Somavaratan (VRS-317) Treatment of Children with Growth Hormone Deficiency (GHD): VISTA Study Results at 2.5 Years (NCT02068521)

G.M. Bright[1], W.V. Moore[2], H.J. Nguyen[3], G.B. Kletter[4], B.S. Miller[5], P.Y. Fechner[6], D. Ng[7], E. Humphriss[1] and J.L. Cleland[1]

[1]Versartis, Inc. Menlo Park, CA; [2]Children's Mercy Hospital and University of Missouri-Kansas City, Kansas City, MO; [3]Sierra Medical Research, Clovis, CA; [4]Mary Bridge Children's Hospital, Tacoma, WA; [5]University of Minnesota Masonic Children's Hospital, Minneapolis, MN; [6]Seattle Children's Hospital, University of Washington, Seattle, WA; [7]ResearchPoint Global, Inc, Austin, TX

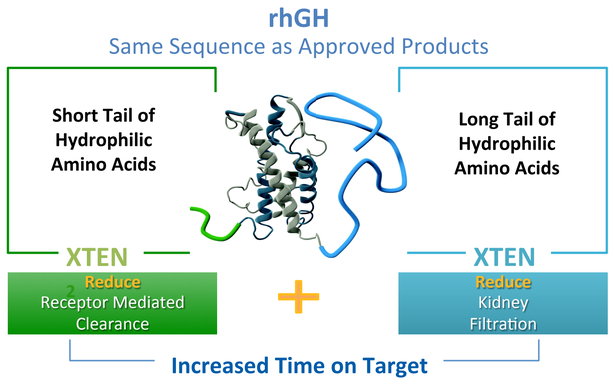
Background:

- Therapeutic potential of daily recombinant human growth hormone (rhGH) is well established and has been the primary treatment for pediatric growth hormone deficiency (GHD) for three decades[1,2]
- Current challenges with daily rhGH preparations include burden of daily subcutaneous (SC) injections,[3] with noncompliance reported in up to 77% of adults and children with GHD[4,5]
- Reduced efficacy of rhGH (decreasing height velocity [HV] standard deviation score [SDS]) is significantly associated with number of missed doses per week[3-6]
- Romer et al reported a ~1.7 cm/year decline in HV from Year 1 to 2 with use of daily rhGH[7]
- Introduction of a long-acting rhGH that reduces injection frequency while maintaining long-term growth response may improve clinical outcomes while reducing burden of daily rhGH injections

Somavaratan (VRS-317)

- Somavaratan is an investigational agent in clinical development for treatment of GHD in children and adults
- 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[8-10]
- 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[8,9]
- 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 magnitude and duration of IGF-I responses[10]
- Clinically meaningful improvements in HV and IGF-I were observed with all 3 dosing schedules, with no study drug-related serious adverse events[10]
- 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



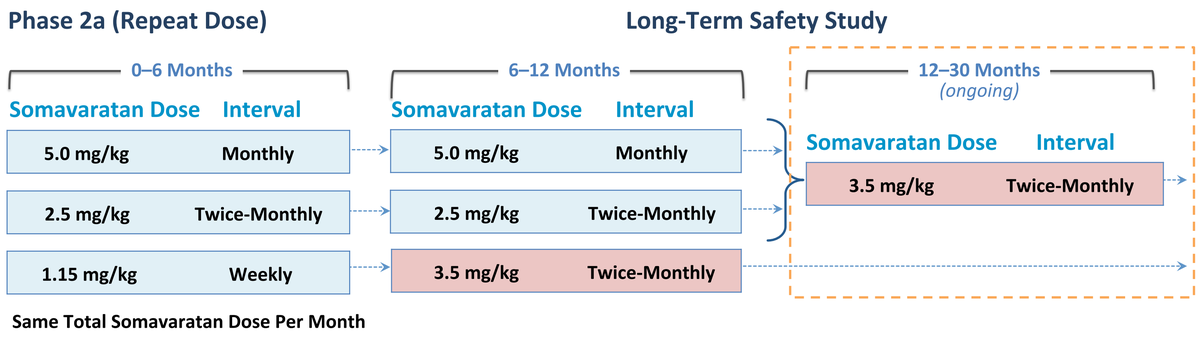
Objective:

- To evaluate maintenance of somavaratan treatment effects in the 2nd treatment year

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-SDS), 2 or more growth hormone stimulation tests, IGF-I SDS, and a delayed bone age

