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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Macimorelin Aeterna Zentaris

macimorelin

Procedure no: EMEA/H/C/004660/P46/004

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On July 08 2020, the MAH Aeterna Zentaris submitted a completed paediatric study (AEZS-130-P01) for macimorelin acetate, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are submitted as part of a post-authorisation measure.

2. Scientific discussion

2.1. Information on the development program

Reference is made to the medicinal product "Macimorelin Aeterna Zentaris 60 mg granules for oral suspension" centrally authorised by EMA on 11 January 2019 (EMEA/H/C/004660) for the indication "diagnosis of growth hormone deficiency (GHD) in adults".

Study AEZS-130-P01 is the first of two studies as mentioned in the Paediatric Investigation Plan agreed with the Agency (EMEA 001988-PIP01-16-M01) and has been completed on 24 January 2020. The MAH Aeterna Zentaris now submits the final results of Study AEZS-130-P01 involving pediatric patients in fulfilment of Article 46 of the pediatric regulation EC No. 1901/2006.

2.2. Information on the pharmaceutical formulation used in the study

Test product: A single-use aluminum pouch (synonymous: sachet) contained 63.6 mg macimorelin acetate, which provides 0.5 mg/mL of macimorelin when dissolved in 120 mL of water.

Dose and mode of administration: Sequential cohorts of trial participants received macimorelin at ascending single oral doses: i.e. 0.25 mg/kg body weight in Cohort 1 (C1), 0.5 mg/kg body weight in Cohort 2 (C2), and 1 mg/kg body weight in Cohort 3 (C3).

Batch number: C1810001

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final clinical study report for a completed paediatric trial (AEZS-130-P01) with macimorelin acetate:

- AEZS-130-P01: Open label, group comparison, dose escalation trial to investigate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of macimorelin acetate after single oral dosing of 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg in pediatric patients with suspected growth hormone deficiency (GHD).

2.3.2. Clinical study

Clinical study

Study No.: AEZS-130-P01

Title of trial: Open label, group comparison, dose escalation trial to investigate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of macimorelin acetate after single oral dosing of 0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg in pediatric patients with suspected growth hormone deficiency (GHD).

Description

Methods

Objective

Primary:

- To investigate the safety and tolerability of macimorelin acetate after ascending single oral doses of macimorelin (0.25 mg/kg, 0.5 mg/kg, and 1 mg/kg) in pediatric patients with suspected growth hormone deficiency (GHD).

Secondary:

- To investigate the PK of macimorelin acetate in pediatric patients with suspected GHD,
- To investigate the PD of macimorelin acetate as measured by growth hormone (GH) release in pediatric patients with suspected GHD,
- To explore the PK/PD relationship following single oral dose administration of macimorelin acetate in pediatric patients with suspected GHD.

Study design

This is an open label, group-comparison, single dose, dose-escalation, multicenter trial that was performed in pediatric patients in whom, based on auxological and clinical criteria, a provocative growth hormone stimulation test (GHST) was indicated as part of the diagnostic work-up of a suspected growth hormone deficiency (GHD).
The investigational macimorelin GHST was performed after the first standard GHST had been completed. A recovery period of at least 1 week and a maximum of 4 weeks was introduced between GHSTs to avoid carry-over effects or interference between subsequent GHSTs and to provide an adequate follow-up period for observation of possibly drug-related adverse events to the previously used provocative agents.
Sequential cohorts of trial participants received macimorelin at ascending single oral doses, ranging from 0.25 mg/kg body weight, which is 50% of the dose used for testing in adults, up to a planned maximum of 1 mg/kg body weight (which is 50% of the highest tested and well tolerated dose in adults).
For determination of the macimorelin PK and PD (GH stimulation) profile, blood samples were collected pre-dose, then 15, 30, 45, 60, 90, 120 and 360 minutes after the administration of macimorelin.
The dose titration program was reconsidered after completion of each dose step and would proceed only if the previous dose step reviewed and confirmed by Data Review Committee (DRC) had shown acceptable safety and tolerability.

