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Plenary: Plenary Session 1

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Genetic diagnosis of growth hormone deficiency in children

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Genetic diagnosis of GHD is important to establish the etiology, predict prognosis including persistence of hormone deficiency as well as development of additional hormone deficiencies, allow genetic counseling and expand the knowledge of mechanisms involved in pituitary organogenesis and GH secretion. Congenital GHD can be isolated (IGHD), combined with deficiency of other pituitary hormones (CPHD), associated to developmental midline facial and/or brain defects, or with syndromes affecting different organs. The study of naturally occurring mutations in transcription factors and signaling molecules in mice and of transgenic animals improved our understanding of pituitary development and led to the diagnosis of several genetic causes of hypopituitarism by the candidate gene approach. The frequency of genetic diagnosis in congenital GHD has been higher in patients with a positive family history and/or offspring of consanguineous parents, usually related to founder effects. In sporadic cases the incidence has been lower and interaction of gene variants with environmental risk factors may explain incomplete penetrance. Hormonal studies and imaging of the hypothalamic-pituitary area and of other brain structures have been useful to select candidate genes for genetic studies. More recently, the advent of massive parallel sequencing has expanded the phenotypes related to known genes and indicated variants in potential novel players and modulating factors whose interpretation has been challenging.

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Current ideas on the biology of IGFBP-6: more than an IGF-II inhibitor?

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IGFBP-6 is unique among the IGFBPs for its ~50-fold preferential binding of IGF-II over IGF-I. It is a relatively selective inhibitor of IGF-II actions, including proliferation, survival and differentiation of a wide range of cells. However, IGFBP-6 has also recently been shown to have a number of IGF-independent actions; for example, IGFBP-6 inhibits angiogenesis in vitro and this was confirmed in vivo during zebrafish development and in rhabdomyosarcoma xenografts. IGFBP-6 expression is decreased in a number of cancer cells and it has been postulated to act as a tumor suppressor, which may be facilitated by these complementary inhibitory effects on IGF-II actions and angiogenesis. However, IGFBP-6 also induces migration of tumor cells including rhabdomyosarcomas by an IGF-independent mechanism. In different cell lines, this chemotactic effect is mediated by p38, ERK and JNK MAP kinases and cross-talk between them. Prohibitin-2 is a ubiquitously expressed protein that modulates a range of cellular functions by its effects in mitochondria and other cellular compartments. IGFBP-6 binds to prohibitin-2 on the cell surface and the latter is required for IGFBP-6-induced migration by a mechanism that is independent of MAP kinases. IGFBP-6 expression is increased in a small number of cancers, which may reflect either IGF-independent actions or a compensatory mechanism to control IGF-II actions. The relative balance of IGF-dependent and IGF-independent actions of IGFBP-6 in vivo together with the related question regarding the roles of IGFBP-6 binding to IGF and non-IGF ligands are keys to understanding the physiological role of this protein.

Parallel Oral Session: Parallel I
Oral Presentations 1 – GH Clinical Correlations

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Results of somavaratan (VRS-317) dose increase in the first two years of treatment in pre-pubertal children with growth hormone deficiency (GHD)

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Background: Somavaratan demonstrated height velocity (HV) and IGF-1 improvements in Phase 2a (n=64), and an ongoing extension study. Dosing frequency varied in Year 1, but all subjects initially received 5 mg/kg monthly (M) in divided doses. By Year 2, 58 subjects increased to 7 mg/kg divided twice-monthly (TM). IGF1-SDS, treatment-related adverse events (AEs), and growth are compared at both doses.
Methods: 23 subjects initially received 5 mg/kg/M, 22 increased to 3.5 mg/kg/TM in Year 2. 20 started on 2.5 mg/kg/TM, 17 increased in Year 2. 21 received 1.15 mg/kg/weekly for 6 months; 1/21 discontinued, 5/21 increased to 3.5 mg/kg/TM at M6, 15/21 increased at M9.
Results: Baseline mean IGF1-SDS for the total cohort was −1.71 (0.78). Dose increase to 3.5 mg/kg/TM increased mean IGF1-SDS peak from 0.09 (1.35) to 0.60 (1.42) and trough from −1.39 (1.03) to −0.67 (1.25). On the lower dose, 7 subjects in the M cohort had IGF1 excursions >2SDS, one of which was >3SDS (range 2.05, 3.75). After dose increase, 12 IGF1-SDS excursions >2 occurred in n=9, 2 of which were >3SDS (range 2.01, 3.67). All peaks >2SDS with subsequent trough values were transient, none were associated with AEs. Fewer subjects reported related AEs after dose increase than before (8 v. 35). No related SAEs were reported. Dose increase maintained annualized HV into the second year of treatment (8.04±2.59 cm/year vs. 7.96±2.32), and HT-SDS continued to improve (−2.3±0.63 vs. −1.7±0.76).

