Design and Clinical Development of TransCon Growth Hormone for Growth Hormone Deficiency

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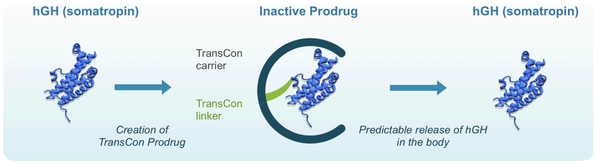
This study was sponsored by Ascendis Pharma A/S.

Background

TransCon Growth Hormone is designed as a once-weekly sustained-release prodrug of recombinant human growth hormone (hGH, somatropin). In its prodrug form, hGH is transiently bound to the TransCon carrier via the TransCon linker. Through auto-hydrolysis, unmodified native hGH is released with a C_{max} and AUC comparable to daily therapy. TransCon Growth Hormone leverages the known pharmacology of daily hGH and is being developed for the treatment of Growth Hormone Deficiency (GHD) in children and adults.



The TransCon hGH prodrug consists of hGH transiently bound to a polyethylene glycol carrier via a TransCon linker. Released hGH is unmodified and designed to maintain the same mode of action and distribution in the body as endogenous hGH.

TransCon hGH, stored at room temperature, can be administered in small volumes with a fine (31G) needle at comparable weekly dose-levels to daily hGH.

Objectives

Leveraging the safety, efficacy, tolerability and immunogenicity of daily hGH dosing established over decades, the objectives were to develop a safe and efficacious sustained-release hGH resulting in both hGH and IGF-1 serum concentrations within therapeutic range.

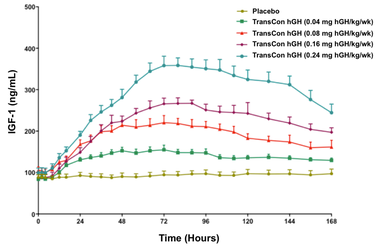
Methods

TransCon Growth Hormone was investigated in two Phase 1 studies of healthy volunteers and two Phase 2 studies in adults and children with GHD. Dose-equivalent daily hGH was included in most of the studies to compare hGH-levels, IGF-1 levels, and height velocity.

Results – Two Phase 1 Studies

Healthy adults (n=68) were included in two Phase 1 single-dose pharmacokinetic (PK) and pharmacodynamics (PD) studies investigating TransCon hGH (0.04 mg to 0.36 mg hGH/kg/week).

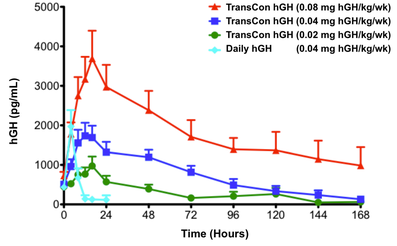
TransCon hGH:
- Was safe and well tolerated,
- Suitable for a once-weekly dosing regimen,
- Provided a hGH (PK) and IGF-1 (PD) response comparable to daily hGH throughout the dosing period.



PD profile of mean plasma IGF-1 levels during the initial 7 days following a single SC dose of TransCon hGH in a Phase 1 study with 44 Healthy Volunteers (M. Beckert et al., ENDO 2010, San Diego; NCT01010425).

Results - Phase 2 Adult GHD Study

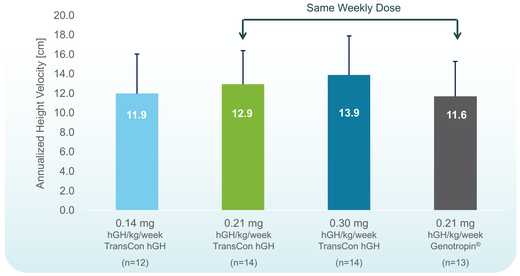
In a Phase 2 study of subjects with Adult Growth Hormone Deficiency (AGHD) (n=37) administered repeat dosings, TransCon hGH demonstrated dose-linearity over a range of 0.02 to 0.08 mg hGH/kg/week and comparable efficacy (IGF-1) to the dose-equivalent daily hGH control group (0.04 mg hGH/kg/week).



PK profile of hGH levels for TransCon hGH and daily hGH at Week 4 in a Phase 2 AGHD study with 37 subjects[1] (NCT01247675).

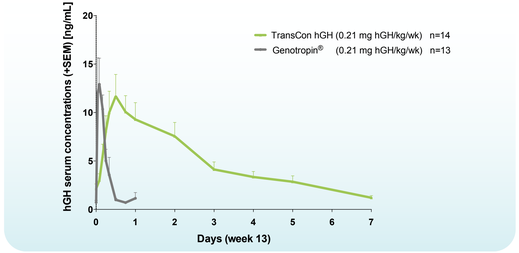
Results – Phase 2 Pediatric GHD Study

A Phase 2 study of pediatric patients with GHD (n=53) confirmed the safety, tolerability, and suitability of TransCon hGH for once-weekly dosing. A TransCon hGH equivalent dose to daily hGH demonstrated slightly higher growth rates.



Annualized Height Velocity (Mean + SD) of 53 patients after 6 months of treatment.

Maximum hGH blood concentration was also comparable between equivalent weekly doses of TransCon hGH and daily hGH.



hGH levels for TransCon hGH (0.21 mg hGH/kg/week) and daily hGH (0.21 mg hGH/kg/week) at Week 13.

Results – Phase 2 Pediatric GHD Study

No drug-related SAEs occurred, and no lipoatrophy, nodule formation, or anti-hGH neutralizing antibodies were seen. IGF-1 changes suggest a dose-response, and levels were in the expected range[2] (NCT01947907).

Phase 3 Pediatric GHD Study Initiated

A randomized, open-label, active-controlled Phase 3 trial investigating the safety, tolerability, and efficacy of TransCon hGH as compared to standard daily growth hormone over 52 weeks in prepubertal children with GHD has been initiated (NCT02781727).

Conclusion

To date, TransCon Growth Hormone has demonstrated efficacy and safety comparable to that observed with daily hGH:

- Injection site reactions were generally mild and similar to daily hGH injections, with no nodule formation or lipoatrophy noted.
- No neutralizing anti-hGH antibodies occurred.
- TransCon hGH was shown to be dose-linear across different dose-levels (hGH and IGF-1).
- TransCon hGH demonstrated the same therapeutic effect (annualized height velocity) to daily hGH at the same weekly dose-level (pediatric GHD study; 0.21 mg hGH/kg/week).
- TransCon hGH can be administered in small volumes with a fine (31G) needle at comparable weekly dose-levels to daily hGH.
- The completed Phase 1 and 2 studies supported the initiation of the heiGHt Trial – a Phase 3 study in pediatric GHD.

heiGHt TRIAL

References:
1. Endocr Connect. 2017 Apr;6(3):129-138. doi: 10.1530/EC-17-0007
2. J Clin Endocrinol Metab 2017 Feb 14. doi: 10.1210/jc.2016-3776. [Epub ahead of print]