Adherence with Twice-Monthly, At-Home Dosing Schedule of Somavaratan (VRS-317) Long-Acting Growth Hormone Treatment in Children with Growth Hormone Deficiency (GHD) in the VISTA Study (NCT02068521)

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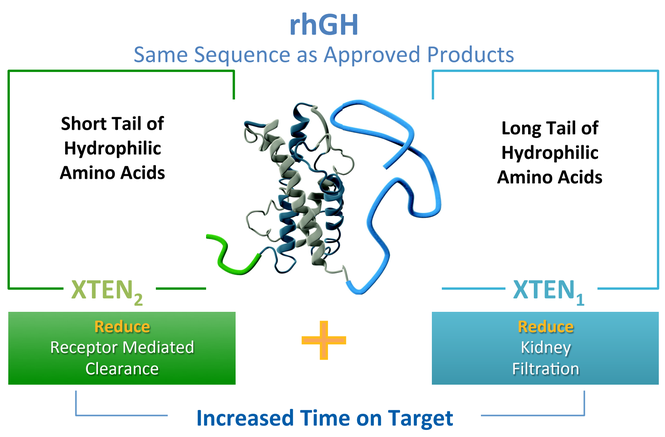
Background:

- Children with GHD are often treated for multiple years with daily injections of recombinant human growth hormone (rhGH) replacement therapy, currently the only treatment available for GHD in North America and Europe
- Treatment adherence to daily subcutaneous (SC) rhGH is a known burden for these patients, with poor adherence negatively impacting treatment outcome[1]
- Noncompliance to daily injections has been reported in up to 66%–77% of adults and children with GHD and is significantly associated with reduced annual height velocity (HV)[2]
- In a study by Cutfield et al, in which 66% of children receiving daily GH missed more than one dose per week, noncompliance was significantly associated with reduced annual HV[3]
- There is a clinical need for a safe and effective long-acting GH treatment for which treatment adherence is attainable
- Development of a long-acting form of rhGH with long-term effectiveness has potential to reduce treatment burden, improve adherence issues, and improve overall treatment outcomes

Somavaratan (VRS-317)

- Somavaratan is an investigational agent in clinical development for treatment of children and adults with GHD
- XTENylation increases half-life through reduced renal and receptor-mediated clearance, potentially allowing for twice-monthly dosing; drug peak and AUC exposure are proportional to dose[4-6]
- Somavaratan has a 30-to 60-fold longer half-life and more durable insulin-like growth factor-I (IGF-I) responses, compared with daily rhGH[5,6]
- A Phase 1b/2a study in 64 pre-pubertal children with GHD previously showed that weekly (W), twice-monthly (TM), or monthly (M) dosing of somavaratan was enabled by dose-proportional increases in magnitude and duration of IGF-I responses[6]
- Clinically meaningful improvements in HV and IGF-I were observed with all 3 dosing schedules, with no study drug-related serious adverse events[6]
- The open-label, long-term safety study (VISTA Study, 13VR3) is ongoing with subjects approaching 3 years of somavaratan exposure

Figure 1. Somavaratan Structure-Function



Objective:

- To evaluate treatment adherence to at-home dosing of W, TM, and M somavaratan dosing schedules in the ongoing, long-term extension study

Methods:

- This long-term safety study (ClinicalTrials.gov Identifier: NCT02068521) 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 (**Figure 2**)
- Patients had GHD confirmed by short stature (height-standard deviation score [SDS]), 2 or more growth hormone stimulation tests, IGF-I SDS, and a delayed bone age

Figure 2. VISTA Study Design

- From the beginning of the 2nd treatment year, all subjects received 3.5 mg/kg somavaratan TM, based on growth and IGF-I responses observed in Year 1[6]
- As of April 2015, dose formulation changed from 50 to 100 mg/mL
- For assessment of treatment adherence, dosing events were reported by the caregiver using a smartphone-compatible electronic patient-reported outcome diary (eDiary; Bracket, Inc.)
- Prior to at-home dosing (initiated at beginning of extension study), caregivers were trained on preparation of somavaratan, SC injection technique, and eDiary use. In-clinic visits were conducted quarterly for patient follow-up, eDiary reprogramming, and re-supply of somavaratan and ancillary supplies
- The eDiary was programmed to provide both assigned injection volume and timing of injection. Caregivers used the eDiary to report injection volume administered and date of administration
- Notifications sent to research nurse for late or missed injections

Results:

Subject Disposition and Characteristics

- Sixty-four subjects enrolled in the Phase 1b/2a study with mean ages of 7.5±2.3, 8.0±2.4 and 8.0±2.5 for the W, TM, and M dosing groups, respectively
- 60 subjects (mean age of 8.3±2.4 at Day 1) elected to remain on somavaratan treatment in the open-label extension study
- Baseline characteristics are consistent with a pediatric population with moderate GHD (**Table 1**)
- All subjects were transitioned to 3.5 mg/kg TM by the 6-month time point in the extension study (12 months of total somavaratan exposure)

Table 1. Extension Study Subject Characteristics

Parameter	Subjects Enrolled in VISTA Study (n = 60)
Baseline age, mean (SD)	7.8 (2.4)
Gender, n (%)	
Female	26 (43%)
Male	34 (57%)
Race, n (%)	
White	50 (83%)
Black	4 (7%)
Asian	3 (5%)
American Indian or Alaska native	1 (2%)
Other	2 (3%)

Treatment Adherence

- Evaluation of completed/expected doses showed 100% event adherence for each of the 3 initial dosing regimens (**Table 2**)
- With over 2200 doses administered in the continuing somavaratan regimen at the 3.5 mg/kg TM dose and schedule, reported dosing adherence was 99.6% (**Table 2**)

Table 2. Reported Treatment Adherence After 30 Months Somavaratan Exposure

	Somavaratan Starting Regimen			Somavaratan Continuing Regimen
	5.0 mg/kg Monthly (n=22)	2.5 mg/kg Twice-Monthly (n=18)	1.15 mg/kg Weekly[a] (n=20)	3.5 mg/kg Twice-Monthly (n=58)
Completed/Expected Doses	131/131	213/213	195/195	2266/2276
Event adherence rate (%)	**100**	**100**	**100**	**99.6**

[a]Expected doses in the weekly dosing group were lower than the 2.5 mg/kg twice-monthly group due to earlier switch to Phase 3 dosing

NOTE: As of April 2015, dose formulation changed from 50 to 100 mg/mL somavaratan.

Reported adherence to somavaratan occurred at nearly 100% over 24 months of at-home dosing

Conclusions:

- Use of an eDiary device/application simplifies parent tracking of timing for and recording of at-home dosing events in this clinical trial
- With at-home dosing and over 2200 doses administered at the Phase 3 dose, treatment adherence rate was 99.6%
- With nearly 100% reported adherence for all dosing schedules over 24 months of at-home therapy, this study provides evidence that long-term adherence to treatment may be improved with long-acting growth hormone preparations in children with GHD
- A Phase 3 study of somavaratan using the eDiary to monitor treatment adherence is ongoing (NCT02339090)

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