Baseline Demographics of the TransCon Growth Hormone Phase 3 heiGHt Trial

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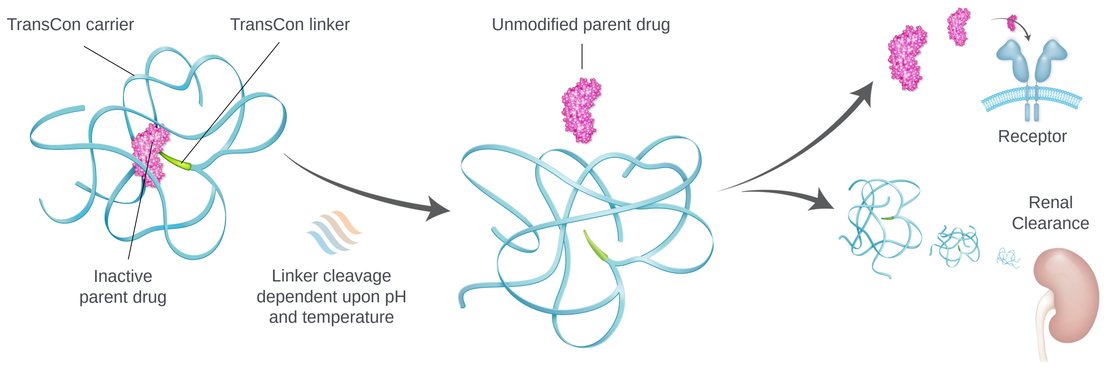
BACKGROUND

TransCon Growth Hormone (GH) is a sustained-release recombinant human GH (hGH; somatropin) prodrug in development for children with growth hormone deficiency (GHD). In its prodrug form, GH is inactive and transiently bound to the TransCon carrier via the TransCon linker. Upon injection and via autohydrolysis of the linker, unmodified GH is sustainably released at physiological pH and temperature and is thus designed to maintain the same mode-of-action and distribution as daily GH replacement therapy but with once-weekly dosing.



In a 6-month phase 2 trial of TransCon GH vs. a daily GH in children with GHD, mean annualized height velocity (HV) for TransCon GH was 12.9 cm/y compared to 11.6 cm/y for a daily GH at an equivalent GH dose (0.21 mg/kg/wk).[1] First year HV is strongly influenced by 'catch-up' growth in the initial 6 months, the effect of which wanes over time. This difference leads to a lower annualized HV in 12-month trials compared to 6-month trials.

Given the goal of optimizing outcomes of GH replacement therapy, Ranke et al developed a model for prepubertal, treatment-naïve children with GHD that provides a mathematical relationship between certain baseline demographic variables and growth response to daily GH.[2] Specifically, age and peak GH response have the most influence on outcomes, with older age and higher peak GH response correlating with less growth. The objective of this analysis was to assess the influence of baseline demographics on the outcome of the 12-month phase 3 TransCon GH heiGHt Trial.

METHODS

The ongoing randomized phase 3 global heiGHt Trial was designed to investigate the efficacy, safety, and tolerability of TransCon GH versus daily GH over 12 months in 150 treatment-naïve prepubertal children with GHD. Participants were randomized in a 2:1 ratio and received either once-weekly TransCon GH 0.24 mg GH/kg/wk or dose-equivalent of a daily GH. Key baseline demographic variables included age, gender, bone age, peak GH response to provocation, height, and insulin-like growth factor-1 (IGF-1). The primary endpoint is annualized HV.

We compared demographic data from the heiGHt Trial and the daily GH cohorts of other recent 12-month phase 3 pediatric GHD registration studies and predicted mean HV using a formula based on the Ranke model (where x is the daily GH cohort of each referenced study):[2-8]

$$HV_{HeiGHt} = HV_x - 1.37*\ln(\text{peak GH}_{HeiGHt}/\text{peak GH}_x) - 0.32*(Age_{HeiGHt} - Age_x) + 1.62*\ln(Dose_{HeiGHt}/Dose_x)$$

A power calculation was also conducted based on the final sample size of the heiGHt Trial.

RESULTS

The heiGHt Trial population has a generally similar demographic profile to all 4 daily GH cohorts from the 3 phase 3 pediatric GHD trials identified; mean age and mean peak GH test results in the heiGHt Trial are both in the range of these trials. The HV prediction for the heiGHt Trial daily arm was calculated based on the HV from the 4 daily GH cohorts corrected for differences in demographics (age, peak GH response, and daily GH dose) between the heiGHt Trial and the daily GH cohorts using the Ranke model; the range of the 4 mean HV predictions was 10.3 to 10.7 cm/y (assuming, due to randomization, similar demographic profiles between the TransCon GH and the daily GH cohort).

