A Six-Month Safety and Efficacy Study of TransCon hGH Compared to Daily hGH in Prepubertal Children with Growth Hormone Deficiency (GHD)

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Background

TransCon hGH is a once-weekly sustained-release prodrug of recombinant human Growth Hormone (hGH) that releases unmodified native hGH into the blood compartment (Figure 1). In Phase 1 Healthy Volunteer and Phase 2 AGHD studies TransCon hGH was shown to:

1) Be safe and well tolerated,
2) Be suitable for a once-weekly dosing regimen,
3) Provide a pharmacokinetic (PK) hGH and pharmacodynamic (PD) IGF-1 response comparable to daily hGH treatment throughout the dosing period.

This pediatric Phase 2 clinical study was designed to investigate the safety, efficacy, pharmacokinetics and pharmacodynamics of TransCon hGH compared to daily hGH over a treatment period of six months (NCT01947907).

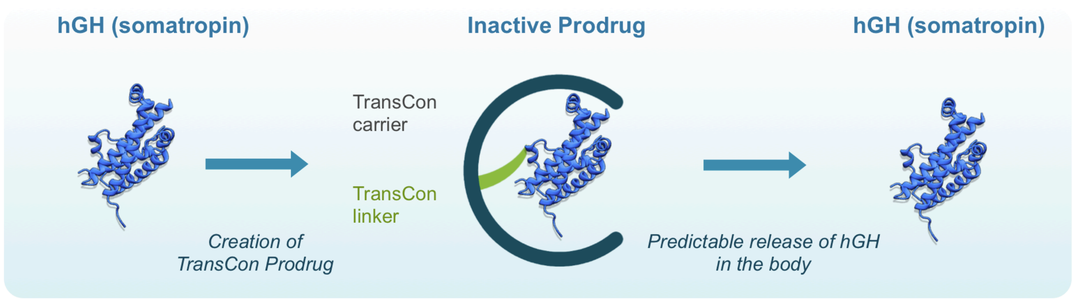

Figure 1: The TransCon hGH prodrug consists of hGH transiently bound to a polyethylene glycol carrier molecule *via* a TransCon linker. The released hGH is unmodified and designed to maintain the same mode of action and distribution in the body as endogenous hGH.

Objectives

The objective of this study was to investigate

1) Safety and Tolerability,
2) Pharmacokinetics and Pharmacodynamics, and
3) Efficacy of TransCon hGH

in children with Growth Hormone Deficiency (GHD).

Design and Methods

Prepubertal, treatment naïve GHD children received s.c. injections of one of three once-weekly TransCon hGH doses (0.14, 0.21 and 0.30 mg hGH/kg/week) or daily hGH (Genotropin®; 0.03 mg hGH/kg/day = 0.21 mg hGH/kg/week) over a six-month treatment period, in a randomized, comparator-controlled dose response Phase 2 study. The patient GHD diagnoses were established in accordance with international consensus guidelines, based on auxology (height and height velocity), GH stimulation tests and IGF-1. Children with Small for Gestational Age (SGA), SHOX gene defect and other genetic growth disorders were excluded.

Baseline Data

Mean + SD	All subjects	0.14 mg hGH/ kg/week TransCon hGH	0.21 mg hGH/ kg/week TransCon hGH	0.30 mg hGH/ kg/week TransCon hGH	0.03 mg hGH/ kg/day Genotropin®
# Subjects	53	12	14	14	13
Age (years) Baseline	8.0 (2.5)	8.2 (2.9)	8.4 (2.1)	7.5 (2.8)	7.7 (2.5)
Height SDS	-3.1 (0.9)	-3.1 (1.1)	-2.8 (0.4)	-3.2 (1.0)	-3.3 (1.1)
GH Stimulation Test * [ng/mL] (Screening)	5.0 (2.8)	5.1 (3.2)	5.2 (2.6)	4.4 (2.8)	5.2 (3.1)
IGF-1 SDS	-2.2 (0.8)	-2.0 (0.7)	-2.0 (0.8)	-2.2 (0.7)	-2.5 (0.9)

* The higher peak of the two performed GH stimulation tests was used for calculation of the mean.

Results - Safety

Injection site reactions were generally mild and similar to what is expected with daily hGH injections, with no nodule formation or lipoatrophy noted.

A treatment-emergent anti-hGH immune response was detected in one subject (0.14 mg hGH/kg/week TransCon hGH), which was confirmed to be non-neutralizing. The presence of anti-hGH antibodies was shown not to impact the subject's pharmacokinetic (TransCon hGH and hGH) or pharmacodynamic (IGF-1) profiles and the subject demonstrated an annualized height velocity of 19.0 cm. Therefore TransCon hGH is considered to have an anti-hGH immunogenic profile comparable to that of daily hGH.

Results - Growth

Annualized height velocities among the three once-weekly TransCon hGH doses ranged from 11.9 cm for the 0.14 mg hGH/kg/week dose to 13.9 cm for the 0.30 mg hGH/kg/week dose, which were comparable to 11.6 cm for the active comparator, daily injections of Genotropin® at a cumulated dose of 0.21 mg hGH/kg/week (Figure 2). Change in height (HT) SDS among the three once-weekly TransCon hGH doses ranged from 0.7 for the 0.14 mg hGH/kg/week dose to 0.9 for the 0.30 mg hGH/kg/week dose, which were comparable to 0.6 for the active comparator, daily injections of Genotropin® (Figure 3).

