support to reach longer persistence of use and subsequently optimal clinical outcomes.

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Pharmacokinetics and Pharmacodynamics of Macimorelin Acetate (AEZS-130) in Paediatric Patients With Suspected Growth Hormone Deficiency (GHD)

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Growth hormone deficiency (GHD) in children is a rare, aetiologically diverse condition that results in growth failure and short stature. Inadequate response to two different growth hormone stimulation tests (GHST) is required for the diagnosis of GHD. Macimorelin acetate, a potent, orally administered growth hormone (GH) secretagogue, is approved by the FDA and EMA for the diagnosis of adult GHD. Study AEZS-130-P01 is the first of two studies to investigate macimorelin acetate as a diagnostic test in children with suspected GHD.

This was an open-label, group comparison, dose escalation trial to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of single-dose 0.25, 0.5 and 1 mg/kg oral macimorelin acetate in paediatric subjects with suspected GHD. The macimorelin GHST was administered between two standard GHST, conducted as per local clinical practice, with a recovery period of 7-28 days between tests. Blood samples were collected pre-dose (±15 min) and 15, 30, 45, 60, 90, 120 and 360 minutes after macimorelin acetate intake.

Overall, 24 paediatric subjects (8 per cohort [C1, C2, C3]) were included in the pharmacokinetic/pharmacodynamic (PK/PD) analysis. Five males and 3 females were observed in C1 and C2, 7 males and 1 female in C3. In all three cohorts, at least 3 subjects represented Tanner stages I or II. All 24 subjects (100%) were white, with a median age of 9.8, 9.0 and 10.5 years (range 4-15 years) and a median body-mass index of 16.1 kg/m^2 (12.4-21.4 kg/m^2) at screening. Overall, 88 adverse events were reported, many related to the standard GHST; none were considered related to the macimorelin test. Maximum plasma concentrations for macimorelin were mainly observed between 30-45 min. The mean C_{max} values were 3.46, 8.13 and 12.87 ng/ml for C1, C2, and C3, respectively. The AUCs increased with dose; the mean AUC_{0-6} values were 6.69, 18.02 and 30.92 h*ng/mL. The mean elimination half-lives were 1.22, 1.61 and 1.71 h, respectively. PK and PD profiles for all three cohorts were comparable, with peak GH levels mainly observed within 30-60 min following macimorelin intake.

Macimorelin acetate was safe and well tolerated in all dosing cohorts. A dose-dependent increase in macimorelin C_{max} and AUC in children and adolescents correlated well with data from adult subjects. A robust dose-proportional GH response was also achieved. PD results showed that GH response was comparable in all dose groups, with a slight shift to earlier t_{max} at higher macimorelin doses.

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Phase 3 Study Evaluating Once Weekly Somatrogon Compared to Daily Genotropin in Japanese Patients With Pediatric Growth Hormone Deficiency (pGHD)

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Objectives: Somatrogon is a long-acting recombinant human growth hormone consisting of the amino acid sequence of human growth hormone and three copies of the carboxy-terminal peptide of human chorionic gonadotropin. Somatrogon is being developed as a once weekly treatment for children with pGHD. A Phase 3 trial was designed to compare the efficacy and safety of somatrogon administered once weekly with Genotropin administered once daily in Japanese patients with pGHD (ClinicalTrials.gov: NCT03874013).

Methods: 44 Japanese pGHD patients (age 3-11 years) were randomized in a 1:1 ratio to receive either once weekly somatrogon (0.66 mg/kg/week) or once daily Genotropin (0.025 mg/kg/day) subcutaneously for 12 months. Somatrogon-treated patients had a pharmacokinetic assessment in the first 6 weeks with dose escalation occurring in 3 steps, at 0.25, 0.48, and 0.66 mg/kg/week, for 2 weeks at each dose. For the remaining 46 weeks, patients in the somatrogon treatment group continued to receive somatrogon at a dose of 0.66 mg/kg/week. The primary endpoint of the study was annualized height velocity (HV) at 12 months.

Results: Baseline characteristics were balanced and comparable between the two treatment groups. The least square means of HV at month 12 were 9.65 cm/year in the somatrogon group (n=22) and 7.87 cm/year in the Genotropin group (n=22), with a point estimate treatment difference of 1.79 cm/year (95% confidence interval: 0.97, 2.60) in favour of somatrogon. The point estimate was greater than the pre-established mean treatment difference

of -1.8 cm/year, which was the non-inferiority margin met in the global Phase 3 study (n=224) with somatrogon (0.66 mg/kg/week) and Genotropin (0.034mg/kg/day) (ClinicalTrials.gov: NCT02968004). Most of the adverse events were mild to moderate in severity and somatrogon was generally well-tolerated with no notable difference in safety between the two treatment groups. Injection site pain was more common in the somatrogon group (somatrogon: 72.7%, Genotropin: 13.6%).
Conclusions: The Japanese Phase 3 trial in patients with pGHD demonstrated that once weekly somatrogon was comparable to daily Genotropin. The annual HV after 12 months of treatment was higher in the somatrogon group than the Genotropin group. Somatrogon administration was generally well tolerated in patients with pGHD. The results of this Japanese Phase 3 study are consistent with the results previously reported from the global Phase 3 study that met its primary endpoint of noninferiority to daily Genotropin.

