HbA_{1c} over Two Years of Treatment with Somavaratan (VRS-317) in Children with Growth Hormone Deficiency (GHD) in the VISTA Study

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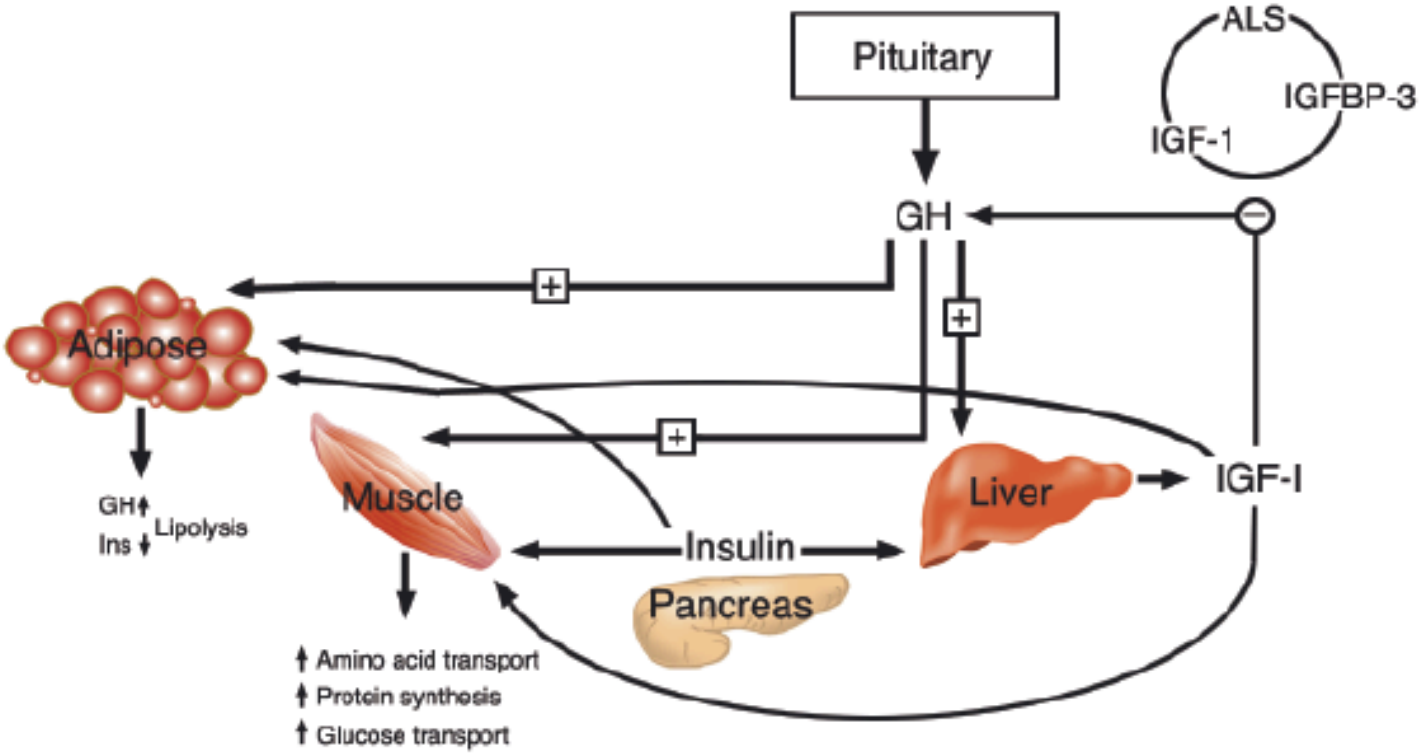
Disclosures

- Will Charlton, MD, Daniela Rogoff, MD, PhD, Eric Humphriss, MBA, and Kelly Di Trapani, RN, BSN, BA, are employees of Versartis, Inc
- Philippe F. Backeljauw, MD, is a consultant for Versartis, Inc
- Somavaratan (VRS-317) is an investigational agent

Growth Hormone and Glucose Homeostasis

- Control of carbohydrate (CHO) and lipid metabolism reflects interplay of nutrient availability, insulin, growth hormone (GH), IGF-I, interactions between CHO and lipid metabolic pathways and a host of other factors
- GH counterregulates peripheral and hepatic effects of insulin on glucose metabolism



IGF-I, insulin-like growth factor

 Møller N and Jørgensen JOL. *Endocrine Rev* 2009;30(2):152-177; Clemmons DR. *J Clin Investigation* 2004;113:25-27.