Demographic data from the *daily* GH arm of 12-month phase 3 pediatric GHD trials

Sponsor	Versartis	LG Life Sciences	Biopartners		**Ascendis Pharma**
Daily GH cohort	Genotropin	Genotropin	Valtropin	Humatrope	**Genotropin**
Dose of daily GH	0.034 mg/kg/d (0.24 mg/kg/wk)	0.030 mg/kg/d (0.21 mg/kg/wk)	0.030 mg/kg/d (0.21 mg/kg/wk)	0.030 mg/kg/d (0.21 mg/kg/wk)	**0.034 mg/kg/d (0.24 mg/kg/wk)**
Subjects	32	87	98	49	**161[e]**
Mean age, yr	7.03	7.80	8.10	8.50	**8.50**
Gender, male %	68.7	63.2	70.4	61.2	**82.0**
Mean bone age, yr	5.29	4.29[a]	5.14	5.50	**5.87**
Mean bone age delay, yr	1.74	3.51	2.96	3.00	**2.63**
Mean peak GH, µg/L	5.87	1.98	3.60[b]	4.90[b]	**5.77**
Mean height SDS	-2.64	-4.36	-3.53[c]	-3.24[d]	**-2.93**
Mean IGF-1 SDS	-1.87	-4.30	NA	NA	**-2.04**
Annualized HV, cm/yr (observed in daily cohort)	10.7	12.0	11.3	10.5	
Model predicted annualized HV of Genotropin arm in heiGHt Trial					**10.3-10.7**

Abbreviations: NA, not available. [a]Derived from BA/CA. [b]Clonidine test only. [c]Average based on -3.54 (n=88) and -3.52 (n=99). [d]Based on n=50. [e]Total study N used because of blinding.

The baseline demographic variables are expected to be similar for both treatment groups of the heiGHt Trial and therefore should have no meaningful impact on statistical power. The final sample size for the heiGHt Trial (n=161) is larger than planned (n=150), which strengthens the study power for noninferiority. The following table compares the power of the heiGHt Trial under various assumptions related to the difference in HV between TransCon GH and daily GH.

heiGHt Trial Power Under Various Assumptions (n=161)

TransCon GH treatment effect compared to daily GH (cm/y)	-0.5	0	0.5
Power	**73%**	**93%**	**99%**

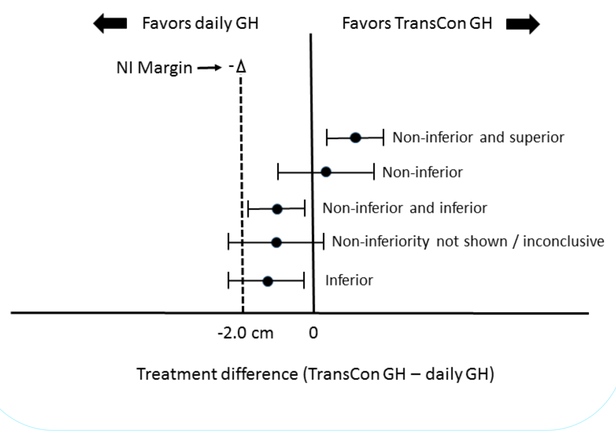
For reference, in the 6-month phase 2 trial, the observed difference in mean annualized HV between TransCon GH and a daily GH was 1.3 cm/y.

LIMITATIONS

The Ranke model was developed based on the KIGS population, which may differ from the heiGHt Trial and the other studies included here. Due to data unreported in different studies, we only included age, peak GH response, and daily GH dose in making the predictions. Further, study results may be reported differently leading to different interpretations. For example, some studies aggregate results from different peak GH stimulation tests while others do not.

STATISTICAL BACKGROUND

A figure has been adapted to illustrate the possible outcomes of a noninferiority trial in terms of annualized HV between the study drug (TransCon GH) and the control (daily GH) based on a prespecified noninferiority (NI) margin and confidence intervals (CI):[9,10] Given a noninferiority margin of 2.0 cm/y, when the lower bound of the 95% CI of the treatment difference is greater than or equal to -2.0 cm/year, a study demonstrates noninferiority, thus meeting its objective. If the lower bound is greater than 0.0 cm/year, then a study demonstrates superiority. If the lower bound is lower than -2.0 cm/y, then a study fails to demonstrate noninferiority.



CONCLUSIONS

The results of the phase 2 TransCon GH trial, which included a daily GH as an active control, informed the phase 3 heiGHt Trial design, allowing the optimization of statistical power. The heiGHt Trial remains extremely well powered to demonstrate noninferiority between TransCon GH and daily GH, and its demographics are in the range of other pivotal GH trials.

REFERENCES:
[1]Chatelain, P., J Clin Endocrinol Metab, 2017. 102(5): p. 1673-1682. [2]Ranke, M.B., J Clin Endocrinol Metab, 1999. 84(4): p. 1174-83. [3]Versartis Inc. *Versartis ENDO 2017*. [4]Versartis Inc., September 21, 2017. [5]Versartis Inc., *Versartis Corporate Presentation*. 2016. [6]Khadilkar, V., J Clin Endocrinol Metab, 2014. 99(1): p. 126-32. [7]Peterkova, V., Horm Res, 2007. 68(6): p. 288-93. [8]CDER Office of Biostatistics, *Application Number: 21-905 Valtropin,* 2006. [9]Mauri, L., N Engl J Med, 2017. 377(14): p. 1357-1367. [10]Schumi, J. and J.T. Wittes, Trials, 2011. 12: p. 106.

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