Safety and Efficacy of Long-Acting Growth Hormone Somavaratan (VRS-317) in Children with GHD: Effects of Dose Change in the Second Treatment Year

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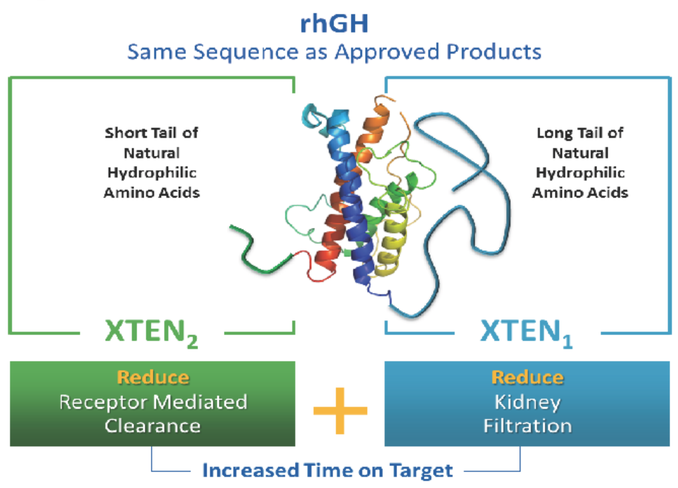
Background:

- Children with growth hormone deficiency (GHD) are often treated for multiple years with daily injections of recombinant human growth hormone (rhGH) replacement therapy; daily rhGH products are the only approved therapy for GHD.
- A significant proportion of patients have compliance issues with daily rhGH injections,[1] which can compromise treatment effects.[2]
- Furthermore, the effectiveness of treatment with daily rhGH products diminishes with each treatment year.[3,4]
- There is a clinical need for a safe and effective long-acting form of rhGH that can improve compliance and whose effectiveness is sustained beyond the first year.
- Development of a long-acting form of rhGH with long-term effectiveness can potentially reduce treatment burden, resolve compliance issues, and improve overall treatment outcomes.

Somavaratan (VRS-317): A Long-Acting Form of rhGH

- Somavaratan is a novel fusion protein of rhGH with amino acid sequences (XTEN) attached to the N- and C-termini (**Figure 1**).
- Somavaratan has a longer half-life than rhGH in animals and adult GHD patients, as well as more durable insulin-like growth factor-I (IGF-I) responses than those of previously studied rhGH products.[5,6]
- Results of a 6-month Phase 1b/2a study[7] of weekly, twice-monthly, or monthly dosing of somavaratan in pre-pubertal children with GHD (N=64) previously showed that the 6-month annualized height velocity (HV) with somavaratan was comparable to that of age-matched historic controls, with no unexpected or serious adverse events.[4]
- A Phase 3 randomized, multi-center, open-label, noninferiority trial comparing twice-monthly somavaratan (3.5 mg/kg) vs. daily rhGH in pediatric GHD is ongoing (ClinicalTrials.gov Identifier: NCT02339090).

Figure 1. Somavaratan Structure-Function



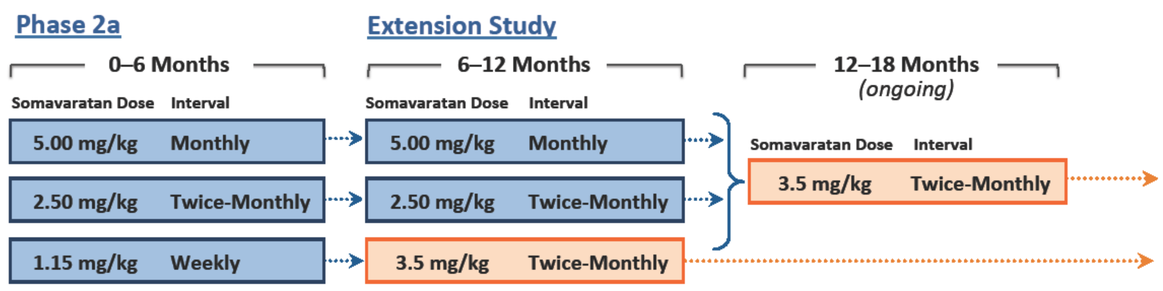
Objective:

- In this ongoing, long-term extension study, we evaluated whether somavaratan at the Phase 3 dose (3.5 mg/kg) given between 12–18 months of treatment can offset the decrease in HVs commonly seen during the second year of daily rhGH treatment.

