Pharmacokinetic and Pharmacodynamic (PK/PD) Analysis of Somavaratan (VRS-317), a Long-Acting rhGH, in Japanese and US Children with Growth Hormone Deficiency (GHD)

Tomonobu Hasegawa[1], Reiko Horikawa[2], Susumu Kanzaki[3], Toshiaki Tanaka[4], Markus Jerling[5], David Ng[6], Eric Humphriss[7], R. William Charlton[7], James A. Zanghi[7], Yuji Hoshino[7]

[1]Keio University School of Medicine, Tokyo, Japan; [2]National Center for Child Health and Development, Tokyo, Japan; [3]Tottori University Faculty of Medicine, Yonago, Japan; [4]Tanaka Growth Clinic, Tokyo, Japan; [5]Markus Jerling Consulting AB, Bromma, Sweden; [6]ResearchPoint Global, Inc., Austin, TX, USA; [7]Versartis, Inc., Menlo Park, CA, USA

Background:

- Somavaratan is a novel long-acting rhGH fusion protein being developed for adult and pediatric GHD (Fig. 1); it has a longer half-life and more durable IGF-I responses than daily rhGH[1,2]
- Somavaratan previously showed clinically meaningful improvements in height velocity and favorable PK/PD and safety profiles in pre-pubertal children with GHD in the US,[2] but little is known about the impact of ethnic factors on outcomes
- Variability in cytochrome P450 (CYP) enzyme activity can alter small-molecule drug metabolism between East Asians and Caucasians;[3] such differences are not anticipated for somavaratan, as neither rhGH nor somavaratan are metabolized by any CYPs tested *in vitro*
- Here we compare PK/PD properties of somavaratan between pre-pubertal children with GHD enrolled in Japanese and US trials (Fig. 2)

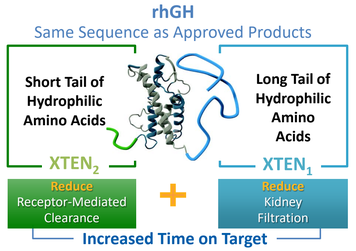
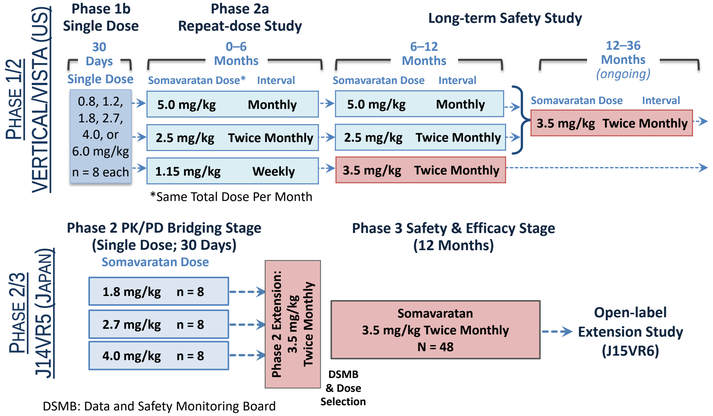


Figure 1. Somavaratan Structure-Function



DSMB: Data and Safety Monitoring Board

Eligible subjects were aged 3 to 9 (girls) or 10 years (boys). GHD was confirmed by height SDS ≤ -2.0, 2 or more GH stimulation tests ≤10.0 ng/mL (US) or <6.0 ng/mL (Japan), IGF-I SDS ≤ -1.0, and a delayed bone age

Figure 2. VERTICAL and J14VR5 Pediatric GHD Study Design

Objective:

- To compare PK/PD properties of somavaratan between pre-pubertal children with GHD enrolled in Japanese and US trials

Methods:

- The PK/PD analysis included J14VR5 subjects randomized to receive a single dose of somavaratan (1.8, 2.7, or 4.0 mg/kg; n = 8 each) and VERTICAL subjects from corresponding dose groups
- Serum PK (peak concentration [Cmax], AUC, total body clearance [CL]) and PD (IGF-I SDS, IGFBP-3 AUC) were evaluated using non-compartmental methods from samples collected on days 1 (pre-dose), ~4, 8, 15, and 30 (and day 22 for VERTICAL)

Results:

Demographics and Baseline Characteristics

- Demographics and baseline characteristics are shown in Table 1
- Patients in VERTICAL were older and had higher body weights than patients in J14VR5

Table 1. Demographics and Baseline Characteristics

	VERTICAL (US) Dose Group			J14VR5 (Japan) Dose Group		
Parameter	1.8 mg/kg	2.7 mg/kg	4.0 mg/kg	1.8 mg/kg	2.7 mg/kg	4.0 mg/kg
Age, years, mean (range)	7.6 (4.6-10.9)	7.6 (4.0-10.5)	7.0 (3.1-10.5)	5.3 (3.3-9.5)	6.9 (4.9-10.1)	5.8 (3.5-8.8)
Male/Female	7/1	6/2	4/4	8/0	7/1	4/4
Race, n (%)						
White	6 (75)	8 (100)	6 (75)	0	0	0
Asian	1 (12.5)	0	1 (12.5)	8 (100)	8 (100)	8 (100)
Other	1 (12.5)	0	1 (12.5)	0	0	0
Weight, kg, mean (range)	19.6 (14.0-27.4)	18.6 (13.2-25.1)	19.1 (10.1-31.7)	14.2 (11.6-21.2)	17.4 (13.0-23.6)	15.2 (11.5-21.7)

