# 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 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 three females were observed in C1 and C2, seven 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 adultsubjects. 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.