Endogenous GH Exerts Different Effects during Fasting & Fed States

- In the fed state, GH-induced stimulation of IGF-I and insulin is important for anabolic storage and growth of:
  - Lean Body Mass (LBM)
  - Adipose tissue
  - Glycogen reserves
- During fasting/catabolic states, GH predominantly stimulates the release and oxidation of free fatty acids (FFA), which leads to:
  - Decreased glucose and protein oxidation
  - Preservation of LBM and glycogen stores
- GH-induced insulin resistance protects against hypoglycemia:
  - Development of “stress diabetes” during fasting and inflammatory diseases
  - “Dawn phenomenon”

GH, growth hormone; IGF-I, insulin-like growth factor

Møller N and Jørgensen JOL. *Endocrine Rev* 2009;30(2):152-177.

Effects of Growth Hormone Deficiency on Glucose Homeostasis

IN CHILDREN AND ADULTS WITH GHD, LOSS OF COUNTERREGULATORY EFFECTS OF GH RESULTS IN DYSREGULATED GLUCOSE HOMEOSTASIS[1]

GHD Children	GHD Adults
• Hyperresponsiveness to insulin[1] • Proneness to hypoglycemia[1] • Delayed recovery from hypoglycemia following IV insulin[1] • Reduced elevation in glucose and insulin following exposure to oral glucose and IV arginine, respectively[1]	• Increased rates of abnormal or impaired glucose tolerance[2] • Loss of insulin sensitivity despite normal or elevated levels of insulin[3] • Decreased insulin-stimulated glycogen synthase activity in skeletal muscle[4]

[1]Møller N and Jørgensen JOL. Endocrine Rev 2009;30(2):152-177; [2]Beshyah SA, et al. Clin Sci (Lond) 1995; 89:321-28; [3]Johansson JO, et al. Metabolism 1995;44:1126-29; [4]Hew FL, et al. J Clin Endocrinol Metab 1996;81:555-564.

General Effects of Exogenous Growth Hormone

MODULATION OF INSULIN SENSITIVITY BY rhGH COMPLEX AND INFLUENCED BY MULTIPLE FACTORS

- Change from an insulin sensitive state to a more insulin resistant state
  - Elevated fasting glucose and insulin (INS > GLU)
  - Elevated glucose and insulin responses to meals (INS > GLU)
  - Increased IGF-I and IGFBPs
  - Changes usually modest and within the normal range
  - Effects may be transient
  - Individuals with glucose intolerance may become overtly diabetic if given rhGH

IGF, insulin-like growth factor; IGFBP, IGF binding protein; rhGH, recombinant human growth hormone

Consensus from 2016 Growth Hormone Safety Workshop: Metabolic Risk

Pediatric GHD

- Very low incidence of developing glucose intolerance or overt type 2 diabetes mellitus (DM) during rhGH treatment
- Lifetime risk of glucose intolerance and type 2 DM higher than background population in a number of conditions treated with rhGH, including Turner syndrome and in short children born SGA
- GH treatment does not increase the incidence of type 2 DM in these conditions in the short term

Adult GHD

- rhGH therapy may be associated with the development of glucose intolerance or type 2 DM in the first year of therapy in high risk adult GHD patients (obesity, family history of type 2 DM)
- Monitoring with HbA_{1c} is important

GHD, growth hormone deficiency; HBA_{1c}, hemoglobin A_{1c}; rhGH, recombinant human growth hormone; SGA, small for gestational age

