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.

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GROWTH AND GROWTH HORMONE

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

Nora Edwards Renthal, MD PhD[1], Priyanka Nakka, PhD[1], John Baronas, MS[1], Henry M. Kronenberg, MD[2], Joel N. Hirschhorn, MD,PhD[1].
[1]Boston Children's Hospital, Boston, MA, USA, [2]Massachusetts Gen Hospital, Cambridge, MA, USA.

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.

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

Ledjona Toni, MD[1], Lukas Plachy, MD[2], Petra Dusatkova, Dr[1], Lenka Elblova, Dr.[1], Shenali Anne Amaratunga, MD[3], Stanislava Kolouskova, MD[1], Barbora Obermannova, MD[1], Marta Snajderova, MD,PhD[4], Zdenek Sumnik, MD,PhD[5], Stepanka Pruhova, PhD[6], Jan Lebl, MD,PhD[7].
[1]Department of Pediatrics, 2nd Faculty of Medicine, Charles University and University Hospital Motol, Prague, Czech Republic, [2]Second Faculty of Medicine, Charles University in Prague, Motol University Hospital, Prague, Czech Republic, [3]Fakultni nemocnice v Motole, Praha - Smchov, Czech Republic, [4]University Hospital, Charles University - 2nd Medical Faculty, Prague 5 - Motol, Czech Republic, [5]Faculty Hospital Motol, Prague, Czech Republic, [6]2nd Medical Faculty Charles University,