Somavaratan (VRS-317) Treatment for Pediatric Growth Hormone Deficiency (GHD): VISTA Study Results at 2.5 Years (NCT02068521)

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Disclosures

- George Bright, MD, and Jeffrey Cleland, PhD, are consultants and hold equity interests in Versartis, Inc
- Huong Jil Nguyen, MD, has received research funding from Versartis, Inc
- Bradley S. Miller, MD, PhD, has received grants from Alexion Pharmaceuticals, Inc., Endo Pharmaceuticals, Genentech, Inc., Novo Nordisk A/S, Orphan Reach/Tolmar, Inc., Sandoz International GmbH, Shire Human Genetic Therapies, Inc. and Versartis, Inc. He has also received honoraria from Ferring Pharmaceuticals, Inc., Genentech, Inc., Novo Nordisk A/S, Sandoz International GmbH, and Versartis, Inc
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- David Ng, PhD, is an employee of ResearchPoint Global, a CRO receiving funding from Versartis, Inc
- Eric Humphriss, MBA, is an employee of Versartis, Inc

- Somavaratan (VRS-317) is an investigational agent

Recombinant Human Growth Hormone (rhGH) for Treatment of Pediatric Growth Hormone Deficiency (GHD)

- Therapeutic potential of daily rhGH is well established and has been the primary treatment for pediatric GHD for three decades[1,2]
- Current challenges with daily rhGH preparations include burden of daily subcutaneous (SC) injections[3]
  - Noncompliance has been reported in up to 77% of adults and children with GHD[4,5]
  - Reduced efficacy (decreasing HV-SDS) is significantly associated with number of missed doses per week[3,5,6]

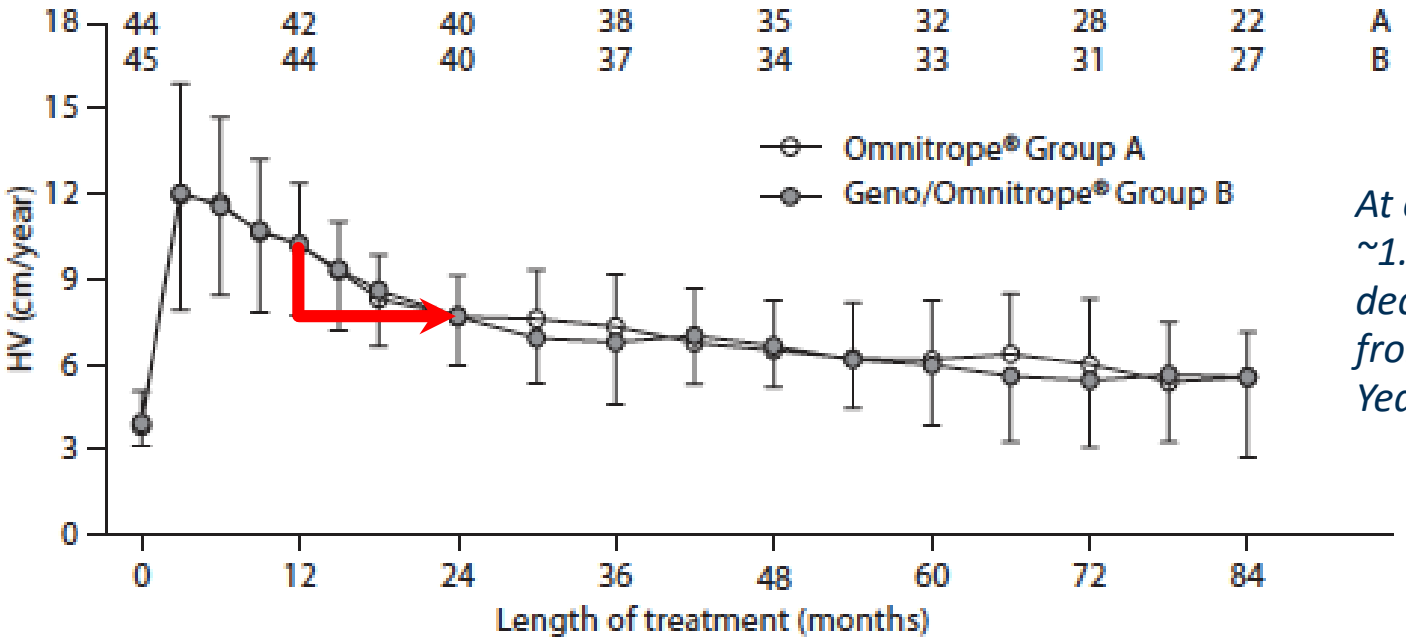
Introduction of a safe and effective long-acting form of rhGH that reduces injection frequency, while maintaining long-term growth response, may improve clinical outcomes while reducing the burden of daily SC injections of rhGH