The selection, performance and evaluation of standard GHSTs followed the established procedures of each participating institution. However, blood samples for GH were analysed at the central laboratory. The analysis of serum samples for GH concentration were carried out at a central laboratory by a validated immunochemiluminometric assay (IDS-iSYS Human Growth Hormone, Immunodiagnostic Systems Ltd [UK]) (Manolopoulou et al., 2012). This assay is standardized to the recombinant growth hormone calibration standard WHO 98/574, and complies with recommendations on assay standardization as outlined by Clemmons (Clemmons et al., 2011).

Study population /Sample size

24 pediatric patients with suspected GHD (8 patients per dose group) were enrolled. Of these 8 patients, at least 3 patients per dose group were pre-pubertal (Tanner Stage I) and pubertal (Tanner Stage II-IV), respectively.

Treatments

Test product, dose and mode of administration, batch number:

Test product:
A single-use aluminum pouch (synonymous: sachet) contained 63.6 mg macimorelin acetate, which provides 0.5 mg/mL of macimorelin when dissolved in 120 mL of water.

Dose and mode of administration:
Sequential cohorts of trial participants received macimorelin at ascending single oral doses: i.e. 0.25 mg/kg body weight in Cohort 1 (C1), 0.5 mg/kg body weight in Cohort 2 (C2), and 1 mg/kg body weight in Cohort 3 (C3).

Batch number: C1810001

Reference therapy, dose and mode of administration, batch number:

Two standard growth hormone stimulation tests (sGHSTs) had to be performed in a patient according to local practice. The sGHST agents were considered as 'background' and not as IMPs.

The following pharmacological agents were accepted for sGHSTs: insulin (insulin tolerance test (ITT)), arginine, arginine/growth hormone releasing hormone (GHRH), clonidine, glucagon, L-dopa.
Single dose of an sGHST agent was administered i.m./i.v./s.c. or peroral (depending on formulation) on the day of the sGHST. sGHST agents were taken from the sites' pharmacy stocks. Batch numbers were recorded on-site in Patient Records and 'standard GHST Patients Accountability Logs'.

Outcomes/endpoints

Safety and Tolerability
- Patientive tolerability (including acceptability of taste and impact on sleep, appetite, and gastrointestinal symptoms), Adverse events (AEs);
- Determination of changes in laboratory parameters which are relevant to safety;
- Influence on vital parameters (pulse rate, blood pressure, ECG).

Pharmacokinetics
- Concentration-time profiles of macimorelin;
- Target parameters: AUC, Cmax, Tmax, $T_{1/2}$

Pharmacodynamics

- Concentration-time profiles of GH;
- Target parameters: Cmax, Tmax;
- Preliminary PK/PD: Tmax for macimorelin vs. Tmax for GH; Cmax for macimorelin vs. Cmax for GH

Other

- Establishment of a recommended dose for diagnostic purposes in pediatric patients with suspected GHD;
- Exploration of a suitable GH cut-off point for a subsequent testing to establish the diagnosis of GHD in pediatric patients.

Statistical Methods

All statistical analyses were considered exploratory in nature. Datasets were analyzed using SAS version 9.3 or above.

In general, summary statistics (n, arithmetic mean, standard deviation, median, minimum, and maximum) for quantitative variables and frequency tables for qualitative data are presented by dose group.

Macimorelin PK: PK parameters were analyzed for the PK Analysis Set (PKS) and are summarized by n (number of measurements), arithmetic mean, standard deviation and coefficient of variation (CV), median, minimum, maximum value and, in addition (Tmax excluded) by geometric mean, geometric standard deviation, and geometric CV. For Tmax additionally frequency counts as well as median, minimum, and maximum are presented.

Macimorelin PD: irrespective of the availability of PK data, GH concentration data were analyzed for the PD Analysis Set (PDS). GH peak concentrations were correlated with the outcome of the clinical diagnostic procedure (diagnosis of GHD confirmed or not confirmed).

