Pharmacokinetics and pharmacodynamics of macimorelin acetate (AEZS-130) in paediatric patients with suspected growth hormone deficiency (GHD)

Poster 3009

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BACKGROUND & AIMS

- Growth hormone deficiency (GHD) in children is characterised by growth failure and short stature, and, if left untreated, can lead to impaired quality of life due to psychological problems such as depression, anxiety, and sleep disturbance.[1,2]
- Macimorelin is a potent, orally administered growth hormone (GH) secretagogue, which was reported as safe and well-tolerated in adult populations,[3,4] and is approved by the FDA and EMA for the diagnosis of adult GHD.[5,6]
- This is the first study to investigate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and tolerability of macimorelin after single oral dosing of 0.25, 0.5, and 1.0 mg/kg in paediatric patients with suspected GHD.

MATERIAL & METHODS

- Open-label, group-comparison, dose-escalation trial (EudraCT 2018-001988-23).
- Inclusion criteria: patients between 2 and <18 years of age; suspected GHD based on auxological and clinical criteria; indication for the performance of provocative growth hormone stimulation tests (GHSTs); patients with sex steroid priming prior to standard GHSTs must also have sex steroid priming for the macimorelin GHST.
- Sequential cohorts received macimorelin at ascending single oral doses of 0.25, 0.5 and 1.0 mg/kg.
- Macimorelin GHSTs were performed between two standard GHSTs conducted according to standard clinical practice at each site (insulin tolerance test, arginine, arginine/growth hormone releasing hormone, clonidine, glucagon, and/or L-dopa).
- Blood samples were collected pre-dose and then 15, 30, 45, 60, 90, 120, and 360 minutes after administration of macimorelin.
- Tolerability was assessed by a GHST Tolerability Questionnaire, which surveyed patients on the acceptability of taste as well as any signs of an impact on sleep, appetite and gastrointestinal symptoms. The responses below were not deemed adverse events (AEs) by the study investigators.

CONCLUSIONS

- Taste was considered acceptable by most patients.
- There were no cases of vomiting nor nausea as a result of macimorelin ingestion.
- No cases of dysgeusia, which had been the most frequently reported AE in a previous adult study, were observed in this paediatric population.[4]
- PK and PD profiles were within the expected range and comparable to those observed in adults.[3,4]
- The data from this study support the choice of 1.0 mg/kg dose of macimorelin for validity testing in a phase 3 trial.

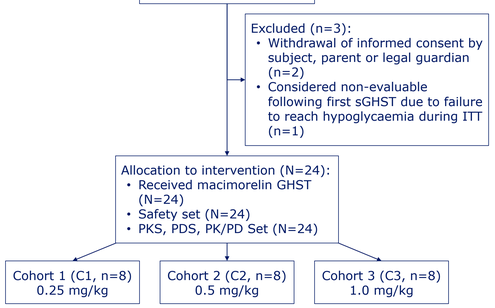
Single doses of macimorelin (0.25, 0.50 and 1.0 mg/kg) were safe and well tolerated in children.
PK and PD were within the ranges expected from the adult development programme.

RESULTS

Patients

- Twenty-four paediatric patients with suspected GHD took part in the study (**Figure 1**).
- Demographic and other characteristics at screening are shown in **Table 1**.

Figure 1: Trial population overview



(s)GHST, (standard) growth hormone stimulation test; ITT, insulin tolerance test; PD, pharmacodynamic; PDS, pharmacodynamic analysis set; PK, pharmacokinetic; PKS, pharmacokinetic analysis set.

Table 1. Demographic and other characteristics at screening

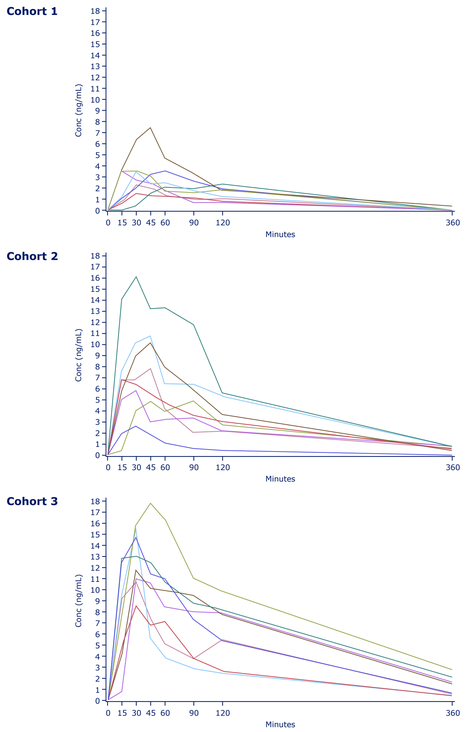
Parameter	Cohort 1 0.25 mg/kg (n=8)	Cohort 2 0.5 mg/kg (n=8)	Cohort 3 1.0 mg/kg (n=8)	Overall (N=24)
Gender, n (%)				
Male	5 (62.5%)	5 (62.5%)	7 (87.5%)	17 (70.8%)
Female	3 (37.5%)	3 (37.5%)	1 (12.5%)	7 (29.2%)
Race, n (%)				
White	8 (100%)	8 (100%)	8 (100%)	24 (100%)
Tanner Status, n (%)				
I	4 (50%)	5 (62.5%)	4 (50%)	13 (54.2%)
II	4 (50%)	3 (37.5%)	4 (50%)	11 (45.8%)
Age (years), mean ± SD	9.8 ± 3.5	9.0 ± 4.2	10.5 ± 3.9	9.8 ± 3.8
Height (cm), mean ± SD	111.19 ± 32.79	118.85 ± 20.95	127.71 ± 19.67	119.25 ± 25.02
Weight (kg), mean ± SD	23.1 ± 10.1	27.0 ± 10.9	29.0 ± 10.0	26.4 ± 10.2
BMI (kg/m²), mean ± SD	14.83 ± 2.56	17.33 ± 2.41	17.09 ± 2.29	16.41 ± 2.59