Figure 2. VISTA Study Design



- 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
- From 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[10] (**Figure 2**)
- As of April 2015, dose formulation changed from 50 to 100 mg/mL
- Peak (Day 4) IGF-I SDS and mean HV were compared before and after the dose change

Results:

Subject Disposition and Characteristics

- 64 subjects enrolled in the 6-month study; 60 entered the long-term safety study
- Baseline characteristics are consistent with a pediatric population with moderate GHD (**Table 1**)

Table 1. Demographics and Baseline Characteristics

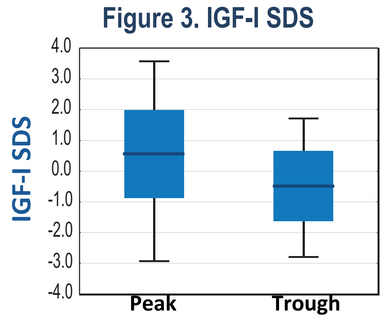
	Subjects Enrolled in Phase 2a (n=64)
Baseline age, years, mean (SD)	7.8 (2.4)
Male, n (%)	37 (58%)
Race, n (%)	
White	53 (83%)
Asian	5 (8%)
Black or African American	3 (5%)
American Indian or Alaska native	1 (2%)
Other	2 (3%)
HT-SDS, mean (SD)	-2.6 (0.6)
IGF-I SDS, mean (SD)	-1.7 (0.8)
Stimulated GH_{max}, ng/mL, mean (SD)	5.4 (2.6)
Bone age, years, mean (SD)	6.4 (2.4)

Results (cont.):

Pharmacodynamics

- During Year 2, IGF-I SDS (drawn every 3 months, measured by mass spectroscopy) was 0.59±1.4 at peak (3-5 days post injection) and -0.47±1.1 at trough (end of dosing cycle; **Figure 3**)
- In all patients receiving 3.5 mg/kg twice-monthly, 8 subjects had peak IGF-I SDS excursions >2, of which 2 were >3.0 (range, 2.01-3.67)

Figure 3. IGF-I SDS

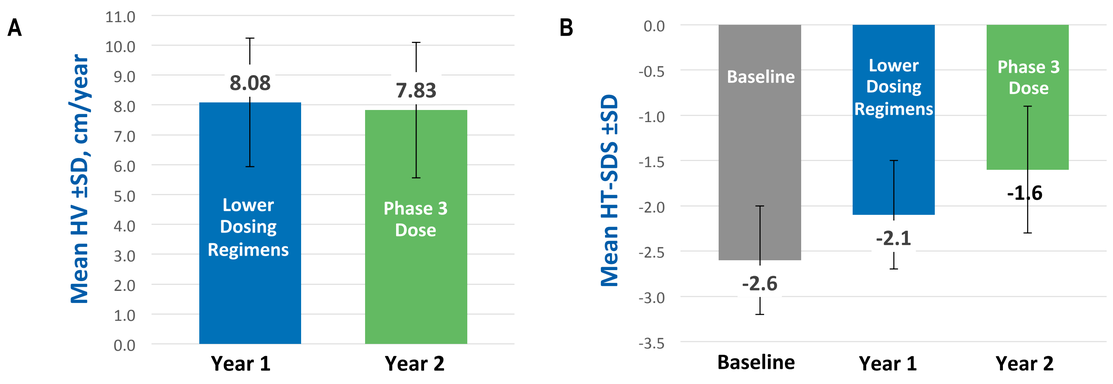


	Screening N=57	Peak n=55	Trough n=48
Mean	-1.49	0.59	-0.47
SD	0.78	1.43	1.14
Range	-3.6, 0.45	-2.9, 3.67	-2.7, 1.77