Pharmacokinetics

- In Japanese subjects, dose-adjusted AUC (Fig. 3) and Cmax (data not shown) showed small differences between dose groups, demonstrating dose proportionality

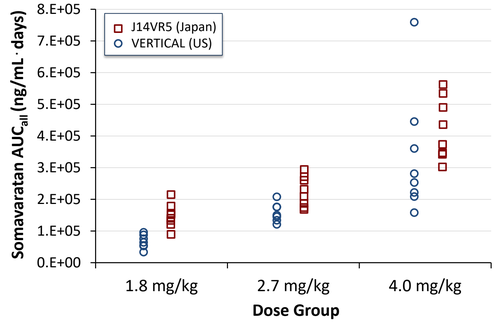


Figure 3. Somavaratan AUC_{all} in Japanese and US Subjects

- Multiple regression analyses revealed a weight effect on Cmax/dose and clearance (Fig. 4)

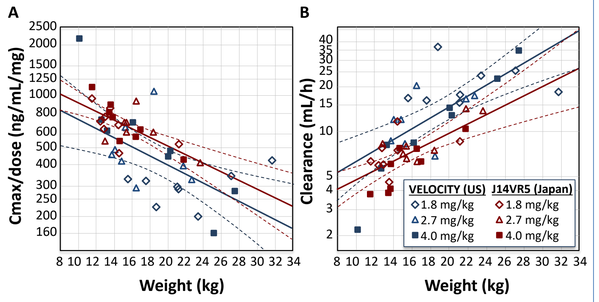


Figure 4. (A) Cmax/dose and (B) Clearance by Body Weight

- To adjust for differences in weight distribution between studies, weight was included as a covariate in Cmax and CL calculations
- Over the 12-24 kg weight range, dose-adjusted Cmax was 25-30% higher, and CL 28-37% lower in Japanese vs. US subjects when accounting for body weight
- Compared to an approximately 3-fold intersubject variability in Cmax/dose and CL within each study, these differences are considered minor

Pharmacodynamics

- PD analysis showed comparable IGF-I SDS and IGFBP-3 responses between US and Japanese populations (Fig. 5)

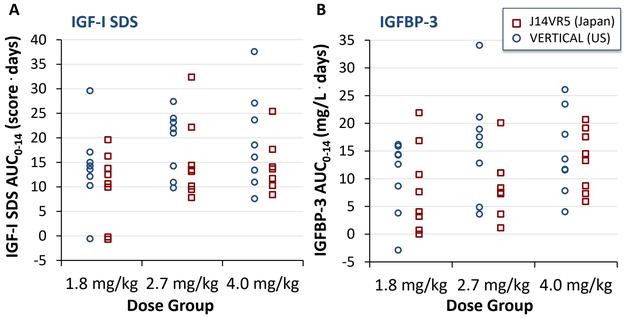


Figure 5. Baseline-Adjusted $AUC_{0\text{-}14}$ for (A) IGF-I SDS and (B) IGFBP-3 in Japanese and US Subjects By Dose Group

Conclusions:

- In line with the body weight effect on somavaratan PK parameters in both studies, the data continue to support weight-based dosing
- After adjusting for differences in body weight, differences in exposure between Japanese and US populations did not merit changes in dosing principles
- PD response to somavaratan was comparable between the two study populations
- Based on the results of this analysis, PK/PD of somavaratan appears to be insensitive to ethnic factors
- The Phase 3 study in Japan continues to enroll patients receiving somavaratan 3.5 mg/kg twice monthly

References: (1) Yuen et al, *J Clin Endocrinol Metab.* 2013;98:2595-2603; (2) Moore et al, *J Clin Endocrinol Metab.* 2016;101(3):1091-1097; (3) Kim et al. J Clin Pharmacol. 2004;44(10):1083-105.

Acknowledgments: We thank ResearchPoint Global for managing the pediatric clinical trials, Investigators and Coordinators for excellent patient care, and patients and their families for participation in the study. Ingrid Koo, PhD, provided editorial support for the poster.

Disclosures: This research was funded by Versartis, Inc. Somavaratan is an investigational agent. Drs. Hasegawa, Horikawa, Kanzaki, and Tanaka are Investigators for Versartis clinical trials. Dr. Jerling is a consultant for Versartis. E. Humphriss, RW Charlton, JA Zanghi, and Y Hoshino are employees and hold ownership interest in Versartis, Inc.