completed 12 months of treatment could be enrolled into an open-label extension (OLE).
**Aims:** Evaluate the safety and efficacy of long-term exposure to somatrogon in pediatric pts with GHD who continued in the OLE for up to an additional 5 years.
**Methods:** Methods for the main phase 2 study were published previously (Zelinska et al, 2017), in which 53 pts were randomized to 1 of 3 weekly somatrogon dose cohorts (0.25, 0.48, and 0.66 mg/kg/week) or the daily Genotropin cohort (0.24 mg/kg/week) for 12 months. After the main study (Periods I/II), 48 pts who consented to participate continued in the OLE, consisting of 3 periods: Period III=12 additional months at original somatrogon dose (Genotropin recipients randomized to 1 of the 3 somatrogon dose regimens); Period IV=subsequent years 2-4 with all pts receiving somatrogon at 0.66 mg/kg/week; Period V=ongoing, with pts transitioned from the vial to a pre-filled pen device at the same somatrogon dose (0.66 mg/kg/week). Data up to 1 year of Period V are reported.
**Results:** Overall subject retention in different periods of this long-term study ranged from 87.5% to 97.7%. 39 pts (81.3%) reported at least one treatment-emergent adverse event (TEAE). Most TEAEs were mild or moderate in intensity and most were classified as unrelated to study treatment. 3 pts (6.3%) reported at least 1 serious adverse event (SAE); most SAEs were considered unrelated to study treatment, except for 1 instance of scoliosis. At the end of Period III, the mean annual height velocity (HV) was similar for the 0.25 and 0.48 mg/kg/week dose cohorts (7.73±1.89 and 7.54±1.28 cm/year, respectively) but was higher in the 0.66 mg/kg/week dose cohort (8.81±1.12 cm/year), consistent with the results of the main study. The HV at Periods IV and V showed sustained growth response. Height SDS showed consistent improvement and near normalization of height for age and gender after up to 6 years on somatrogon, irrespective of initial cohort assignment; height SDS at baseline of the main study was -3.98±1.22 and was well within the normal range at -0.69±0.87 at the end of Year 1 in Period V. IGF-1 SDS values remained above baseline and were maintained within the therapeutic target range with weekly somatrogon treatment at all time points in all OLE periods. Anti-drug antibodies (ADAs) were reported in 18 pts, of which 10 pts had ADAs in the main study. The presence of ADAs did not impact efficacy or safety.
**Conclusions:** Somatrogon administered once weekly for up to 5 years after the main study was generally well tolerated and participants showed sustained improvement in annual HV, height SDS, and delta height SDS.

# Pediatric Endocrinology
## GROWTH AND GROWTH HORMONE

### *Specificity for the Epiphyseal Round Cell Layer is Significantly Associated With Height GWAS*

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Human height is a model polygenic trait with thousands of height-related SNPs identified in GWAS to date. An important determinant of height is the proliferation and hypertrophy of growth plate chondrocytes during childhood long bone elongation. Connecting the expression of specific genes that affect skeletal biology to associated variants in GWAS remains a difficult challenge. To connect the genetics of height and growth plate gene expression, we studied the relationship between gene expression in the murine growth plate and common-variant associations from GWAS of height. To obtain gene expression data from the growth plate, we dissected three layers of murine tibial growth plates, extracted RNA from each layer, and measured expression using the Affymetrix GeneChip 430 3.0. For each gene, we derived a specificity score for each growth plate layer, and SNP-level p-values from a published GWAS of height (N~700000) were combined into gene-level p-values using MAGMA. We then used MAGMA to test for association between specificity of expression for each growth plate layer and the GWAS gene level p-values for height. We found that specificity for the round cell layer is significantly associated with height GWAS p-values ($p = 8.5x10^{-9}$). This association remains when we condition on each of the other cell layers and on membership in a set of genes from OMIM that cause skeletal growth disorders ($3.3x10^{-8} < p < 4.1x10^{-6}$). We replicated this result in a RNA-seq dataset of maturing chondrocytes sampled at three time points during development in vitro (days 3, 5, and 10): we found that z-scores for expression in the earliest two days of development are significantly associated with gene-level p-values from height GWAS ($p_{Day3} = 1.2x10^{-21}$ and $p_{Day5} = 2.0x10^{-20}$) and that this association remains after conditioning on the other timepoints and on the OMIM gene set ($3.1x10^{-20} < p_{Day3} < 8.3x10^{-5}$; $3.7x10^{-19} < p_{Day5} < 0.002$). We then performed pathway analysis of genes that are both highly specific to the round layer and highly significant in GWAS using Enrichr. Together, our results suggest that genes expressed in early chondrocyte development (the round cell layer) are particularly relevant to the contribution of growth plate-expressed genes to height. This conclusion both sheds light on the regulation of human skeletal growth and also helps prioritize relevant genes implicated from the height GWAS in skeletal biology.

