IGF Family Biomarkers in the Diagnosis of Pediatric Growth Hormone Deficiency (PGHD) in Somavaratan Clinical Trials

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Background:

- PGHD is traditionally diagnosed from medical history, auxology, pituitary imaging, skeletal age, and growth hormone (GH) determinations during pharmacological stimulation and/or frequent nocturnal sampling
- The insulin-like growth factor (IGF) family biomarkers (IGF-I, IGFBP-3, and ALS) depend on exposure to GH and may aid in discriminating between PGHD and non-GH-dependent forms of growth failure
- Within-subject reproducibility of GH testing is often poor and limits the reliability of GH testing; less is known about the within-subject variability of IGF biomarkers

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- Novel fusion protein of rhGH and XTEN (Fig. 1)[1]
- Long half-life suitable for twice-monthly dosing[2,3]
- Continued catch-up growth for up to 3 years in PGHD[4]
- Phase 3 PGHD study of 136 subjects underway

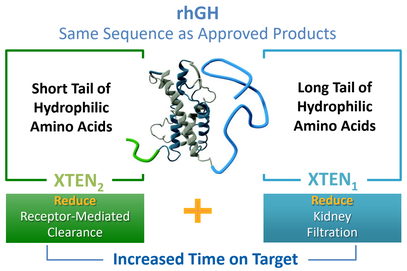

Figure 1. Somavaratan Structure-Function

Objective:

To evaluate the within-subject variability of IGF biomarkers in pediatric patients from somavaratan clinical studies

Methods:

- Pooled data from Phase 2 and Phase 3 PGHD studies of somavaratan were included in this analysis
- IGF-I sampled at screening and before treatment (Day 1)
- IGF-I measured by liquid chromatography-mass spectroscopy (Q2 Solutions)
- IGF-I standard deviation score (SDS) calculator devised from >1200 samples from healthy normal children[5]

Results:

- The study population were pre-pubertal children with bone age delay ≥6 months and IGF-I SDS <-1; characteristics at screening are presented in Table 1
- The mean number of days between screening and Day 1 was 29.9 ± 31.9

Table 1. Patient Characteristics at Screening

Parameters, mean (SD)	Female (n = 81)	Male (n = 115)	All (N=196)
Age, years	6.9 (2.0)	7.3 (2.3)	7.1 (2.2)
Height SDS	-2.8 (0.7)	-2.6 (0.5)	-2.7 (0.6)
BMI SDS	-0.09 (0.89)	-0.03 (0.80)	-0.06 (0.84)
Bone age, years	5.1 (2.0)	5.6 (2.2)	5.4 (2.1)
GH_{max}, ng/mL	5.6 (2.5)	5.9 (2.6)	5.8 (2.6)
IGF-I SDS	-1.7 (0.7)	-1.8 (0.7)	-1.8 (0.7)

IGF-I at Baseline

- IGF-I levels at screening correlated with paired Day 1 pre-exposure IGF-I levels (r^2 = 0.64; Fig. 2)
- A slight increase in mean concentration was noted in the pre-exposure samples (68 ± 39 ng/mL [screening] vs. 73 ± 44 ng/mL [pre-exposure], P <0.005)

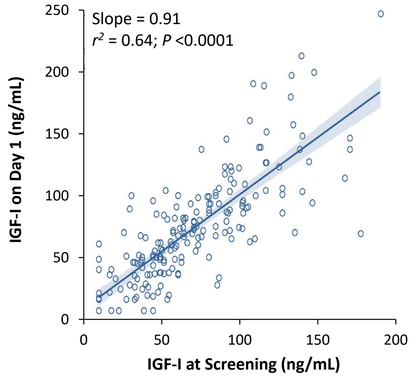

Figure 2. IGF-I Concordance Between Screening and Day 1

- The mean within-subject IGF-I difference was 5.4 ng/mL (median, 4.5 ng/mL; interquartile range, -9.5 to 18 ng/mL; Fig. 3)

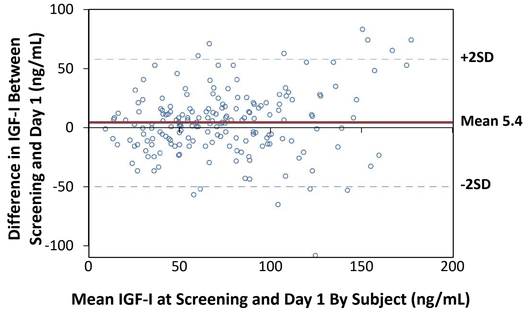

Figure 3. Within-Subject Differences in IGF-I Between Screening and Day 1

- By multiple regression analysis, the difference was greater with older children (P<0.001), lower IGF-I screening values (P<0.0001), and higher GH_{max} (P<0.01), but not affected by gender or the time between sampling days (Table 2)

Table 2. Factors Affecting IGF-I Differences

Factor	Estimate	Std. Error	*P*
Age	5.5	1.07	<0.0001
IGF-I at screening	-0.32	0.06	<0.0001
GH_{max}	2.24	0.77	<0.01
Female gender	3.12	3.76	0.41
Elapsed days from screening to Day 1	-0.04	0.06	0.52

IGF-I SDS

- Various levels of IGF-I SDS have been proposed to aid in PGHD diagnosis
- The likelihood that a second IGF-I SDS value exceeded a proposed SDS cutoff depended on the cut-off level chosen; in this population, the percentage of Day 1 samples exceeding a proposed cutoff was 32% at IGF-I SDS -2, 26% at SDS of -1.5, and 13% at SDS of -1.0 (Fig. 4)

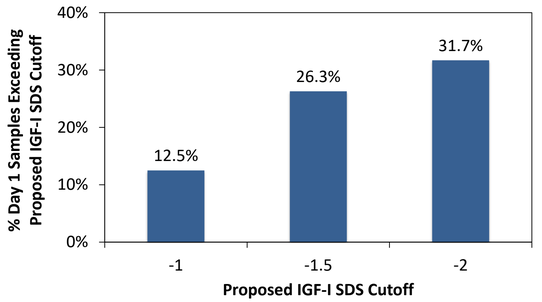

Figure 4. Percentage of Day 1 IGF-I SDS Samples Exceeding Screening IGF-I Cut-off Values of -1, -1.5, and -2

- Fourteen (7.1%) of screening IGF-I values were below the lower limit of detection for IGF-I by LCMS (16 ng/mL); in general, these children had lower GH_{max} (mean, 2.3 ng/mL)

Conclusions:

- This description of within-subject variability of IGF-I shows concordance of paired pretreatment IGF-I in the majority of pre-pubertal PGHD patients
- However, concordance is adversely affected by selection of lower IGF-I SDS cut-off values, and differences in paired IGF-I samples tend to increase at lower IGF-I concentrations and at older ages
- The treatment outcome predictive value of pretreatment IGF-I samples and within-subject variability is under study

References: (1) Cleland et al. *J Pharm Sci.* 2012;101(8):2744-54; (2) Yuen et al. *J Clin Endocrinol Metab.* 2013;98:2595-2603; (3) Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097; (4) Moore et al. ENDO 2017 Annual Meeting. April 1-4, 2017, Orlando, FL; (5) Chandler et al. *Growth Hormone & IGF Research.* 2010;20(Suppl. 1):S65 (Abstract #P74)

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