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

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Somavaratan is a novel rhGH fusion protein in clinical development as a long-acting agent for treatment of adults and children with GHD. Somavaratan previously demonstrated clinically meaningful improvements in height velocity and favorable PK/PD and safety profiles in pre-pubertal children with GHD in the US (1), but little is known about the impact of geographical/racial differences on treatment effects. Variability in cytochrome P450 (CYP) enzyme activity can alter small molecule drug metabolism between East Asians and Caucasians (2). Such differences are not anticipated for somavaratan, as neither hGH 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: J14VR5 is an ongoing, randomized, Phase 2/3, open-label, multicenter, PK/PD, safety and efficacy trial in Japan, including a PK/PD stage in which subjects initially received a single subcutaneous dose of somavaratan (1.8, 2.7, or 4.0 mg/kg; n = 8 each) (NCT02413138); VERTICAL was a randomized, Phase 1b/2a, open-label, multicenter US trial, including a single-ascending, dose-finding phase (NCT01718041) (2), from which 24 subjects with matching doses were compared. Serum PK (peak concentration [Cmax], time to Cmax [Tmax], area-under-the-curve [AUC], half-life [$t_{1/2}$], total body clearance [CL]) and PD (IGF-I SDS, IGFBP-3) were evaluated using non-compartmental methods from samples collected on days 1 (pre-dose), ~4, 8, 15, and 30. The VERTICAL study had an additional sampling time on Day 22. 24 subjects enrolled in J14VR5 (19 male, 5 female, 100% Asian), mean age 6.0 years, mean weight 15.6 kg and were compared to 24 dose-matched subjects in VERTICAL (17 male, 7 female, 83% Caucasian, 8% Asian), mean age 7.4 years, mean weight 19.1 kg. Tmax and $t_{1/2}$ were similar between populations. Distribution of body weight differed between studies with higher weights in VERTICAL. Multiple regression analyses revealed a weight effect on some PK parameters; therefore, weight was included as a covariate to adjust for the difference in weight distribution between studies in the comparison of Cmax and CL. Over the weight range of 12-24 kg, dose adjusted Cmax (Cmax/dose) was 25-30% higher and CL was 28-37% lower in Japanese vs. US subjects when accounting for body weight. Due to approximately 3-fold intersubject variability in Cmax/dose and CL within each study, these differences are considered minor. PD analysis showed comparable

increases in IGF-I SDS and IGFBP3 in both populations. In summary, somavaratan demonstrates prolonged elimination half-life with low variability between Japanese and US studies. The small differences in exposure between populations do not merit changes in dosing principles. Results of this study support use of the same dosing regimen in Japan and the US.

Disclosure: TH: Investigator and Member of Advisory Committee, Versartis, Inc.. RH: Investigator and Member of Advisory Committee, Versartis, Inc.. SK: Investigator and Member of Advisory Committee, Versartis, Inc.. TT: Investigator and Member of Advisory Committee, Versartis, Inc.. MJ: Consultant, Versartis, Inc.. DN: Employee of CRO, Versartis, Inc.. EH: Employee, Versartis, Inc., Employee, Versartis, Inc.. RWC: Employee, Versartis, Inc., Employee, Versartis, Inc.. JZ: Employee, Versartis, Inc., Employee, Versartis, Inc.. YH: Employee, Versartis, Inc., Employee, Versartis, Inc..

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