Table 1 (abstract 72)
Clinical characteristics of children and young adults who had a cerebrovascular event based on risk group

Risk group category	No of patients (sex)	Age median (range)	Age at AE median (range)	GH dose at AE in mg/kg/wk median (range)	SAE	Causality	Outcome	Crude incidence rates per 100,000 p/years (95% CI)
Gp1 (low): IGHD, ISS and SGA (low)	5 (1F, 4M)	8.6 (3.9–11.8)	9.8 (5.2–17.4)	0.27 (0.21–0.39)	5 Yes	4 No 1 Missing	2 recovered 2 recovered with a sequelae 1 unknown	2.7 (1.2–6.4)
Gp2 (intermediate): Organic GHD, severe chronic pediatric diseases, TS and PWS	8 (3F, 5M)	6.6 (1.0–12.7)	9.9 (7.9–17.8)	0.21 (0.14–0.32)	7 Yes, 1 No	6 No 2 Missing	2 recovered 5 deaths 1 unknown	10.1 (5.1–19.9)
Gp3 (high): Organic GHD (malignant tumor), craniopha-ryngioma and CRI	14 (6F, 8M)	9.3 (2.6-15.6)	13.1 (6.4–17.5)	0.21 (0.12–0.31)	14 Yes 2 Yes 1 Missing	11 No	4 recovered 1 recovering 6 recovered with a sequelae 3 deaths	52.8 (31.4–88.5)

Conclusions: Increasing somavaratan dose to 3.5 mg/kg/TM safely improved IGF1-SDS and HV. Transient IGF1 excursions occurred in a small number of subjects, without apparent clinical significance.

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Cerebrovascular morbidity and mortality in GH-treated children and adults: experience from KIGS (Pfizer International Growth Database) and KIMS (Pfizer International Metabolic Database)

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Background: GH treatment (GHT) of children with growth disorders and adults with GH Deficiency (GHD) is considered to be safe and efficacious. A recent study evaluated the incidence of stroke morbidity and mortality in GHT French patients prompting a thorough review of all cases of cerebrovascular (CV) hemorrhagic and ischemic strokes reported under GHT in children and adults enrolled in KIGS and KIMS.
Methods: In KIGS, 82,658 (males 58 %) patients up to 18 years of age, the crude Incidence/100,000 patient-yrs of treatment was calculated in 3 risk categories. In addition 771 KIMS patients (males 64%) with childhood onset GHD were followed from entry into KIMS to age 40 or last visit, if it occurred earlier.
Results: 27 CV events, 10 hemorrhagic and 17 ischemic strokes were reported in KIGS. GHT mean (SD) duration: 3.2 (3.0) years; dose (mg/kg/w): 0.23 (0.06); follow-up time until CV event: 3.4 (3.0) years. Crude incidence rates/100000 p-years (95% CI) were in GHD, ISS and SGA (n=56,380) 2.7 (1.2-6.4), in Organic GHD, TS and PWS (n=18,969) 10.1 (5.1–19.9) and in organic GHD secondary to a malignant tumor, craniopharyngioma and CRI (n=7,309), 52.8 (31.4–88.5). Eight patients died, none in a low- risk category (IGHD, ISS or SGA). One case, who recovered, was reported in KIMS during 4178 p-years (TIA; GH dose 0.38 mg/day).
Conclusions: The risk of ischemic or hemorrhagic stroke in GH treated children, without known risk factors, is within the reported range in population based studies. Study limitations include lack of appropriate comparator groups and short-term follow-up.

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GH actions during fasting in obese human subjects: impact of GH blockade

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Background: Obesity is associated with insulin resistance and metabolic inflexibility. Prolonged fasting is a useful model to investigate the shift in metabolism from glucose to lipid oxidation and the induction of insulin resistance. Since GH promotes lipolysis we aimed to study the impact of GH blockade by means of pegvisomant administration in fasting obese subjects.
Methods: Nine obese males were studied on three occasions in a randomized, single-blinded, cross-over trial: After an overnight fast, after 72 hours of fasting and concomitant saline injections, and after 72 hours of fasting and concomitant pegvisomant injections (20 mg × 3).
Results: Pegvisomant reduced the glucose infusion rate during the clamp owing to a lower hepatic glucose production without significantly increased peripheral glucose uptake (P=0.18). GHR blockade also enhanced the fasting-induced IGF-I reduction (P<0.05) without enhancing the fasting-induced increase in GH levels (P>0.05). Fasting alone induced a marked increase in FFA levels and lipid oxidation, which was not influenced by pegvisomant, but pegvisomant as compared with saline increased glycerol levels during fasting (P<0.05). Fasting furthermore decreased basal glucose oxidation independent of pegvisomant (P<0.05).
Conclusions: 1) Pegvisomant-induced suppression of GH activity during fasting in obese subjects reverses hepatic—but not peripheral—insulin resistance and lowers hepatic IGF-I production, 2) Pegvisomant also resulted in elevated circulating glycerol levels without affecting serum FFA levels or lipid oxidation 3) Our data support a role for GH in the regulation of glucose and fat metabolism during fasting in obese subjects.

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Candidate selection of a long-acting growth hormone antagonist to treat acromegaly

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Background: Pegvisomant, a growth hormone antagonist (GHA) controls disease in >95% cases, but requires high dose daily injections and was not considered cost-effective in the UK (2). We developed a technology for a long-acting GH through fusion to its binding protein (GHBP) (2). We adapted this technology to generate a GHA.