# Pediatric Endocrinology
## GROWTH AND GROWTH HORMONE

### *Stratifying the Genetic Aetiology in Children Born Small for Gestational Age With Persistent Short Stature (SGA-SS)*

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**Background:** Ten percent of children born small for gestational age with a birth weight and/or length of below -2 SD for their gestational age fail to catch-up and remain short during childhood (SGA-SS). The etiology of SGA-SS is heterogeneous: some children have specific phenotypic features that allow targeted genetic testing; in others, elucidating genetic or environmental background is more challenging. **Aim:** To decipher genetic etiologies among a large single-center cohort of SGA-SS children and to stratify them according to molecular mechanisms leading to pre- and postnatal growth failure. **Patients/Methods:** In our center 447 children (223 females) fulfilled the criteria of SGA-SS. Of these 182 families agreed to take part and offered the child's and both parents' DNA for genetic testing by a panel of 399 growth-related genes, or by Whole Exome Sequencing (WES). The results were processed by a bioinformatic pipeline and detected variants were filtered using variant analysis software. Pathogenic or likely pathogenic variants (according to ACMG standards and guidelines) were confirmed by Sanger sequencing. **Results:** The genetic etiology was elucidated in 73/182 (40%) children so far. We confirmed (likely) pathogenic gene variants affecting pituitary development and/or the GH-IGF-1 axis in 10/73 (14%) patients (*PTCH1, HGMA2* [in two]*, OTX2, LHX4, GHSR, STAT3, IGFALS, IGF1R* [in two]), abnormal components of cartilaginous matrix in 17/73 (23%) (*ACAN* [in two]*, FLNB* [in three]*, FBLN5, COL11A1*[in four]*, COL1A2, COL2A1*[in five]*, MATN3*), impaired paracrine regulation of chondrocytes in 4/73 (6%) *(NPR2* [in three]*, FGFR3)*, *SHOX* gene defects in 12/73 (16%), gene variants affecting other components of intracellular regulation and signaling in 9/73 (12%) (*CDC42, KMT2A, KMT2D, NSD1, SRCAP, PRG4, PTPN11, SON, LMNA*), Silver-Russell syndrome (11p15 [in seven] or UPD7) in 11/73 (15%), and miscellaneous single-gene or chromosomal conditions (*TRPS1, TRHR, RAI1*, chromosomal microdeletions and/or translocations) in an additional ten (14%) children. **Conclusions:** In our study we showed that by using current genetic techniques we were able to elucidate the genetic cause in a significant number of patients born SGA-SS. The genetic etiology spectrum of SGA-SS reflects the complex system of growth regulation, with a significant role of growth plate genes that are causative in 33/73 (45%) cases clarified thus far. **Acknowledgements:** The study was co-funded by grants AZV NV18-07-00283 and GAUK 408120.

# Pediatric Endocrinology

## GROWTH AND GROWTH HORMONE

### *Sub-Optimal Adherence With Daily Growth Hormones Increases With Each Year of Treatment in a US Commercial Claims Database*

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**Introduction and Objective:** Pediatric growth hormone deficiency (pGHD) occurs in approximately 1 in 4,000 children. The main manifestation is short stature managed with daily injections of somatropin, a recombinant human growth hormone (r-hGH). Prior research has shown that children with good adherence with r-hGH have significantly greater linear growth compared to those with sub-optimal adherence. While previous studies have found sub-optimal adherence with daily r-hGH injectables among children with pGHD, to date, r-hGH adherence has not been studied among large, usual-care populations using validated measurements of adherence. We describe adherence to somatropin treatment over 4 years in a population-based study.
**Materials and Methods:** A retrospective cohort analysis of commercially insured patients ≥3 and <16 years, diagnosed with pGHD, newly treated with somatropin from 01 January 2002 through 31 December 2019 (study time period) was conducted using Optum De-identified Clinformatics Data Mart database. Index date was defined as the first prescription for somatropin between 01 July 2002 to 30 September 2019. Four patient cohorts were identified (12, 24, 36, and 48 months of post-index continuous enrollment). The demographic and clinical profiles of children with pGHD treated with daily injections of somatropin who have good adherence and those with sub-optimal adherence were characterized. Good adherence was defined as medication possession ratio (MPR) of ≥ 80%, sub-optimal adherence as MPR <80%. Logistic regression models will evaluate the relationship between demographic characteristics (age, gender, race/ethnicity) and adherence (good vs. sub-optimal).
**Results:** Patient characteristics were similar across each cohort; in the 12-month cohort (n=3091), mean age was 11.34 ±2.89 years, 75.9% were male, 70.9% white, 9.4% Hispanic, 3.6% Asian, and 3.1% black. At 48 months, 1193 (38.6%) of the 12-month cohort remained for follow-up. At 12 months, 80.1% had good adherence and mean (95% CI) MPR was 0.89 (0.88-0.89) while mean (95% CI) MPR at 48 months was 0.82 (0.81-0.83). The proportion with good adherence at months 24, 36, and 48 were 70.2%, 65.6%, and 64.0%, respectively. Adherence was not associated with age or gender. Blacks and Hispanics consistently exhibited lower adherence. At 12 months, good adherence was observed among 85.7% of Asians, 80.0% of whites, 77.2% of Hispanics, and 76.0% of blacks; at 48 months, good adherence was observed among 73.9% of Asians, 65.4% of whites, 56.8% of blacks, and 55.2% of Hispanics. Logistic regression model results will be provided.
**Conclusion:** Although the majority of children with pGHD demonstrated good adherence with a daily r-hGH regimen, sub-optimal adherence increases with treatment duration and is higher among black and Hispanic children. Strategies that facilitate good adherence to r-hGH may support improved clinical outcomes.

# Pediatric Endocrinology

## GROWTH AND GROWTH HORMONE

### *Switch Data From the Open-Label Extension of the Pivotal Phase 3 Study of Once Weekly Somatrogon Compared to Daily Somatropin in Pediatric Patients With Growth Hormone Deficiency (pGHD)*