HV-SDS, height velocity-standard deviation score

[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

rhGH in Pediatric GHD: Decreasing HV After 1st Year

Mean HV Over 7 Years of rhGH Treatment in Children with GHD



At constant dose, ~1.7 cm/year decline in HV from Year 1 to Year 2

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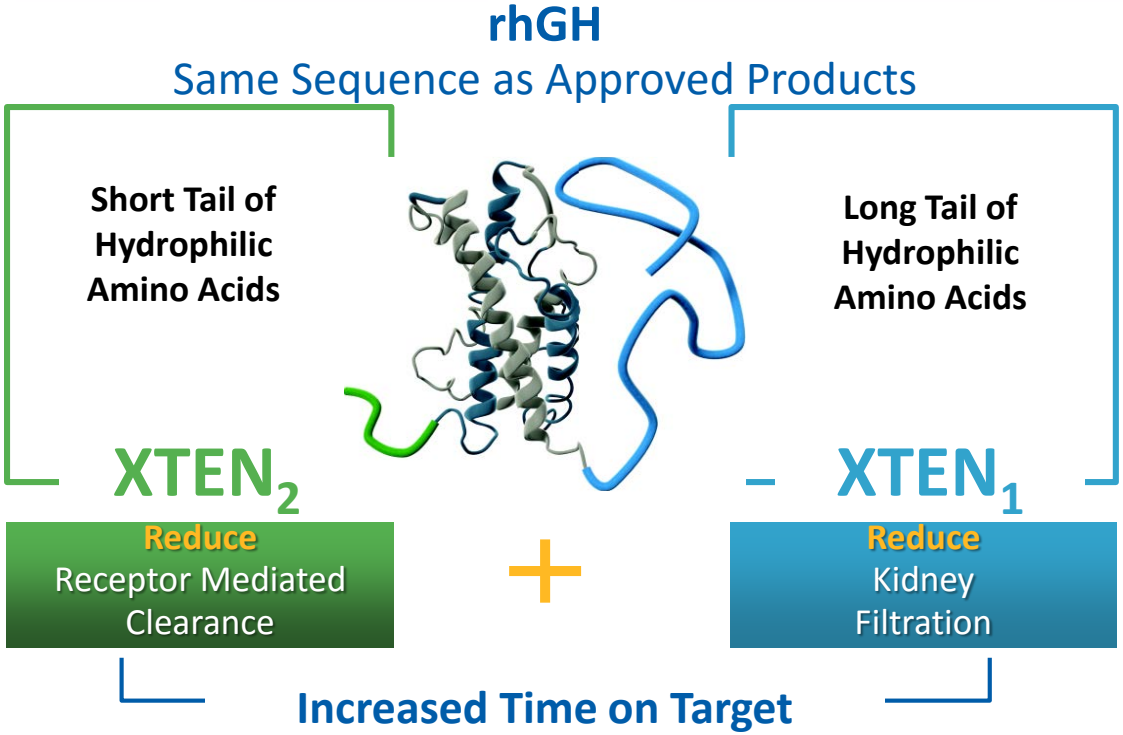
[4] Romer et al. *Hormone Research*. 2009;72:359-369.

Somavaratan (VRS-317)



- In clinical development for treatment of children and adults with GHD
- XTENylation increases half-life through reduced renal and receptor-mediated clearance[1-3]
- Drug peak and AUC exposure proportional to dose[2,3]
- Twice-monthly dosing

[1]Cleland et al. *J Pharm Sci.* 2012;101(8):2744-54; [2]Yuen et al. *J Clin Endocrinol Metab*. 2013;98:2595-603; [3]Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097. [4]Podust et al. *Journal of Controlled Release.* 2015; in press

