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

Poster 6904

Violetta Csákváry[1], Agota Muzsnai[2], Dmitri Raduk[3], Tetyana Chaychenko[4]*, Birgitte Bentz Damholt[5,6], Nicky Kelepouris[7], Michael Teifel[8,9] and Nicola Ammer[8]

[1]Department of Paediatrics, Markusovszky Teaching Hospital, Szombathely, Hungary; [2]Buda Children's Hospital, Budapest, Hungary; [3]HCI 2nd Children's City Clinical Hospital, Minsk, Belarus; [4]Department of Paediatrics № 1 and Neonatology, Kharkiv National Medical University, Kharkiv, Ukraine; [5]Novo Nordisk A/S, Global Development, Søborg, Denmark; [6]Current affiliation: Novo Nordisk A/S, Stem Cell Development, Måløv, Denmark, [7]Novo Nordisk Inc., Plainsboro, New Jersey, USA; [8]Aeterna Zentaris GmbH, Frankfurt, Germany; [9]Current affiliation: Cleara Biotech BV, Utrecht, The Netherlands. *presenting author

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.

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.

Materials & 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.

Results

Patients

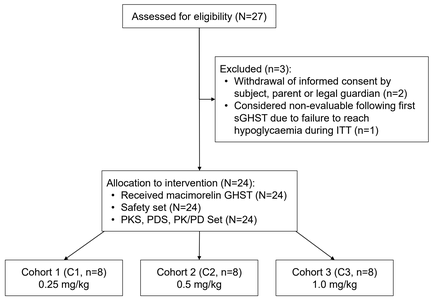
- Twenty-four paediatric patients with suspected GHD took part in the study (**Figure 1**).
- Demographic and other characteristics at screening are shown in **Table 1**.

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.

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.

Results

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.

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**).

Safety & tolerability

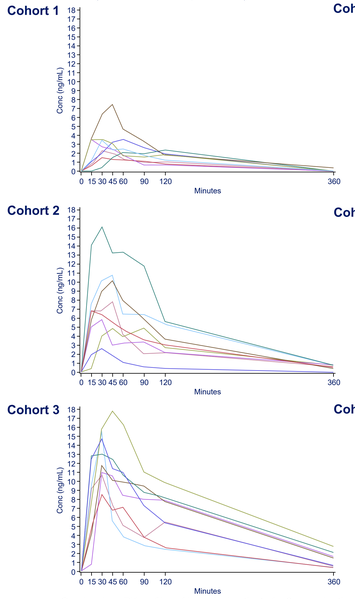
- Overall, 88 AEs and 70 treatment-emergent adverse events (TEAEs) were reported.
- No TEAEs were considered to be related to the macimorelin test (**Table 2**).
  - 7 out of 8 patients in each cohort experienced AEs related to standard GHSTs (**Table 2**).
- No serious AEs or TEAEs were reported.
- 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)

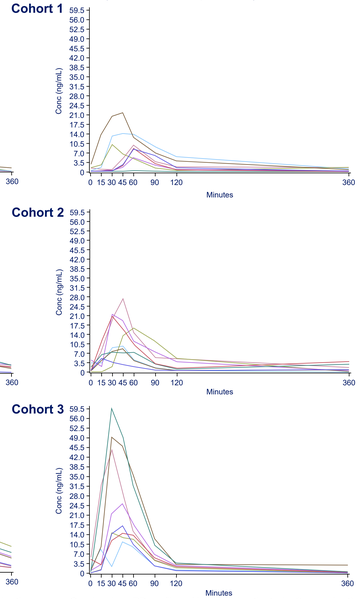
*Number of patients receiving each sGHST at Visit 1 (before macimorelin) and Visit 3 (after macimorelin). AEs were recorded from the moment of informed consent until the end of the trial. TEAEs were all AEs recorded after administration of the trial drug. AE, adverse event; GHST, growth hormone stimulation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

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



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

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).

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.

References

1. Abe, S. et al. 2009 J Paediatr Child Health 45 (11), 636-40
2. Attanasio, A. F. et al. 2005 J Clin Endocrinol Metab 90 (8), 4525-9
3. Klaus, B. et al. 2020 Growth Horm IGF Res 52 101321
4. Garcia, J. M. et al. 2013 J Clin Endocrinol Metab 98 (6), 2422-9
5. FDA 2017 MACRILEN (macimorelin) - Prescribing information
6. EMA 2019 Macimorelin - EPAR product information

Acknowledgments and Disclosures

This study was sponsored by Aeterna Zentaris GmbH in cooperation with Novo Nordisk. Medical writing support was provided by Physicians World Europe GmbH, Mannheim, Germany, funded by Novo Nordisk.

Violetta Csákváry, Agota Muzsnai, Dmitri Raduk and Tetyana Chaychenko served as investigators as well as members of the data review committee in this study. Birgitte Bentz Damholt was an employee of Novo Nordisk at the time this trial was conducted and is a holder of Novo Nordisk stocks. Nicky Kelepouris is an employee of Novo Nordisk and holder of Novo Nordisk stocks. Michael Teifel was employee of Aeterna Zentaris GmbH at study initiation and currently serves as an advisor to Aeterna Zentaris. Nicola Ammer is an employee of Aeterna Zentaris GmbH.

This poster was previously presented at the European Congress of Endocrinology 2020 (eECE 2020 virtual meeting; 5–9th September 2020)

Presented at the 103rd Annual Meeting of The Endocrine Society (ENDO 2021 virtual meeting; 20–23rd March 2021)