Methods:

- This long-term extension study followed the 6-month, randomized, open-label, safety and efficacy stage of a Phase 1b/2a study (ClinicalTrials.gov Identifier: NCT01718041) evaluating 3 somavaratan dosing regimens conducted in 25 pediatric endocrinology clinics in the United States.

Figure 2. Extension Study Schema



- Subjects had GHD confirmed by short stature, 2 or more growth hormone stimulation tests, IGF-I standard deviation (SDS) scores, and a delayed bone age.
- In the 6-month Phase 2a stage of the study, subjects were randomized to somavaratan 1.15 mg/kg weekly, 2.5 mg/kg twice-monthly, or 5.0 mg/kg monthly for 6 months.
- At the start of the extension study, subjects in the 1.15 mg/kg weekly group were switched to 3.5 mg/kg twice-monthly. Subjects in the 5.0 mg/kg monthly and 2.5 mg/kg twice-monthly groups received the same Phase 2a dose for the first 6 months of the extension study, then increased dose to 3.5 mg/kg twice-monthly (**Figure 2**).
- Peak (Day 4) IGF-I SDS and mean HV were compared before and after the dose change.

Results:

Subject Disposition and Characteristics

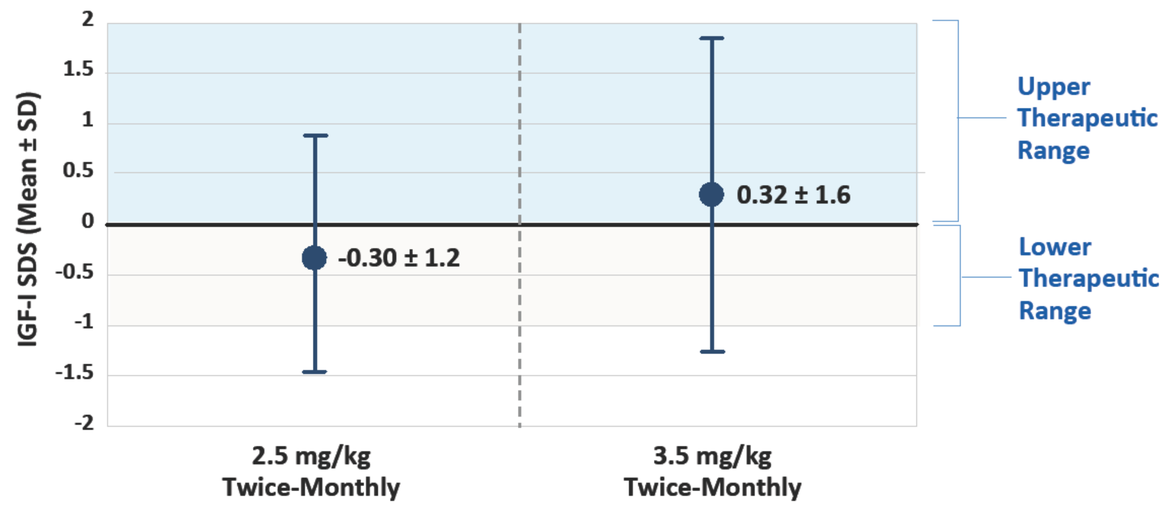
- 63 of 64 enrolled pre-pubertal GHD children completed the 6-month study of weekly, twice-monthly, or monthly dosing (5.0 mg/kg per month).
- 56 subjects have completed 18 months of treatment.
- The mean age at Month 18 was 9.28 years; all but 2 subjects remained pre-pubertal.

Results (cont.):

Pharmacodynamics

- Increasing the dose in the twice-monthly dose group (n=17) from 2.5 to 3.5 mg/kg somavaratan led to increased mean peak IGF-I SDS from -0.30 ± 1.2 to 0.32 ± 1.6 (P=0.007, paired t-test; **Figure 3**).
- At the 3.5 mg/kg dose across all cohorts (n=56), there were three IGF-I SDS > 2 and none > 3.

