

Design of a Bracketed Dosing Regimen for the Administration of TransCon hGH, a Once Weekly Growth Hormone Product

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Background

Ascendis Pharma is developing TransCon Growth Hormone, a once-weekly sustained-release prodrug of recombinant human growth hormone (hGH, somatotropin) for the treatment of Growth Hormone Deficiency (GHD) in children and adults.

Current treatment of growth hormone disorders involves daily injections of hGH over many years. Patients are typically diagnosed and initiated on treatment in childhood, and adherence is critically important to treatment outcomes.

Therefore, devices for hGH administration must be simple to use and well accepted.

To achieve these goals, we developed the TransCon hGH auto-injector using dual chamber cartridges, supporting room temperature stability. Each cartridge contains a specific mg quantity of TransCon hGH supporting a specific weight range. Literature data from the KIGS database and clinical data with TransCon hGH supported increases between dose brackets of 20%.

TransCon hGH auto-injector's characteristics include:

- Simple operation with few user steps
- Single use, weekly, low-volume injections (<0.6 mL)
- Small needles (31G, 4mm) comparable to daily hGH
- Room temperature storage
- No waste, empty-all design
- Device lifetime 4 years
- Enabled for Bluetooth® connectivity

Design of Brackets

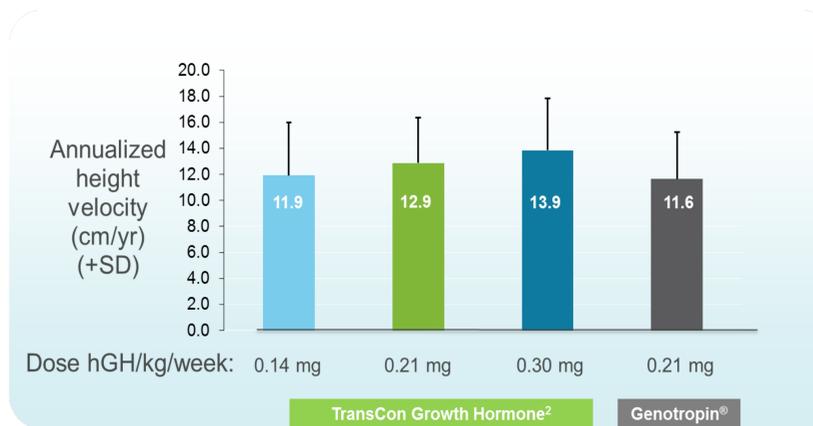
Published formulas, derived from growth outcomes of children with short stature treated with daily hGH, are available to predict height velocity (HV) as a function of hGH dose. Using the KIGS database, Ranke et al. performed multiple regression analysis, developing a formula including a quantification of the effect of daily hGH dose on HV.

$$1.62 \times \text{hGH dose (ln IU/kg/week)}^1$$

The formula predicts annual HV at either extreme of a dose bracket with 20% increments to vary only by ~0.3 cm/year.

Clinical Confirmation

To validate that HV was comparable at the two extremes of a given dosing bracket of TransCon hGH, 6-month annualized HV was obtained from the TransCon hGH Phase 2 trial completed in children with GHD (NCT01947907).



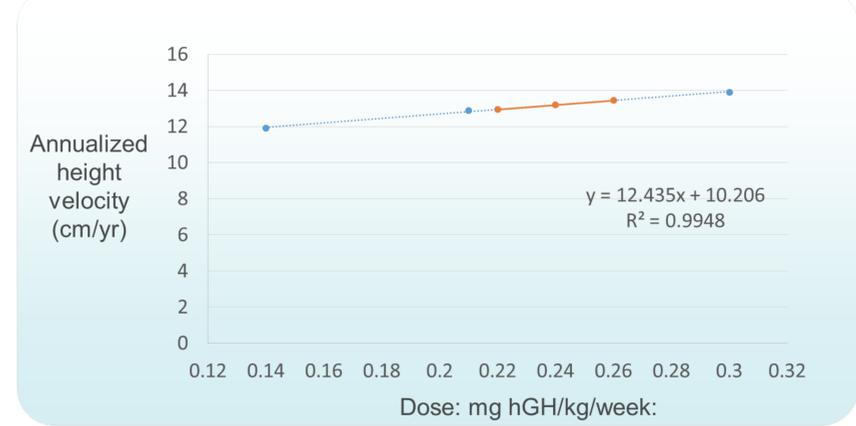
Clinical Confirmation

In this trial, TransCon hGH provided comparable growth to daily hGH and demonstrated a dose-response over the dose range of 0.14 to 0.30 mg/kg/week.²

Based on these Phase 2 results, linear regression was performed to predict annualized HV at the 0.24 mg hGH/kg/week dose used in the TransCon hGH Phase 3 trial (NCT02781727) and either extreme of the bracket dose (0.22 and 0.26 mg/kg/week).

The estimated 6-month annualized HV for the TransCon hGH Phase 3 dose of 0.24 mg/kg/week was 13.2 cm/year. At either extreme of the dose bracket (0.22 and 0.26 mg/kg/week) the predicted HV was 13.0 and 13.5 cm/year, respectively.

The clinical data with TransCon hGH correlates well with the KIGS data, demonstrating very little variability in HV over a dose bracket of 20% (0.5 cm/year compared to 0.3 cm/year based on the formula derived by Ranke et al).



Conclusion

The auto-injector was designed to simplify administration and improve adherence to hGH therapy for GHD patients.

Bracketed dosing enables flexibility as patients grow, with a single-use, weekly, low volume injection (<0.6 mL) for all patients.

TransCon hGH is stable at room temperature eliminating the need for cold storage. Empty-all design eases everyday use by eliminating waste and patient inconvenience.



¹ Ranke et al; JCEM 1999 84: 1174 -1183

² Chatelain et al; JCEM 2017; Published online 14. Feb

