deficiency

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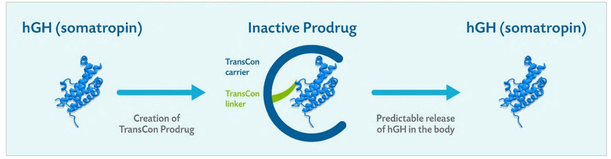
Background

TransCon Growth Hormone (hGH) is a novel sustained-release recombinant human GH (somatropin) prodrug in development for children with growth hormone deficiency (GHD) intended to provide comparable efficacy, safety, tolerability, and immunogenicity to daily hGH with once-weekly dosing.



Objective

Based on results from a Phase 2 trial, which demonstrated comparable safety, efficacy, immunogenicity, and tolerability of once-weekly TransCon hGH to daily hGH therapy in children with GHD, a Phase 3 trial has been initiated.

TransCon Growth Hormone Target Product Profile

- ✓ Efficacy
- ✓ Safety (including immunogenicity)
- ✓ Tolerability

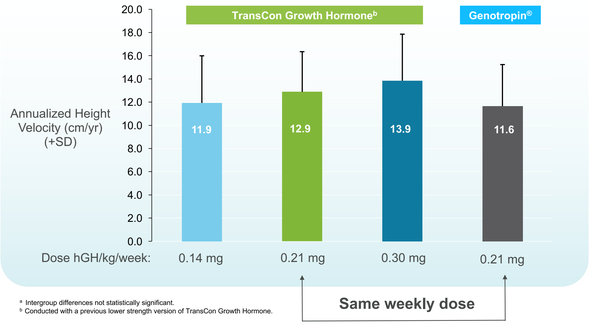
= **Comparable to Daily Human Growth Hormone**

- ✓ Weekly subcutaneous administration
- ✓ Single injection/dose
- ✓ Convenience
  - ✓ 31G needle
  - ✓ Room temperature storage
- ✓ Device
  - ✓ Easy to use
  - ✓ Empty-all design (controlled substance)

Phase 2 Trial Results

The Phase 2 pediatric trial was designed to compare the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of three TransCon hGH doses to that of commercially available daily hGH in prepubertal children with GHD.[1]

Growth Comparable to Daily hGH in Phase 2 Trial[a]



[a] Intergroup differences not statistically significant.
[b] Conducted with a previous lower strength version of TransCon Growth Hormone.

No Serious Adverse Events (SAEs) related to trial drug
- Adverse events consistent with daily hGH therapy observed and not different between cohorts

Immunogenic profile comparable to daily hGH
- Favorable immunogenic profile comparable to daily hGH
- No occurrence of neutralizing antibodies

Injection site tolerability comparable to daily hGH
- >1100 TransCon Growth Hormone injections administered in the Phase 2 pediatric trial
- No reports of lipoatrophy or nodule formation

The results suggest that long-acting TransCon hGH was comparable to daily Genotropin for PK, PD, safety, and efficacy, and supported advancement into Phase 3 development.

Phase 3 heiGHt Trial Design

A global Phase 3 randomized open-label active-controlled parallel-group trial has been initiated to investigate the safety, tolerability, and efficacy of weekly TransCon hGH versus standard daily hGH over 52 weeks in prepubertal children with GHD. Approximately 100 sites in 20 countries in North America, Europe, the Middle East, North Africa, and Oceania have been selected with plans to enroll approximately 150 treatment-naïve prepubertal children with GHD.

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

Subjects will be randomized in a 2:1 ratio and receive either once-weekly TransCon hGH 0.24 mg/kg/week or dose equivalent once-daily somatropin for 52 weeks.

Key Endpoints
- Annualized height velocity (HV) at 52 weeks (primary endpoint)
- Annualized HV at earlier time points
- Change in height SDS over 52 weeks
- Change in serum IGF-1 and IGFBP-3* levels
- Change in IGF-1 SDS and IGFBP-3 SDS
- Normalization of IGF-1 SDS

*insulin-like growth factor-binding protein 3

Auto-injector for commercialization in Extension Trial

Key Device Features
- Easy to operate with few user steps
- Weekly, single low-volume injections (<0.6 mL)
- Small needle (31G, 4mm)
- Room temperature storage
- No waste (empty-all design)
- Reusable, with a 4-year lifespan
- Bluetooth®-enabled

Comments

The Phase 2 trial demonstrated safety and efficacy of TransCon hGH 0.14, 0.21, and 0.30 mg/kg/week. In the Phase 3 trial, TransCon hGH 0.24 mg/kg/week will be used to accommodate global dosing practices. The length of the trial is 12 months to qualify as a pivotal trial. Following completion of the trial, subjects will be invited to participate in an extension trial to evaluate long-term safety and efficacy. During the extension trial, subjects will be switched from TransCon hGH in vials to an auto-injector.

heiGHt TRIAL

References:
1: JCEM 2017 Feb 14. doi: 10.1210/jc.2016-3776. [Epub ahead of print]