PK/PD Analysis: Plasma concentrations of macimorelin of individual patients were correlated with the respective GH concentrations at the same time points, as well as the outcome of the clinical diagnostic procedure (diagnosis of GHD confirmed or not confirmed).

Results

Recruitment/ Number analysed

Out of a total of 27 patients screened, 24 patients were administered the macimorelin test, with 8 patients in each of the three dosing cohorts (C1, C2, and C3).

Thus, the safety population (SAF) as well as the PK analysis set (PKS), PD analysis set (PDS), and PK/PD set consisted of 24 patients.

Baseline data

In total, 17 (70.8%) of patients were male, 7 (29.2%) female, and 100% were of white origin. At screening, the median parameters for all three dosing cohorts were for age 10.5 years (range: 4 – 15 years), height 123.35 cm (range: 46.0 – 152.5 cm), weight 25.5 kg (range: 12 – 43 kg) and body mass index (BMI) 16.1 kg/m2 (range: 12.4– 21.4 kg/m2).

The Tanner status was distributed as following: in C1 as well as C3, 4 patients showed Tanner I and 4 patients Tanner II , and in C2 5 patients showed Tanner I and 3 patients Tanner II. Sex steroid priming was applied in two male patients in C3 by i.m. administration of a testosterone depot preparation.

Concerning the baseline medical history, only for two patients in C2 a deficiency of other pituitary axes (i.e., thyroidal deficiency) was reported. As part of the standard 'diagnostic work-up', IGF-1 and IGF-BP3 values were captured in the electronic case report form (eCRF) as collected according to the local diagnostic standard. IGF-1 values were presented for 7 patients in C1, and for 8 patients each in C2 and C3, with a median of 88.00 µg/L (SD 68.72) in C1, 100.00 µg/L (SD 97.90) in C2, and 119.50 µg/L (SD 68.88) in C3. IGF-BP3 values became available for one patient in C3.

The bone age showed in median a value of 102.2 months (range: 24 – 156 months). As part of auxology parameters, height SDS was in median -2.35 (range -3.2 – 1.7), BMI SDS -0.60 (range -2.1 – 2.0), and annualized height velocity SDS -1.50 (range: -3.3 – 0.5).

Pharmacokinetic and Pharmacodynamic (PK/PD) results

Pharmacokinetic results:
The AUCs and Cmax of macimorelin show a dose-dependent increase with an arithmetic mean AUC0-6 of 6.69 h*ng/mL in C1, 18.02 h*ng/mL in C2, 30.92 h*ng/mL in C3, and an arithmetic mean Cmax of 3.46 ng/mL in C1, 8.13 ng/mL in C2, and 12.87 ng/mL in C3 (Table 1).

Mean Tmax is comparable between all three groups with an arithmetic mean of 45.5 min in C1, 40.6 min in C2, and 31.9 min in C3. Mean T1/2 shows a slight increase with higher doses, i.e. 73.18 min in C1, 96.31 min in C2, and 102.85 min in C3.

Table 1: Summary of main pharmacokinetic parameters of macimorelin (PK Set, N=24)

Cohort	Statistics	AUC 0-6 (h*ng/mL)	C_{max} (ng/mL)	T_{max} (min)	$T_{1/2}$ (min)
Cohort 1	n	8	8	8	4
	Arithmetic Mean (SD)	6.685 (3.093)	3.460 (1.783)	45.5 (32.8)	73.183 (29.437)
	Arithmetic CV (%)	46.273	51.543	72.1	40.225
	Min - Max	3.35 - 12.49	1.51 - 7.44	15 - 120	39.45 - 105.96
Cohort 2	n	8	8	8	7
	Arithmetic Mean (SD)	18.015 (9.800)	8.126 (4.176)	40.6 (22.3)	96.307 (41.031)
	Arithmetic CV (%)	54.399	51.393	54.8	42.604
	Min - Max	3.28 - 35.98	2.62 - 16.1	15 - 90	41.39 - 151.01
Cohort 3	n	8	8	8	8
	Arithmetic Mean (SD)	30.920 (11.510)	12.868 (3.011)	31.9 (5.3)	102.851 (19.938)
	Arithmetic CV (%)	37.227	23.402	16.6	19.385
	Min - Max	16.31 - 49.73	8.5 - 17.79	30 - 45	77.66 - 133.36

