Safety Profile of Somavaratan (VRS-317), a Novel Long-Acting rhGH Fusion Protein, in Pre-Pubertal Children with Growth Hormone Deficiency (GHD)

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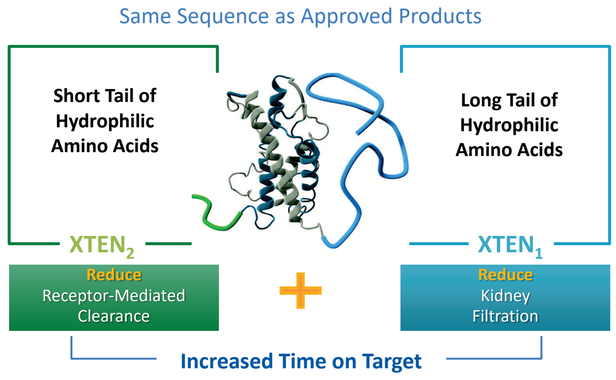
Background:

- Daily recombinant human growth hormone (rhGH) has been the mainstay of treatment for children with growth hormone deficiency (GHD) for three decades[1,2]
- The daily requirement for subcutaneous (SC) injections of rhGH is a treatment burden for patients and their caregivers.[3] Non-compliance is reported in up to 77% of adults and children with GHD[4,5]
- Efficacy of daily rhGH is compromised when patients do not adhere to daily regimens; height velocity (HV) and standard deviation score (SDS) are significantly associated with rate of missed doses[3-6]
- Introduction of a long-acting rhGH that reduces injection frequency while maintaining long-term growth response may reduce the burden of daily rhGH injections, without compromising safety or efficacy

Somavaratan (VRS-317)

- Somavaratan is an investigational agent in clinical development for treatment of pediatric and adult GHD
- XTENylation increases half-life through reduced renal and GH receptor-mediated clearance, potentially allowing for twice-monthly dosing; drug peak and area under the curve (AUC) exposure are proportional to dose[7-9]
- Somavaratan has a 30- to 60-fold longer half-life in humans and yields more durable insulin-like growth factor-I (IGF-I) responses than historically demonstrated with daily rhGH[7,8]
- A Phase 1b/2a study in 64 pre-pubertal children with GHD previously showed that weekly, twice-monthly, or monthly dosing of somavaratan was enabled by dose-proportional increases in the magnitude and duration of IGF-I responses[9]
- Clinically meaningful improvements in HV and IGF-I were observed with all 3 dosing schedules, as well as up to 24 months with the 3.5 mg/kg twice-monthly dose, with no study drug-related serious adverse events (SAEs)[9,10]
- An open-label, long-term safety study (VISTA Study, 13VR3) is ongoing

Figure 1. Somavaratan Structure-Function



Objective:

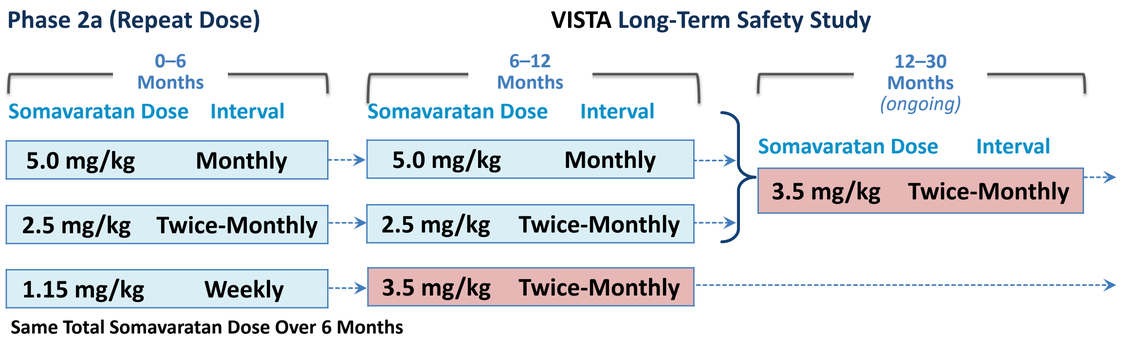
- To evaluate the safety profile of somavaratan in the VISTA study