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Pituitary Hypoplasia Is the Best MRI Predictor of the Severity and Type of Growth Hormone Deficiency in Children With Congenital Growth Hormone Deficiency

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Background and Objectives: Congenital idiopathic growth hormone deficiency(GHD) is associated with various MRI abnormalities, including both sellar anomalies such as pituitary hypoplasia, ectopic pituitary, empty sella and abnormalities of the pituitary stalk and extrasellar abnormalities such as Arnold Chiari malformation, corpus callosum agenesis, arachnoid cyst, septum pellucidum agenesis, enlarged ventricles, vermis dysplasia, and sphenoid cyst. However, it remains contentious whether MRI brain findings could provide an additional avenue for precisely predicting the differentiation of GHD based on severity(severe or partial) and type(isolated GHD or multiple pituitary hormone deficiency MPHD). This study aimed to ascertain the abnormality that is the best predictor of severe GHD and type of GHD amongst the different MRI findings. **Methods:** This was an analytical cross-sectional study conducted from 2018-2020. During the study period, we included a total of 100 subjects diagnosed to have idiopathic GHD after the exclusion of syndromic causes, system illness, presence of pituitary mass, and those with h/o cranial irradiation. Patients were divided into severe GHD and partial GHD based on peak stimulated GH of <5 ng/dl and ≥ 5 ng/dl respectively and into groups based on isolated GHD and MPHD. Patients were further divided into groups based on the presence of pituitary hypoplasia,extrasellar brain abnormalities (EBA), and presence of ectopic posterior pituitary and/or pituitary stalk abnormalities(EPP/PSA), respectively. Analyses were performed using SPSS version 24.0 software. **Results:** Amongst 100 subjects with idiopathic congenital GHD, 66 (66%) subjects had Isolated GHD while the remaining 34 (34%) had MPHD. 71 had severe GHD, and 29 had partial GHD. Amongst the MRI findings, pituitary hypoplasia was the most common finding observed in 53% of patients, while 23(23%) had EBA, and 25(25%) had EPP/PSA. Pituitary hypoplasia was observed to be the best predictor of severity of GHD with an odds ratio(OR) of 10.8 (95% CI 3.38-29.6) followed by ectopic posterior pituitary /pituitary stalk abnormalities (OR =2.8, 95% CI 1.5-9.5) while the presence of extrasellar abnormalities was the weakest predictor (OR =1.8, 95% CI 1.05-3.2). Pituitary hypoplasia was the only finding to significantly predict MPHD (OR=9.2). On ROC analysis, a Pituitary height SDS of -2.03 had a 73.2 % sensitivity and specificity of 79.3%(AUC =0.787,95% CI 0.7-0.873) for severe GHD and a sensitivity of 88.2 % and specificity of 66.7% (AUC =0.745, 95% CI 0.68-0.877) for MPHD. **Conclusion:** We observed Pituitary hypoplasia to be not only the most frequent MRI abnormality but also the best predictor of severe GHD and MPHD amongst various sellar and extrasellar abnormalities.

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Pituitary Volume Cutoffs as Another Tool for Determining Growth Hormone Treatment Eligibility

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Background: The GH stimulation test (GHST) is the gold standard for the diagnosis of GH deficiency (GHD), yet a significant number of short children fail to be diagnosed as GHD. We have speculated that pituitary volume (PV) could be used in conjunction with results from the GHST to diagnose GHD; however, cutoff values for low PVs need to be further explored.
Objective: To define a diagnostic cutoff value of PV for determining GH treatment eligibility for patients (PTs) with short stature.
Patients and Methods: The database of GHST results at a Pediatric Endocrinology center was queried for PTs aged 6-18 yrs who underwent a GHST, MRI, and blood work between 1/2018 - 6/2019. PTs with relevant comorbidities were excluded. Clonidine and L-dopa were used to induce GH secretion during the GHST. GHD was defined as a peak GH ≤ 10 ng/mL. MRIs were acquired on a Philips 1.5 or 3.0 T scanner (1mm slices) and PV was calculated using the ellipsoid formula (LxWxH/2). 144 PTs were the subjects of this study. ROC curve analysis was utilized to generate cutoff values. PV was used to predict GHD in prepubertal (age < 11 yrs) and pubertal (age > 11 yrs) children. The value with the greatest Youden index (J) was selected as the definitive cutoff.
Results: The mean (MN) and median (MD) ages of PTs were 12.2 ± 2.2 and 12.3, respectively. The MN and MD ages of prepubertal PTs (n=43) were 9.4 ± 1.1 and 9.7, respectively. The MN and MD ages of pubertal PTs (n=103) were 13.4 ± 1.4 and 13.2, respectively. Initially, 10 ng/mL was utilized as the cutoff for GHD. For predicting GHD from PV in