Pharmacodynamic results:
Following macimorelin administration, peak GH levels were observed in C1 within 0.5 – 1 h (mean Tmax at 52.5 min (SD 11.3)), in C2 within 0.25 – 1 h (mean Tmax 37.5 min (SD 13.9)) , and in C3 within 0.5 – 0.75 h (mean Tmax 37.5 min (SD 8.0)) (cf. Table 2).

Table 2: Summary of pharmacodynamic parameters/ peak GH levels (PK/PD Set, N=24)

Cohort	Statistics	C_{max} (ng/mL)	T_{max} (min)
Cohort 1	n	8	8
	Arithmetic Mean (SD)	9.791 (6.226)	52.5 (11.3)
	Arithmetic CV (%)	63.585	21.6
	Median	9.195	60.0
	Min - Max	0.51 - 21.73	30 - 60
Cohort 2	n	8	8
	Arithmetic Mean (SD)	14.590 (8.046)	37.5 (13.9)
	Arithmetic CV (%)	55.149	37.0
	Median	13.040	37.5
	Min - Max	5.06 - 27.42	15 - 60
Cohort 3	n	8	8
	Arithmetic Mean (SD)	29.533 (18.829)	37.5 (8.0)
	Arithmetic CV (%)	63.757	21.4
	Median	21.100	37.5
	Min - Max	11.35 - 59.73	30 - 45

Exploratory Analyses for the GH cut-off point:

Peak GH values by GHD diagnosis were compared based on GHST results and investigator's assessment. Diagnostic characteristics of GH values (i.e. sensitivity, specificity, and Youden indices (non-weighted, weighted)) tested as cut-off points were listed with the most solid expression of diagnostic characteristics to be noted for C1 at a peak GH of 10.03 ng/mL, for C2 at a peak GH of 10.43 ng/mL, and for C3 at 17.13 ng/mL.

Furthermore, the diagnostic results can be summarized as following (Table 3): the macimorelin GHST shows 'GHD not confirmed' only in 1 (9.09%) patient in C2 from overall 11 patients assessed as 'GHD' by the investigator in all three cohorts.

From a total of 13 patients assessed by the investigator as 'not confirmed' of having GHD, the macimorelin GHST confirmed GHD in 3 (23.08%) patients in C1 and in 1 (7.69%) patient in C3, respectively.

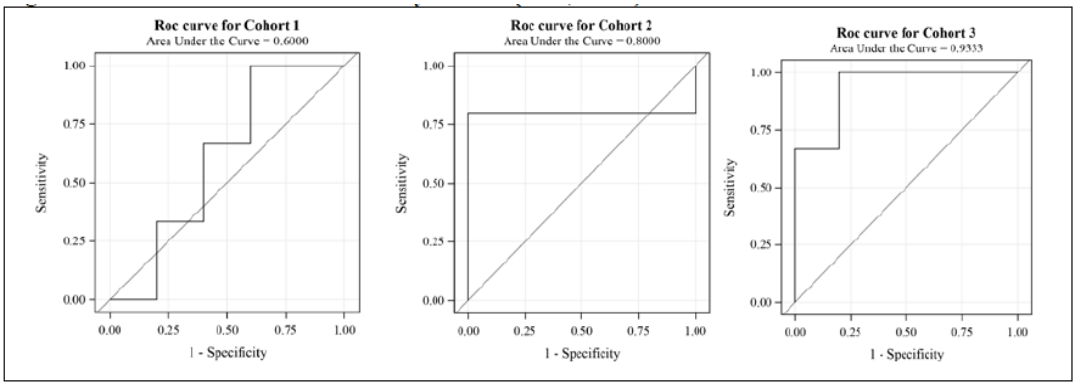
Table 3: Summary of Diagnostic Results of Macimorelin GHST vs. sGHST and vs. Investigator's Assessment