Methods:

VISTA Study Design

- A 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**)

Figure 2. VISTA Study Design



GHD was confirmed by height SDS ≤ -2.0, 2 or more GH stimulation tests ≤ 10.0 ng/mL, IGF-I SDS ≤ -1.0, and a delayed bone age

- During the 6-month Phase 2a stage of the study, subjects were randomized to somavaratan 1.15 mg/kg weekly (n = 21), 2.5 mg/kg twice-monthly (n = 20), or 5.0 mg/kg monthly (n = 23) for 6 months
- By the beginning of the second treatment year, all subjects received 3.5 mg/kg somavaratan twice-monthly, based on growth and IGF-I responses observed in Year 1[9] (**Figure 2**)
- As of April 2015, the somavaratan dose formulation changed from 50 to 100 mg/mL

Safety Assessments

- Safety assessments included adverse events (AE), physical examination including injection site evaluations, vital signs, ocular fundoscopy, and clinical laboratory evaluations
- Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 AEs were classified according to severity and relationship to study drug

Results:

Subject Disposition and Characteristics

- 64 subjects enrolled in the 6-month Phase 2a stage; 60 entered the VISTA study
- Baseline characteristics are consistent with a pediatric population with moderate GHD (**Table 1**)

Table 1. Demographics and Baseline Characteristics

Parameter	N=64
Baseline age, years, mean (SD)	7.8 (2.4)
Male, n (%)	37 (58%)
Race, n (%)	
White	53 (83%)
Asian	5 (8%)
Black or African American	3 (5%)
American Indian or Alaska native	1 (2%)
Other	2 (3%)
HT-SDS, mean (SD)	-2.6 (0.6)
IGF-I SDS, mean (SD)	-1.7 (0.8)
Bone age, years, mean (SD)	6.4 (2.4)

Results (cont):

Safety

- Treatment-related AEs were reported in 39 of 64 subjects. All were mild or moderate and transient
- Treatment-related AEs occurring in > 1 subject are presented in **Table 2**
- No treatment-related SAEs were reported
- Subject withdrawals were at expected rates for long-term clinical studies

Table 2. Treatment-Related AEs Occurring in >1 Subject

Adverse Event, n (%)	N=64
Any AE	39 (61)
Injection site pain	31 (48)
Injection site erythema	6 (9)
Headache	5 (8)
Pain in extremity	4 (6)
Arthralgia	4 (6)
Injection site reaction	2 (3)
Increased IGF-I*	2 (3)
Musculoskeletal pain	2 (3)

*As reported by treating physician

- Frequency of related AEs declined substantially after the initial 6-month exposure period (**Table 3; Figure 3**)
- Of 31 subjects initially reporting injection site pain, 6 had recurrent events in months 6-12, 2 in months 12-18, and 1 in months 18-24
- No reports of injection site erythema occurred after month 6
- Two subjects reported headaches in months 0-6, and in 1 subject in each subsequent 6-month period