Allen DB, et al. *Euro J Endocrinol* 2016 Feb;174(2):P1-9

Effects of rhGH on Insulin Sensitivity in GHD

- Treatment of GHD with daily rhGH reduces insulin sensitivity, with effects correlating positively to dose and inversely with duration of treatment[1]
- While rhGH-treated GHD adults predisposed to DM are prone to impaired glucose tolerance or overt DM, children on rhGH rarely develop either, but may develop modest insulin resistance[2]
- Long-acting forms of rhGH are being developed to improve treatment outcomes by reducing treatment burden and improving adherence issues; effects of these agents on glucose homeostasis are not well understood[3]

OBJECTIVE

To determine whether somavaratan, a long-acting form of rhGH, has distinct metabolic effects by evaluating its effects on HbA_{1c} in pre-pubertal GHD children

DM, diabetes mellitus; GHD, growth hormone deficiency; rhGH, recombinant human growth hormone

[1]Møller N and Jørgensen JOL. *Endocrine Rev* 2009;30(2):152-177; [2]Allen DB, et al. *Euro J Endocrinol* 2016 Feb;174(2):P1-9; [3]Saenger PH and Mejia-Corletto J. *Endocr Dev* 2016;30:79-97.

Methods

- 64 subjects received somavaratan for 6 months in the Phase 1b/2a study
- 60 elected to remain on somavaratan in the open-label, long-term safety study (13VR3, VISTA)
- All patients transitioned to 3.5 mg/kg twice-monthly by the 6-month time point in VISTA (after 12 months total somavaratan exposure)
- HbA_{1c} was measured at VISTA study entry and yearly thereafter, correlating to months 6, 18, and 30 of somavaratan exposure

Baseline Characteristics are Consistent with a Pediatric Population with Moderate GHD

Patient Demographics and Baseline Characteristics

	Subjects Enrolled in VISTA Study (n=60)
Baseline age, years, mean (SD)	7.8 (2.4)
Gender, n (%)	
Female	26 (43%)
Male	34 (57%)
Race, n (%)	
White	50 (83%)
Asian	4 (7%)
Black or African American	3 (5%)
American Indian or Alaska native	1 (2%)
Other	2 (3%)
Baseline BMI, mean (SD)	16.3 (2.1)