Somavaratan: Clinical Experience

- **Phase 1 - Adults[1]**
  - 30- to 60-fold increase in elimination half-life and longer IGF-I responses, compared with daily rhGH (N=50)
  - Dose-proportional increases in magnitude and duration of IGF-I responses for up to 1 month after a single dose
  - No study drug related serious adverse events

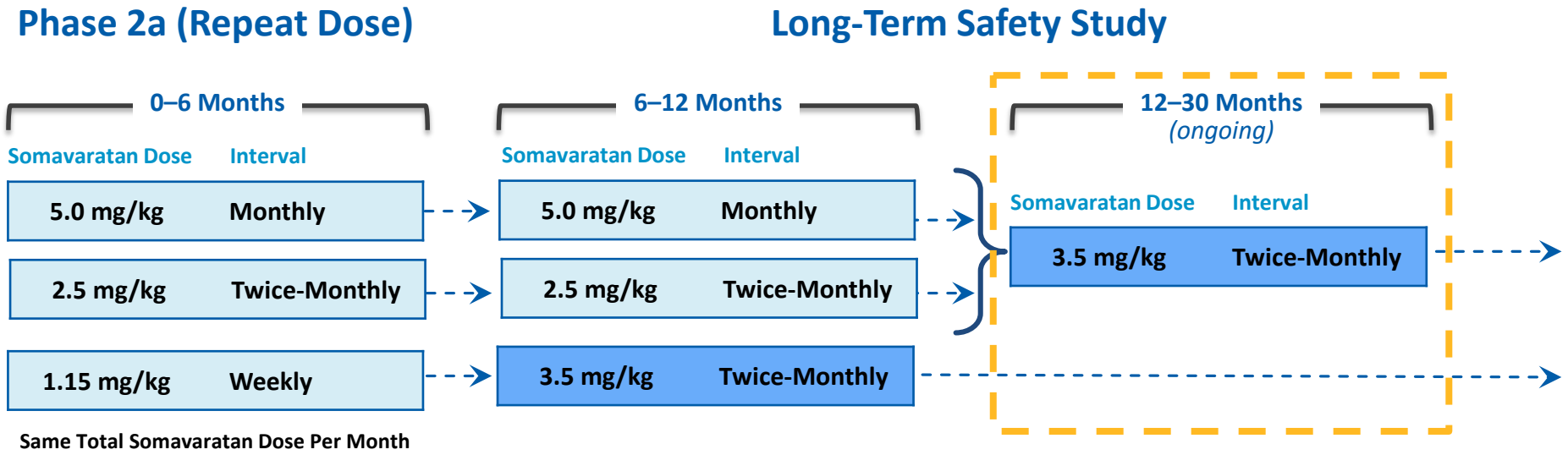
- **Phase 1b/2a - Pre-Pubertal Children[2]**
  - Weekly, twice-monthly, and monthly dosing enabled by dose-proportional increases in magnitude and duration of IGF-I responses
  - Clinically meaningful improvements in height velocity (HV) and IGF-I with all 3 dosing schedules (Phase 2a; N=64)
  - No study drug related serious adverse events

The Open-Label, Long-Term Safety Study (VISTA Study, 13VR3) continues with subjects approaching 3 years of somavaratan exposure

[1]Yuen et al. *J Clin Endocrinol Metab.* 2013;98:2595-603; [2]Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097.

VISTA Study Design

NAÏVE TO TREATMENT PRE-PUBERTAL CHILDREN WITH GHD* IN US



*GHD confirmed by short stature (height-SDS), 2 or more growth hormone stimulation tests, IGF-I SDS, and delayed bone age

- 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[1]
- As of April 2015, dose formulation changed from 50 to 100 mg/mL

 [1]Moore et al. *J Clin Endocrinol Metab.* 2016;101(3):1091-1097.

