Achievement of a Suitable Basis of Comparison in Phase 2 and Phase 3 Pediatric Somavaratan Clinical Trials (VERTICAL, VISTA, and VELOCITY Studies) and for the Comparison of Somavaratan to Daily rhGH

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Background:

- Therapeutic potential of daily recombinant human growth hormone (rhGH) is well established and has been the primary treatment for pediatric growth hormone deficiency (PGHD) for three decades[1]
- Efficacy may be compromised when patients do not adhere to burdensome regimens of daily subcutaneous injections[2]

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

- Somavaratan is a novel long-acting rhGH fusion protein being developed for adult and pediatric GHD (Fig. 1);[3] it has a longer half-life and more durable insulin-like growth factor I (IGF-I) responses than daily rhGH[4,5]

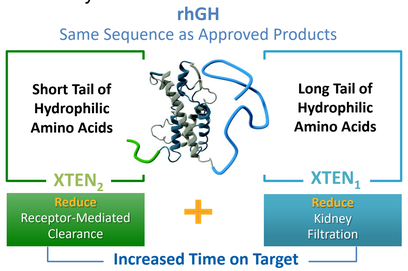

Figure 1. Somavaratan Structure-Function

- In the Phase 1b/2a study (VERTICAL) of pre-pubertal PGHD children (N = 64), primary determinants of first-year height velocity (HV) included age at treatment onset and baseline IGF-I standard deviation score (SDS)[5]
- 136 subjects are participating in a Phase 3 non-inferiority trial (VELOCITY) of somavaratan versus daily rhGH
- Subjects from the Phase 2 VERTICAL and Phase 3 VELOCITY studies are eligible to enter the long-term safety study (VISTA; Fig. 2)
- Through 3 years experience with VERTICAL/VISTA subjects, IGF-I, HV, height SDS, and catch-up growth continued to increase, and treatment-related adverse events were generally mild or moderate[6]

Objective:

- Valid comparison of efficacy outcomes requires similar distribution of clinical characteristics known to affect HV between trials and treatment arms of a trial
- To evaluate if a suitable basis of comparison exists between somavaratan PGHD Phase 2 and Phase 3 treatment populations

Methods:

- Similar inclusion/exclusion criteria are used for PGHD trials (Table 1)
- A stratification procedure was employed for randomization to daily rhGH or somavaratan based on:
  - Region
  - Expected median age
  - Expected median baseline IGF-I SDS
- VERTICAL, VISTA & VELOCITY study designs and eligibility criteria are described in Fig. 2 and Table 1

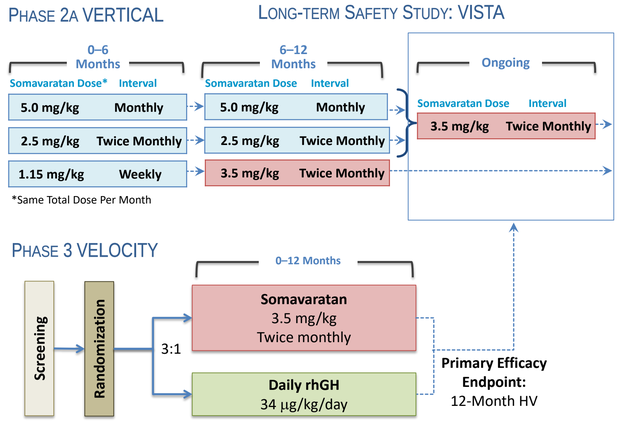

Figure 2. Study Schemas for VERTICAL, VISTA & VELOCITY Trials

Table 1. Comparison of VERTICAL vs. VELOCITY

Phase 2a VERTICAL (N = 64)	Phase 3 VELOCITY (N = 136)
Study Design	
• Randomized, multi-center, open-label • 6 months with option to continue in long-term safety study • Somavaratan monthly, twice monthly, or weekly → twice monthly by Year 2	• Randomized, multi-center, open-label • 12-months duration • Somavaratan twice monthly vs. daily rhGH
Primary Efficacy Endpoint: HV	**Primary Efficacy Endpoint:** HV
Key Inclusion Criteria	
• Chronological age ≥ 3.0 years and ≤10.0 years (girls) and ≤11.0 years (boys) • Pre-pubertal status • Diagnosis of GHD (2 GHD stimulation test results ≤10.0 ng/mL) • Height-SDS ≤-2.0 at screening • IGF-I SDS ≤-1.0 at screening • Delayed bone age • Weight for stature ≥10th percentile	• Chronological age ≥3.0 years and ≤11.0 years (girls) and ≤12.0 years (boys) • Pre-pubertal • Diagnosis of GHD (2 GHD stimulation test results ≤ 10.0 ng/mL) • Height-SDS ≤-2.0 at screening • IGF-I SDS ≤-1.0 at screening • Delayed bone age ≥6 months
Key Exclusion Criteria	
• Prior treatment rhGH or IGF-I therapy • Significant gene mutations (other than those that cause GHD)	• Prior treatment with rhGH or IGF-I therapy • Significant gene mutations (other than those that cause GHD)

Results:

Subject Disposition and Characteristics

- In VELOCITY, 104 subjects were randomized to somavaratan and 32 to daily rhGH; 64 subjects were enrolled in VERTICAL
- Numerical differences in baseline mean ages, maximal-stimulated GH, height SDS, IGF-I SDS, and bone ages were not clinically meaningful between the VELOCITY treatment arms (Table 2)
- No clinically meaningful differences were found between the Phase 2 and Phase 3 somavaratan trials in PGHD (Table 2)

Table 2. Baseline Characteristics in VERTICAL & VELOCITY

	Phase 2a VERTICAL	Phase 3 VELOCITY	
Parameter	Somavaratan N = 64	Somavaratan n = 104	Daily rhGH n = 32
Mean age, years (SD)	7.8 (2.4)	7.1 (2.0)	7.03 (2.4)
Female, n (%)	27 (42.2)	46 (44.2)	10 (31.3)
Mean GH_{max}, ng/mL (SD)	5.4 (2.6)	5.8 (2.6)	5.9 (2.5)
Mean height SDS (SD)	-2.6 (0.6)	-2.8 (0.7)	-2.6 (0.7)
Mean IGF-I SDS (SD)	-1.7 (0.8)	-1.7 (0.7)	-1.9 (0.9)
Mean bone age, years (SD)	6.4 (2.4)	5.3 (1.9)	5.3 (2.2)

Conclusions:

- Consistent eligibility criteria and stratification procedure to balance arms for clinical characteristics yielded similar treatment populations
- Based on current program results, a valid basis of comparison for somavaratan PGHD trials has been achieved

No clinically meaningful differences within Phase 3 VELOCITY somavaratan and daily rhGH arms or between Phase 2 VERTICAL and Phase 3 VELOCITY trials

References: (1) GH Research Society. *J Clin Endocrinol Metab.* 2000;85:3990-3; (2) Cutfield et al. *PLoS One.* 2011;6(1):e16223; (3) Cleland et al. *J Pharm Sci.* 2012;101(8):2744-54; (4) Yuen et al. *J Clin Endocrinol Metab.* 2013;98:2595-2603; (5) Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097. (6) Moore et al. ENDO 2017. April 1-4, 2017, Orlando, FL.

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