BMI, Body Mass Index

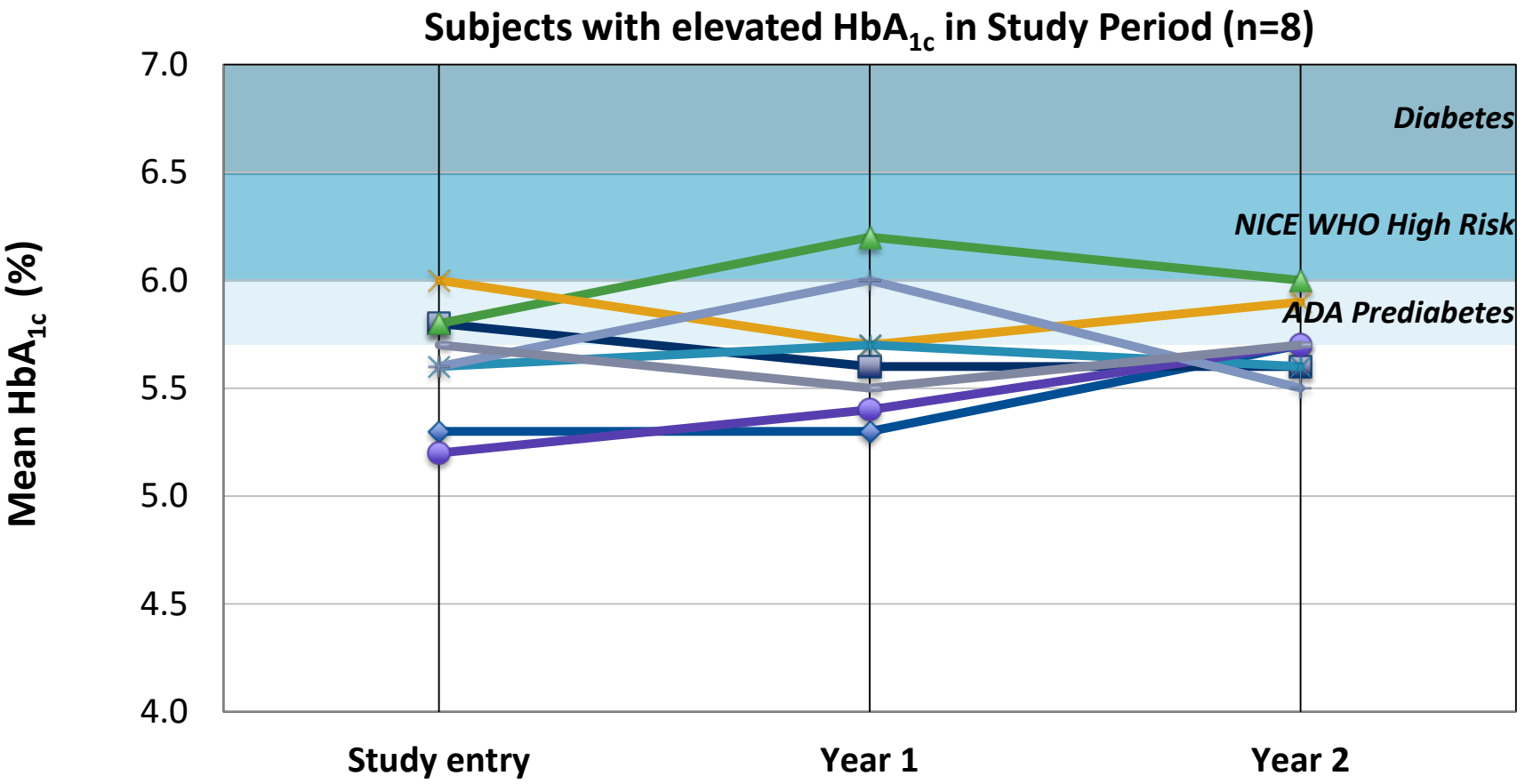
HbA_{1c} in Diagnosis of Diabetes Mellitus

HbA_{1c}		%	mmol/mol
NICE Guidelines[1]	Normal	Below 6.0%	< 42
	High Risk	6.0% to 6.4%	42 to 47
	Diabetes	≥ 6.5% or over	≥ 48
American Diabetes Association 2016 Guidelines[2]	Normal	Below 5.7%	< 39
	Prediabetes	5.7 to 6.4%	39-46
	Diabetes	≥ 6.5%	≥ 48

- The World Health Organization (WHO) recommends a level of 48 mmol/mol (6.5%) for HbA_{1c} as the cut-off point for diagnosing type 2 diabetes[3]