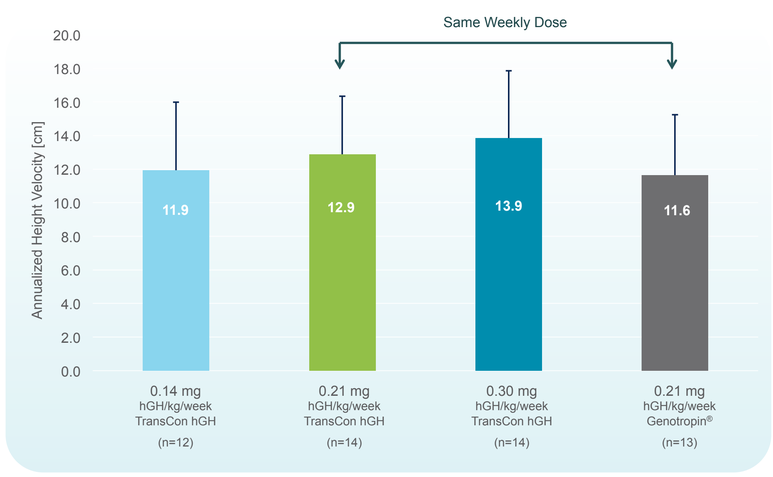

Figure 2: Annualized Height Velocity (Mean + SD) of full dataset of 53 patients after 6 months of treatment.

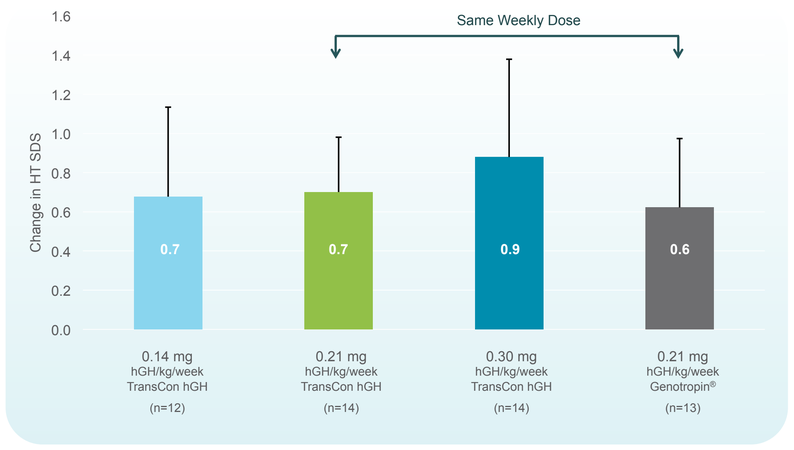

Figure 3: Change in HT SDS (Mean + SD) of full dataset of 53 patients from baseline to 6 months.

Results - PK/PD

A full PK/PD profile was established in Week 13. Maximum hGH blood concentration was comparable between equivalent weekly doses of TransCon Growth Hormone and daily hGH (Figure 4). IGF-1 levels (SDS) increased dose-proportionally and were normalized for all dose groups (Figure 5) following dosing of the three TransCon Growth Hormone dose levels.

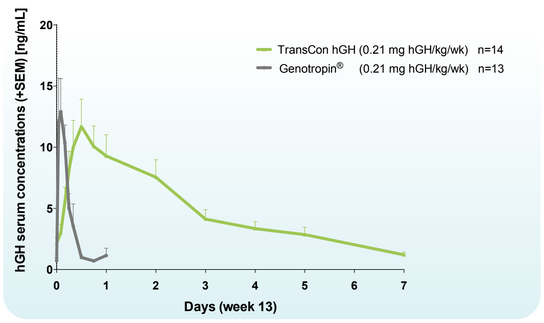

Figure 4: hGH levels for TransCon hGH (0.21 mg hGH/kg/week) and daily hGH (0.21 mg hGH/kg/week).

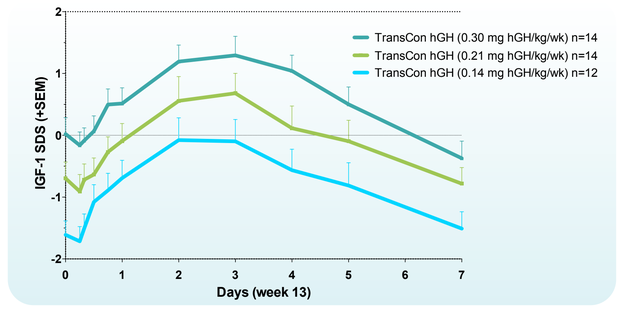

Figure 5: IGF-1 SDS levels increased dose-proportionally and were normalized for all dosing groups following dosing of the three TransCon hGH dose levels.

Conclusion

The results of this Phase 2 study in pediatric patients with GHD confirmed the safety, tolerability and the suitability of TransCon hGH for once-weekly dosing. An equivalent dose-level to daily hGH demonstrated slightly numerically higher growth rates compared to daily hGH treatment. No drug-related SAEs occurred, no lipoatrophy, nodule formation or anti-hGH neutralizing antibodies were seen. Changes in IGF-1 suggest a dose response and levels were in the expected range. Hence, this TransCon hGH Phase 2 study supports Phase 3 development.

Disclosure Statement: Authors marked 1, 2, 3 and 4 above are investigators of the study. Author marked 5 is employee and shareholder of Ascendis Pharma.

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