Efficacy

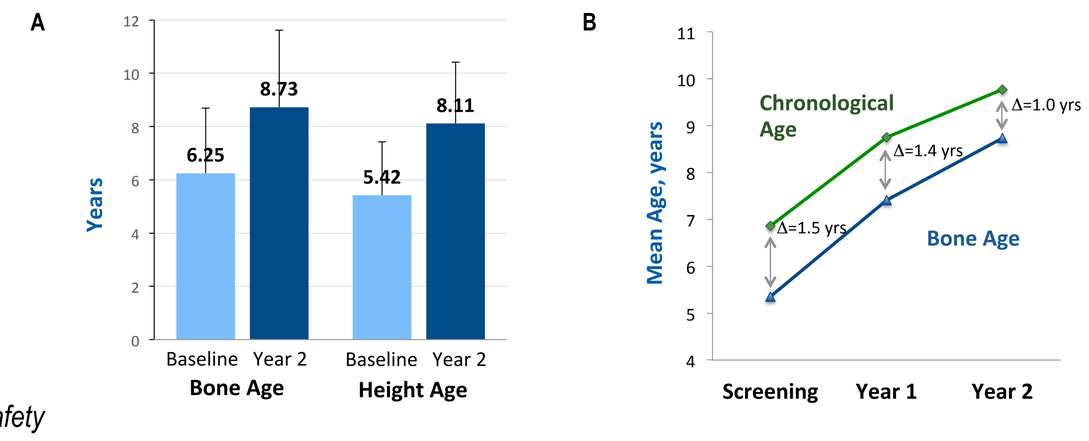
- Increasing the somavaratan dose to 3.5 mg/kg twice-monthly resulted in Year 2 HV comparable to Year 1 and continued improvement in HT-SDS (**Figure 4**)
- Mean increase in bone age and height age exceeded years on study, while differences between chronological and bone age decreased over time (**Figure 5**)

Figure 4. (A) Mean HV and (B) HT-SDS in All Evaluable Patients at 2 Years



Selection of the somavaratan 3.5 mg/kg twice-monthly dose is supported by similarities in 2nd year HV (7.83 cm/year) to US estimates (7.9 cm/year) from the National Cooperative Growth Study (NCGS)[11]

Figure 5. Change in bone age. (A) Bone and height age over time; (B) Chronological vs. bone age



Safety

Table 2. 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)	2(4)
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)

ITT Population; reported in >1 subjects on somavaratan for up to 30 months
*As reported by treating physician

- No related serious adverse events, no lipoatrophy or nodule formation
- Related adverse events (AEs) generally mild and transient
- Frequency of AEs declined substantially after initial 6 month exposure period (**Table 2**)
- Dose increase and new formulation gave no change in incidence, type, duration or severity of AE
- Subject withdrawals at expected rate in long-term clinical studies

Somavaratan safety/tolerability profile was comparable to daily rhGH

Conclusions:

- Ph 3 dose selection supported by VISTA study results for subjects switched to 3.5 mg/kg twice-monthly
- Phase 3 dose (3.5 mg/kg, twice-monthly) was safe and well tolerated in this study
- Frequency and severity of treatment-related adverse events indicate no safety concerns
- Mean peak IGF-I SDS at Phase 3 dose was in upper half of normal range
- Catch-up growth supported by mean increase in bone age and height age exceeding years on study, with gap between chronological and bone age closing over the course of the study
- Improvement in HT-SDS continued in Year 2
- Year 2 HV comparable to US daily dosing data from NCGS

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

Acknowledgements: We thank the investigators and coordinators for excellent patient care, and patients and their families for participation in the study. We thank Leslie Jones and Morgan Seaman of ResearchPoint Global and F. Naureen Sheikh, PhD, and Lynda Chaplin of Versartis, Inc. for managing clinical operations. Ingrid Koo, PhD, provided editorial support for the poster.

Disclosures: Research was funded by Versartis, Inc. Somavaratan is an investigational agent. E. Humphriss is an employee and holds equity interests in Versartis, Inc. G.M. Bright and J.L. Cleland are consultants and hold equity interests in Versartis, Inc. Drs. Moore, Nguyen, Kletter, Miller, and Fechner are Investigators for Versartis-sponsored trials. D. Ng is an employee of ResearchPoint Global.

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(2):143-54; (5) Cutfield et al. *PloS One.* 2011;6(1):e16223; (6) De Pedro et al. *Growth Hormone & IGF Research.2016;* 26:32-35; (7) Romer et al. *Hormone Research*. 2009;72:359-369; (8) Cleland et al. *J Pharm Sci.* 2012;101(8):2744-54; (9) Yuen et al. *J Clin Endocrinol Metab*. 2013;98:2595-603; (10) Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097; (11) Bakker et al. *Hormone Research.* 2008;97(suppl 1):P2-d1-327.

Presented at the 55th Annual Meeting of the European Society for Paediatric Endocrinology. 10-12 September, 2016. Paris, France

55ESPE 8--1-RFC

Growth: Clinical

Ingrid Loo

DOI: 10.3252/pso.eu.55ESPE.2016

Poster presented at: ESPE 2016 PARIS

PosterSessionOnline.com