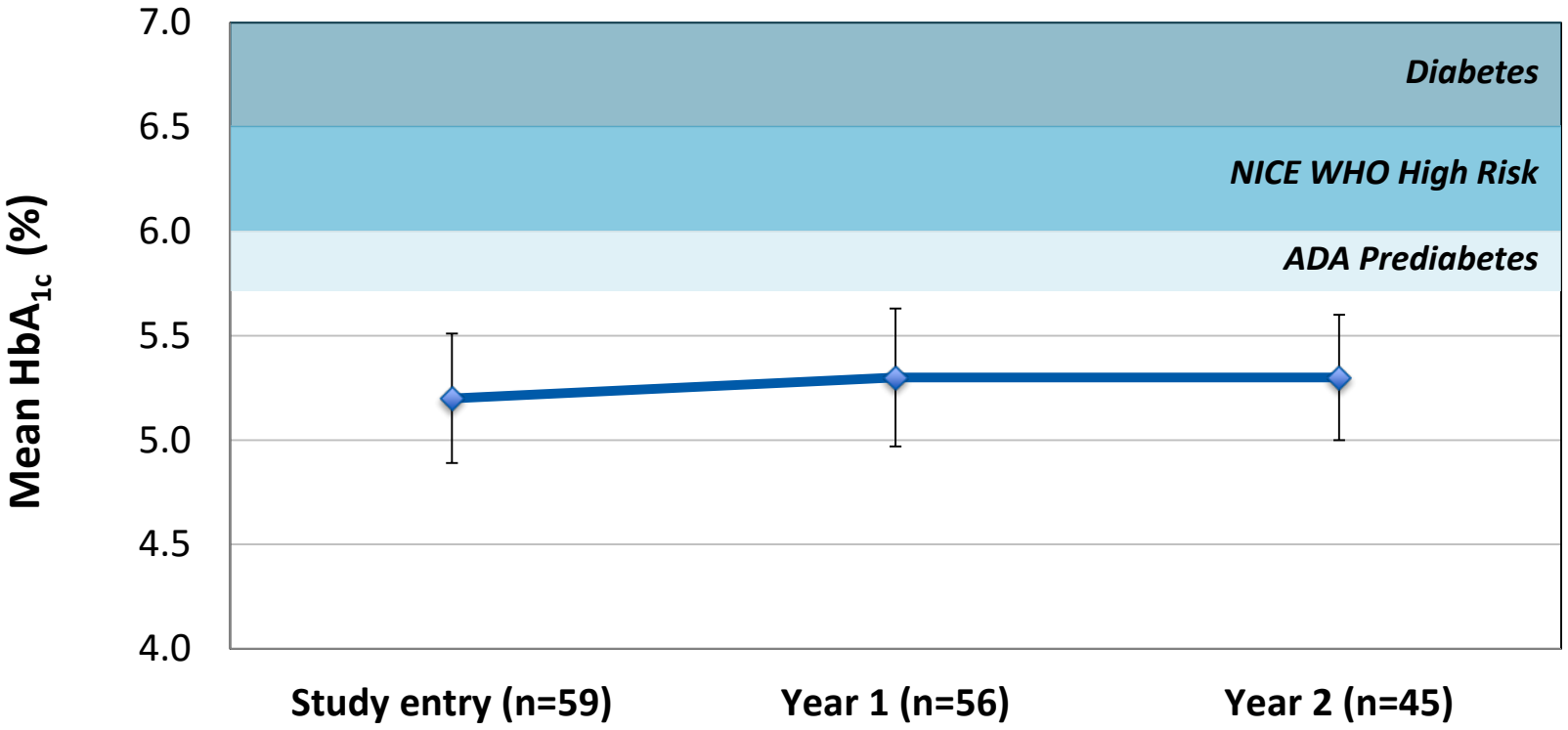
[1]Type 2 diabetes: prevention in people at high risk. Public health guideline. Published: 12 July 2012. http://nice.org.uk/guidance/ph38. [2]American Diabetes Association. Standards of medical care in diabetes—2016. *Diabetes Care*. 2016;39(suppl 1):S1-S106. [3]Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus, Abbreviated Report of a WHO Consultation. 2011.

Results: Individual Subjects with Elevated HbA_{1c} in Study Period



Modest HbA_{1c} Changes in a Few Individual Subjects
No Clear Pattern

Results: Mean HbA_{1c} Over Time in All Subjects



- No changes in mean HbA_{1c} were observed with increased exposure to somavaratan
- No development of overt diabetes mellitus (DM)
- No clinically significant changes in HbA_{1c}

HbA_{1c} was Stable in Pre-Pubertal Children Treated with Somavaratan, and No Subjects Developed Overt DM

Conclusions

- HbA_{1c} was stable in pre-pubertal GHD children treated with somavaratan
- Individual subjects (n=8) showed minor changes in HbA_{1c} over time, and no subjects developed diabetes mellitus
- These findings suggest that somavaratan does not elicit detrimental effects on insulin sensitivity in pre-pubertal GHD children in the current population treated
- Further characterization of the metabolic effects of somavaratan are warranted and are underway

A Phase 3 study of 3.5 mg/kg Twice-Monthly Somavaratan is Ongoing (NCT02339090)

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