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) prodiging in development for children with growth hormone deficiency (GHD). In its produg form, hGH 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 hGH 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.

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 once-weekly TransCon GH 0.24 mg GH/week 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 height.

RESULTS

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 GH/week).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.

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 trial).3,4

\[ \text{HV}_{\text{heiGHt}} = \text{HV}_{\text{day}} - 1.37 \times \text{peak GH}_{\text{Genotropin, peak GH}} - 0.32 \times (\text{Age}_{\text{day}} - \text{Age}_{\text{Genotropin}}) + 1.62 \times (\text{Dose}_{\text{Genotropin}} - \text{Dose}_{\text{Day}}) \]

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

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.

<table>
<thead>
<tr>
<th>Power</th>
<th>-0.5</th>
<th>0</th>
<th>0.5</th>
</tr>
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<tbody>
<tr>
<td>73%</td>
<td>93%</td>
<td>99%</td>
<td></td>
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</tbody>
</table>

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 KGS 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 assess results from different peak GH stimulation tests while others do not.

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.

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1 Based on data from Biopartners (Uppsala, Sweden) and Ascendis Pharma A/S, in support of the TransCon GH 0.24 mg/kg/week for growth hormone deficiency phase 3 clinical program.
2 Based on data from Biopharmaceuticals (Koln, Germany) and Ascendis Pharma A/S, in support of the TransCon GH 0.24 mg/kg/week for growth hormone deficiency phase 3 clinical program.
3 Based on data from Biopharmaceuticals (Koln, Germany) and Ascendis Pharma A/S, in support of the TransCon GH 0.24 mg/kg/week for growth hormone deficiency phase 3 clinical program.
4 Based on data from Biopharmaceuticals (Koln, Germany) and Ascendis Pharma A/S, in support of the TransCon GH 0.24 mg/kg/week for growth hormone deficiency phase 3 clinical program.