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-naive children with GHD that provides a mathematical relationship between certain baseline demographic variables and growth response to daily GH. Specifically, age and peak GH response have the most influence on outcomes, with older age and higher peak GH response correlating with lower 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

We compared demographic data from the heiGHt Trial and the daily GH cohorts of other recent 12-month phase 3 pediatric GH 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).2,3

$$HV_{\text{heiGHt}} = HV_{\text{observed}} - 1.37 \times \text{peak GH}_{\text{heiGHt}} \times \text{peak GH}_{\text{GH}} + 0.32 \times (\text{Age}_{\text{observed}} - \text{Age}_{\text{r}}) + 1.62 \times (\text{Dose}_{\text{r}} - \text{Dose}_{\text{heiGHt}})$$

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 GH 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).

We predicted that the peak GH variability in the TransCon GH cohort was lower than that in the daily GH cohort, which may result in a lower overall variability in the predicted HV.

CONCLUSIONS

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>TransCon GH treatment effect compared to daily GH (cm/y)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.5</td>
<td>73%</td>
</tr>
<tr>
<td>0</td>
<td>93%</td>
</tr>
<tr>
<td>0.5</td>
<td>99%</td>
</tr>
</tbody>
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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.

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.

<table>
<thead>
<tr>
<th>Model predicted annualized HV of Genotropin arm in heiGHt Trial</th>
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<tr>
<td>10.3 - 10.7</td>
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Abbreviations: NA, not available. *Dose in mg/kg/wk. **Daily GH only. ***GH/kg/year.