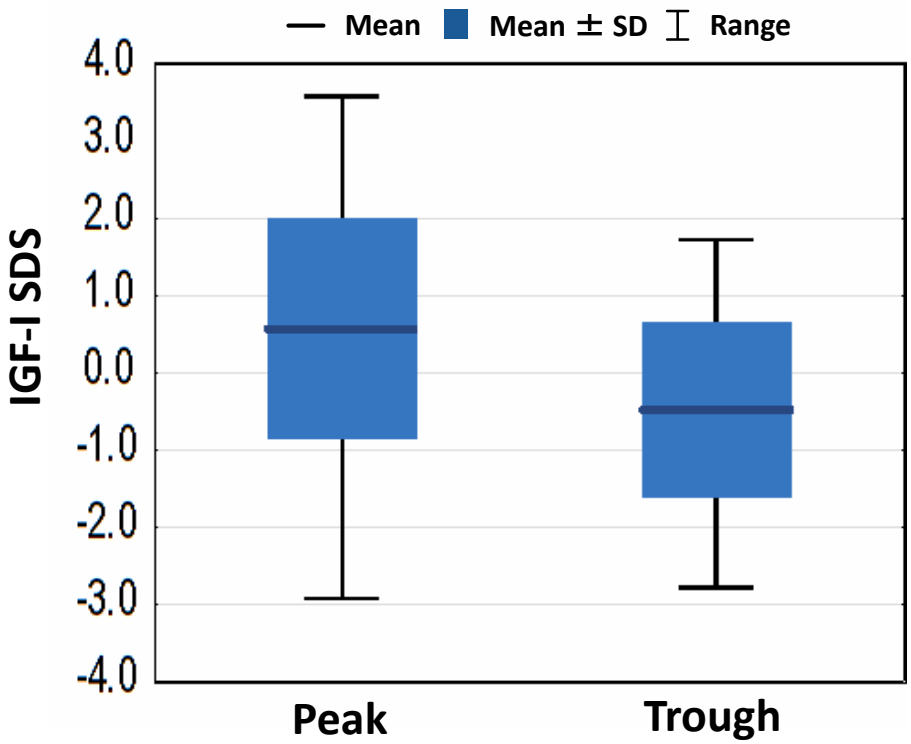
Patient Demographics and Baseline Characteristics

	Subjects Enrolled in Phase 2a (n=64)
Baseline Age, yeaers, mean (SD)	7.8 (2.4)
Gender, n (%)	
Female	27 (42%)
Male	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%)
Height 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)

Baseline characteristics are consistent with a pediatric population with moderate GHD

Results: Pharmacodynamics

During Year 2, IGF-I samples drawn every 3 months, alternating between "peak" (3-5 days after injection) and "trough" (end of dosing cycle), measured by mass spectroscopy