		PI's Assessment		sGHST	
	Macimorelin GHST	GHD (N=11)	Non GHD (N=13)	Confirmed (N=8)	Not Confirmed (N=16)
Cohort 1	Confirmed, n (%)	3 (27.27 %)	3 (23.08 %)	1 (12.50 %)	5 (31.25 %)
	Not Confirmed, n (%)	0	2 (15.38 %)	0	2 (12.50 %)
	Total, n (%)	3 (27.27 %)	5 (38.46 %)	1 (12.50 %)	7 (43.75 %)
Cohort 2	Confirmed, n (%)	4 (36.36 %)	0	3 (37.50 %)	1 (6.25 %)
	Not Confirmed, n (%)	1 (9.09 %)	3 (23.08 %)	1 (12.50 %)	3 (18.75 %)
	Total, n (%)	5 (45.45 %)	3 (23.08 %)	4 (50 %)	4 (25 %)
Cohort 3	Confirmed, n (%)	3 (27.27 %)	1 (7.69 %)	3 (37.50 %)	1 (6.25 %)
	Not Confirmed, n (%)	0	4 (30.77 %)	0	4 (25 %)
	Total, n (%)	3 (27.27 %)	5 (38.46 %)	3 (37.50 %)	5 (31.25 %)

Receiver Operating Characteristic (ROC) Analysis

For all GH cut-off points tested, the ROC curve for C1 shows the lowest sensitivity and specificity if being compared with C2 and C3 (Figure 2). The related area under the curve (AUC) is increasing with ascending dose.

Figure 2: ROC of Macimorelin GHST by Cohort (PDS, N=24)



When comparing the characteristics of GH cut-off points between the three cohorts, the cut-off point of 17.130 ng/mL GH for C3 shows the strongest test characteristics with a sensitivity of 1.0, specificity of 0.8, Youden indices ≥ 0.80, and a ROC AUC of 0.93 (cf. Table 4).

A sensitivity analysis was performed observing the ROC AUC development based on the test outcome of the sGHSTs categorized as 'confirmed' vs. 'not-confirmed'. Again, strongest test characteristics are expressed for C3, with e.g. a sensitivity of 1.00, specificity of 0.80, and a ROC AUC of 0.933, in comparison with C2 (sensitivity 0.75, specificity 0.75, ROC AUC 0.563) and C1 (sensitivity 1.0, specificity o.71, ROC AUC 0.714).

Table 4: Summary of ROC Analysis: AUC and Characteristics of Cut-off Points by Cohort (PDS, N=24)

Statistics	Cohort 1 (N=8)	Cohort 2 (N=8)	Cohort 3 (N=8)
Peak GH cut-off point (ng/mL)	10.030	10.430	17.130
Specificity	0.40	1.00	0.80
Sensitivity	1.00	0.80	1.00
Youden-index	0.40	0.80	0.80
Weighted Youden-index (w=0.6)	0.52	0.76	0.84
Weighted Youden-index (w=0.7)	0.64	0.72	0.88
NPV	1.00	0.75	1.00
PPV	0.50	1.00	0.75
ROC AUC	0.60	0.80	0.93

NPV = negative predictive value, PPV = positive predictive value

PK and PD Summary

Overall, the macimorelin PK and PD of C1, C2, and C3 show comparable profiles:

- the macimorelin Tmax is comparable for all three groups with mean Tmax values of about 0.5–0.75 h
- the mean macimorelin Cmax shows a dose-proportional increase;
- the AUC increases with the macimorelin dose;
- maximum GH release is observed at 0.25 – 2 h after macimorelin administration, with mean Tmax values of about 0.5 – 1 h.