BMI, body mass index; SD, standard deviation.

PK

- Macimorelin plasma concentrations increased in a dose-dependent manner (**Figure 2**).
- Mean maximum plasma concentration (C_{max}) values for macimorelin were 3.46, 8.13, and 12.87 ng/mL for C1, C2, and C3, respectively.
- Mean AUC_{0-6} values were 6.69, 18.02, and 30.92 h*ng/mL for C1, C2, and C3, respectively.

Figure 2 Individual macimorelin concentration vs time by cohort (linear scale; N=24)

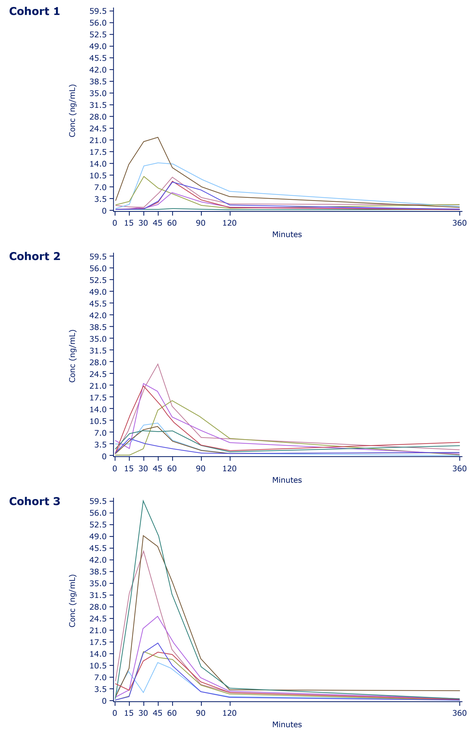


Graphs show PK profiles of individual patients (n=8 per cohort).

PD

- In all patients, GH plasma concentration increased following macimorelin administration (**Figure 3**).
- There was a tendency to higher GH plasma values with increased dose (**Figure 3**).

Figure 3 Individual growth hormone concentration vs time by cohort (linear scale; N=24)



Graphs show PD profiles of individual patients (n=8 per cohort).

Safety & tolerability

- Overall, 88 AEs and 70 treatment-emergent adverse events (TEAEs) were reported.
- No TEAEs were considered to be related to the macimorelin test (**Table 2**).
  - 7 out of 8 patients in each cohort experienced AEs related to standard GHSTs (**Table 2**).
- No serious AEs or TEAEs were reported.
- Macimorelin was well tolerated in all three cohorts.
  - Two patients (n=1, C1; n=1, C3) reported disagreeable taste in the questionnaire, one patient (C1) reported stomach feeling unwell the following day, and one patient (C1) reported an unusual bowel movement the following day.

Table 2. Summary of AEs and TEAEs [patients (events)]

Category	Cohort 1 0.25 mg/kg (n=8)	Cohort 2 0.5 mg/kg (n=8)	Cohort 3 1.0 mg/kg (n=8)
AEs	8 (27)	8 (28)	7 (33)
TEAEs	8 (22)	6 (24)	7 (24)
Macimorelin-related TEAEs	0 (0)	0 (0)	0 (0)
sGHST-related AEs	7 (25)	7 (27)	7 (25)
Pts receiving ITT (Visit 1/3)*	n=0/8	n=2/5	n=3/4
ITT-related AEs	7 (21)	7 (27)	7 (14)
Pts receiving Clonidine (Visit 1/3)*	n=2/0	n=5/2	n=4/3
Clonidine-related AEs	2 (2)	0 (0)	5 (11)
Pts receiving Arginine (Visit 1/3)*	n=6/0	n=1/0	n=1/0
Arginine-related AEs	1 (2)	0 (0)	0 (0)
Pts receiving Glucagon (Visit 1/3)*	n=0/0	n=0/1	n=0/1
Glucagon-related AEs	0 (0)	0 (0)	0 (0)

*Number of patients receiving each sGHST at Visit 1 (before macimorelin) and Visit 3 (after macimorelin). AEs were recorded from the moment of informed consent until the end of the trial. TEAEs were all AEs recorded after administration of the trial drug. AE, adverse event; GHST, growth hormone stimulation test; ITT, insulin tolerance test; Pt, patient; sGHST, standard growth hormone stimulating test; TEAE, treatment emergent adverse event.

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