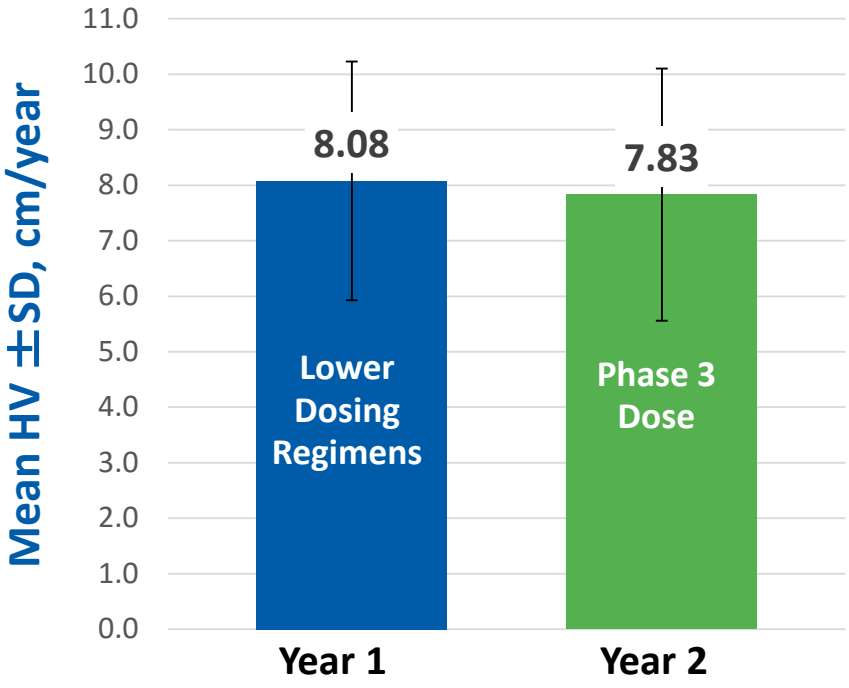


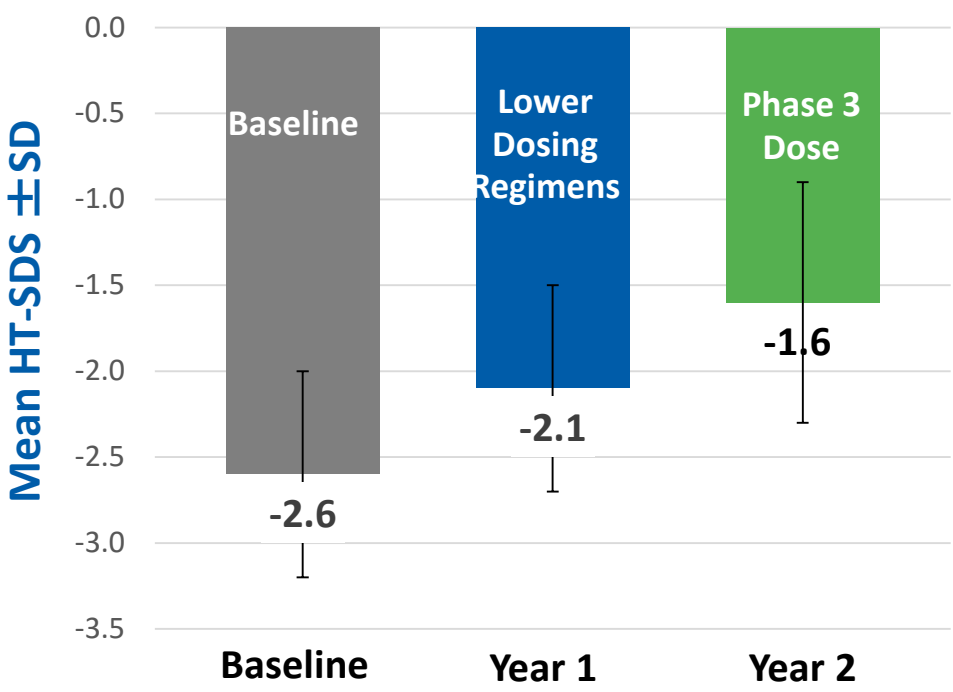
	Screening N=57	Peak n=55	Trough n=48
Mean	-1.49	0.59	-0.47
SD	0.78	1.43	1.14
Range	-3.6, 0.45	-2.9, 3.67	-2.7, 1.77

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)

Results: Efficacy – Height Velocity and Height-SDS

Mean Height Velocity (HV) and Height-SDS in All Evaluable Patients at 2 Years (n=57)