Figure 3. Most Common Treatment-Related Adverse Events Over Time

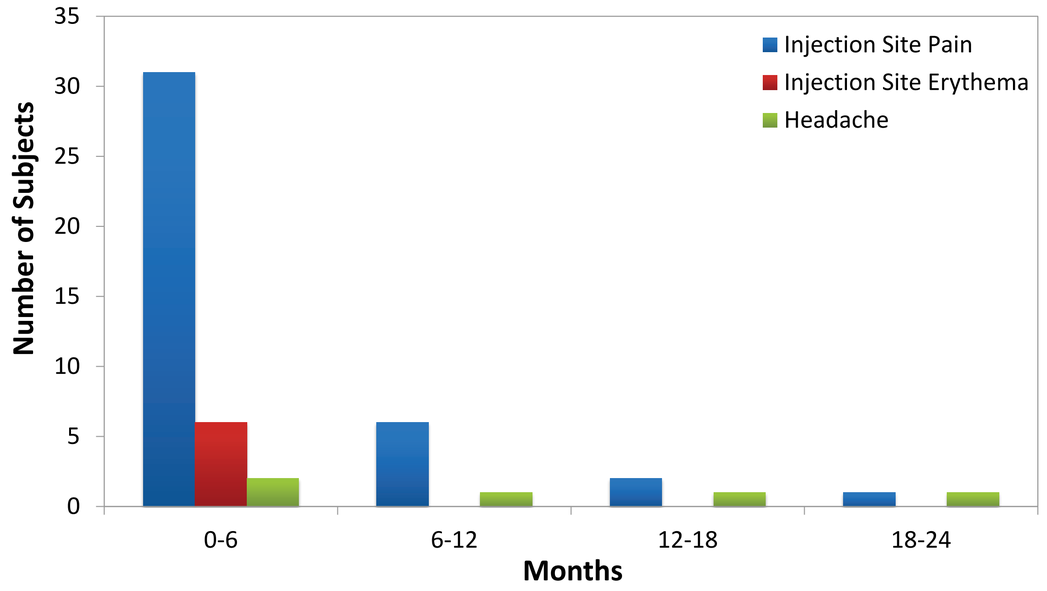


Table 3. Treatment-Related Adverse Events Over Time

Adverse Event, n (%)	Treatment Period				
	Months 0-6 (n=64)	Months 6-12 (n=60)	Months 12-18 (n=57)	Months 18-24 (n=53)	Months 24-30 (n=48)
All AEs	34 (53)	10 (17)	6 (11)	4 (8)	6 (13)
Injection site pain	31 (48)	6 (10)	2 (4)	1 (2)	3 (6)
Injection site erythema	6 (9)	0	0	0	0
Headache	2 (3)	1 (2)	1 (2)	1 (2)	0
Pain in extremity	2 (3)	0	1 (2)	1 (2)	0
Arthralgia	2 (3)	1 (2)	1 (2)	2 (4)	1 (2)
Injection site reaction	1 (2)	0	0	1 (2)	0
Increased IGF-I*	0	0	0	0	2 (4)
Musculoskeletal pain	0	0	0	2 (4)	0

*As reported by treating physician

The safety profile of somavaratan after 2.5 years of treatment was consistent with historical experience with daily rhGH, with no new safety signals revealed

Conclusions:

- Somavaratan at the 3.5 mg/kg twice-monthly dose was well tolerated in the VISTA long-term safety study
- Rates of related AEs in VISTA declined after the initial 6-month exposure period
- Frequency and severity of treatment-related adverse events indicated no safety concerns

Somavaratan, 3.5 mg/kg twice-monthly, is now under study in a randomized, Phase 3, non-inferiority trial vs. daily rhGH in pre-pubertal children with GHD (NCT02339090) - The VELOCITY Study

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References: (1) Ergun-Longmire and Wajnrajch. *Endotext*. http://www.ncbi.nlm.nih.gov/books/NBK279142; (2) Ranke et al. *J Clin Endocrinol Metabol.* 2005;90:1966; (3) Saenger and Mejia-Corletto. *Adv Ther Ped Endocrinol Diabetes.* 2016;30:79-97; (4) Rosenfeld and Bakker. *Endocr Pract.* 2008;14:143-54; (5) Cutfield et al. *PloS One.* 2011;6:e16223; (6) De Pedro et al. *Growth Horm IGF Res.2016;* 26:32-35; (7) Cleland et al. *J Pharm Sci.* 2012;101:2744-54; (8) Yuen et al. *J Clin Endocrinol Metab*. 2013;98:2595-603; (9) Moore et al. *J Clin Endocrinol Metab.* 2016;101:1091-1097; (10) Bright et al. 2016 ESPE Annual Meeting. Sept. 10-12, 2016; Paris, France.