Figure 3. Pharmacodynamics Response to Increased Somavaratan Dose (n=17)

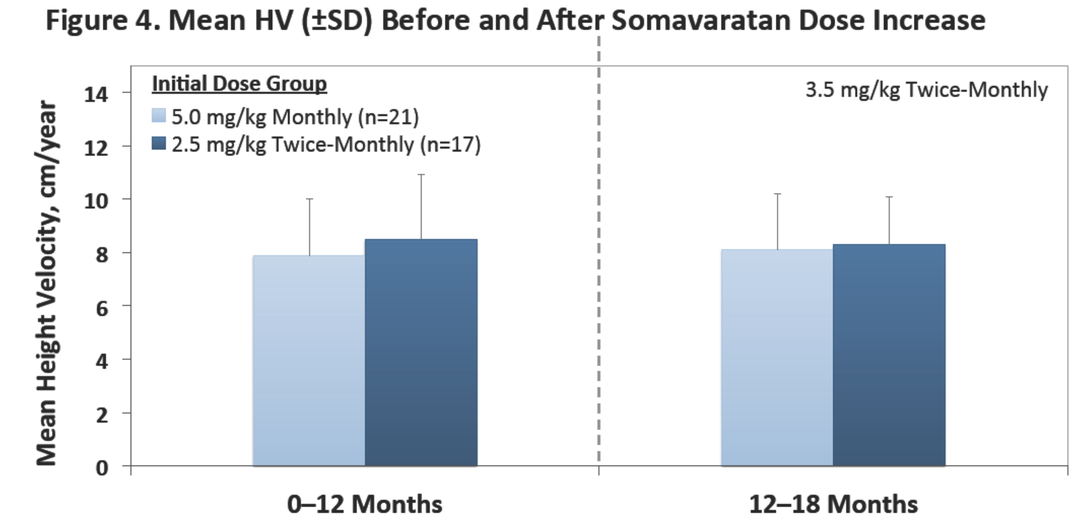


Mean peak IGF-I SDS increased with increased dosing given between 12–18 months

Efficacy

- The anticipated decline in 2nd year HV was not observed with the 3.5 mg/kg dose:
  - The anticipated decline from the first to the second year is between 1.4 and 2.4 cm (for 3- to 11-year-old GHD children) or approximately 2 cm/year.[3,4]
  - During the initial 12 months of treatment, mean HV was 7.9 ± 2.1 cm/year and 8.5 ± 2.1 cm/year for subjects in the 5.0 mg/kg monthly and 2.5 mg/kg twice-monthly dose groups, respectively (**Figure 4**).
  - After 18 total months of treatment, the last 6 months at 3.5 mg/kg twice-monthly, the mean (annualized) 12-18 month HV was 8.1 ± 2.4 cm/year and 8.3 ± 1.8 cm/year for each dose group, respectively.

Figure 4. Mean HV (±SD) Before and After Somavaratan Dose Increase



The anticipated decline in 2nd year HV was not observed with 3.5 mg/kg somavaratan

Safety

- Treatment-related adverse events (AEs) between 12-18 months were reported in 7 patients (12.5%) with the 3.5 mg/kg dose.
- Only mild and transient treatment-related AEs were observed.
- Injection site pain or discomfort decreased with time on treatment, with only 4 subjects (7.1%) reporting pain or discomfort between 12-18 months.
- Safety profiles were similar pre- and post-dose increase.

Immunogenicity

- Anti-drug antibodies were detected but had no significant effect on PK, PD, safety, or efficacy.

Conclusions:

- Transitioning patients to the Phase 3 somavaratan dose (3.5 mg/kg twice-monthly) at the start of the 2nd year of treatment led to an increase in mean peak IGF-I SDS, with similar safety profiles pre- and post-dose increase.
- After 18 months of continuous exposure to somavaratan and at least 6 months at the Phase 3 dose, the anticipated decline in 2nd-year HV was not observed.

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