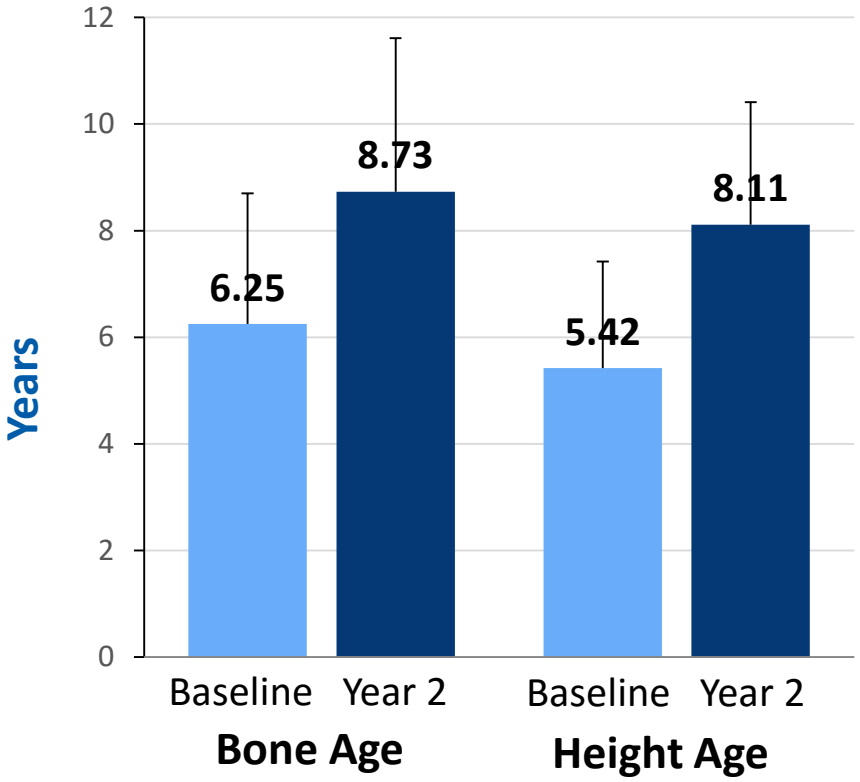




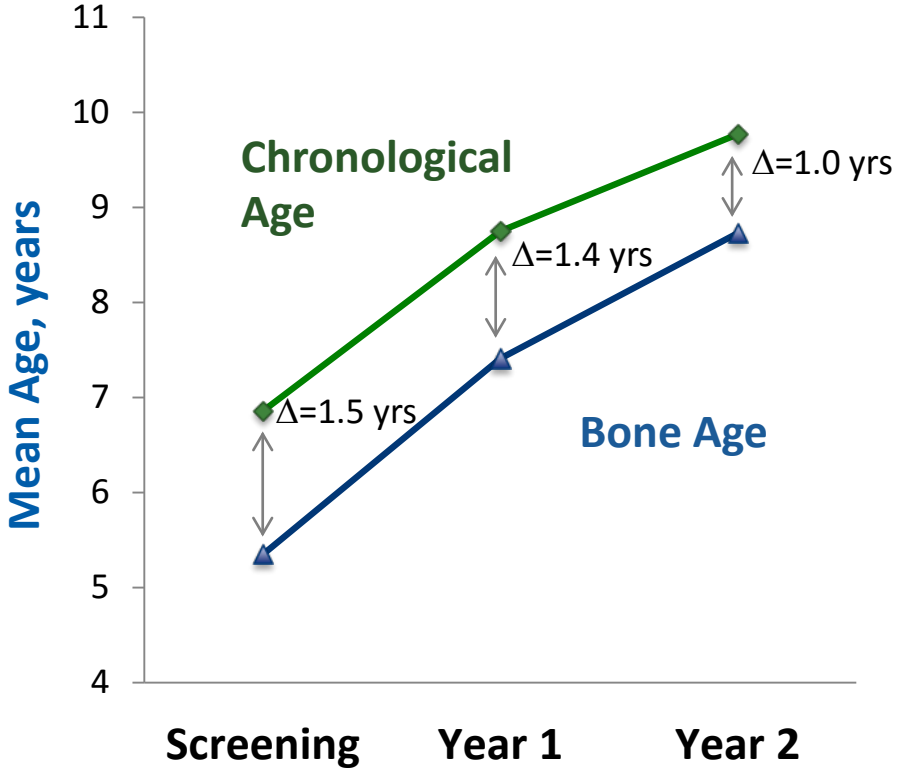
Increasing the somavaratan dose to 3.5 mg/kg twice-monthly resulted in Year 2 HV comparable to Year 1 and continued improvement in HT-SDS

Results: Efficacy – Bone, Height, and Chronological Age

Bone and Height Age Over Time



Chronological Age vs. Bone Age



Mean increase in bone age and height age exceeded years on study, while differences between chronological and bone age decreased over time

Year 2 Efficacy Comparators

STUDY	Second Year Height Velocity (cm/year)
Somavaratan – 3.5 mg/kg twice-monthly	
All subjects with 2-year data (n=57)	7.83 (±2.27)
Daily rhGH in 8-year-old children with moderate GHD	
KIGS database estimates[1] 34 μg/kg/day (European daily dose)	6.9
NCGS database estimates[2] 43 μg/kg/day (US daily dose)	7.9

KIGS, Kabi Pharmacia International Growth Study; NCGS, National Cooperative Growth Study

Selection of the somavaratan 3.5 mg/kg twice-monthly dose is supported by similarities in second year HV (7.83 cm/year) to US estimates (7.9 cm/year) from NCGS

[1]Ranke et al. *J Clin Endocrinol Metab.* 2010;95:1229-1237; [2]Bakker et al. *Hormone Research.* 2008;97(suppl 1):P2-d1-327.

Results: Safety

Treatment-Related Adverse Events (AEs) Occurring in >1 Subject

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 SAEs, no lipoatrophy or nodule formation
- Related AEs were generally mild and transient
- Frequency of AEs declined substantially after initial 6 month exposure period
- 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

- Phase 3 dose selection supported by VISTA study results for subjects switched to 3.5 mg/kg twice-monthly
- 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
- 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

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 Trial

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