Maximum values for AUC and Cmax are observed in C3 at a macimorelin dosing of 1.0 mg/kg body weight. Furthermore, the sensitivity analysis supports the dosing in C3 with strongest test characteristics expressed at a cut-off point of approximately 17 ng/mL GH, with a specificity of 0.80, a sensitivity of 1.00, a Youden-index of 0.80 and an ROC AUC of 0.933.

Safety results

Overall, all three macimorelin doses (i.e. 0.25 mg/kg in Cohort 1 (C1), 0.5 mg/kg in Cohort 2 (C2), and 1 mg/kg in Cohort 3 (C3) were found to be safe and well tolerated in the pediatric population observed. Not any TEAE was reported in causal relationship to macimorelin. Especially, neither vomiting nor nausea were to be noted in children after swallowing of the macimorelin suspension.
No SAEs or serious TEAEs were reported in the course of this trial.
In adult trials, the most frequently reported adverse events judged likely related to oral macimorelin 0.5 mg/kg were dysgeusia (7%), diarrhea and headache (2% each). In the pediatric population observed, bitter taste was commented by two patients in C3 on the GHST Tolerability Questionnaire. These comments were not assessed as AEs by the investigator but as characteristic of the suspension only and thus considered as a technical complaint.

Clinical laboratory, vital signs, physical findings, ECG:
No clinically significant changes were observed for the safety clinical laboratory parameters, vital signs and physical examination. No clinically significant abnormalities and no significant changes in ECG parameters were described.

2.3.3. Discussion on clinical aspects

This trial was performed to investigate the safety, tolerability, PK and PD of macimorelin acetate after single oral dosing of 0.25 mg/kg, 0.5 mg/kg, and 1.0 mg/kg in pediatric patients with suspected growth hormone deficiency (GHD). Furthermore, it served to identify a suitable macimorelin dose for further testing in a test validation trial, and to explore a GH cut-off point for testing.

In general, the PK parameters in the pediatric population were in a similar range to those in adults.

Tmax of macimorelin was comparable for all three groups with mean Tmax values of about 0.5–0.75 h. A dose-dependent increase of macimorelin Cmax (3.46 vs. 8.13 vs. 12.87 ng/mL) as well as of the mean $AUC_{0\text{-}6h}$ (6.69 vs. 18.02 vs. 30.92 h*ng/mL) was observed. The elimination half-lives $t_{1/2}$ were in the range of 1.25 – 1.75 h. Maximum GH release occurred at 0.25 – 2 h after macimorelin administration, with mean Tmax values of about 0.5 – 1 h.

A macimorelin dose of 0.25 mg/kg (C1) has not resulted in a maximum stimulation of GH secretion in children, which becomes evident in the review of PK/PD data as well as comparison with the agreement between an explored GH cut-off point versus PI assessment and results of sGHSTs.

A dose of 0.5 mg/kg (C2) showed strong GH release, a high level of agreement between the principal investigator (PI) assessment based on the macimorelin GHST vs. sGHST as well as a ROC AUC of 0.80.

However, a dose of 1.0 mg/kg (C3) appears to lead to a more consistent, strong GH stimulation, most probably due to sufficiently high macimorelin exposure in all subjects.
Finally, the sensitivity analysis supports a dose of 1.0 mg/kg (C3) with strongest test characteristics expressed at a cut-off point of approximately 17 ng/mL GH, with a specificity of 0.80, a sensitivity of 1.00, a Youden-index of 0.80 and a ROC AUC of 0.93.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

In all three dosing cohorts, i.e. 0.25 mg/kg body weight in Cohort 1 (C1), 0.5 mg/kg body weight in Cohort 2 (C2), and 1 mg/kg body weight in Cohort 3 (C3), macimorelin has shown good safety and tolerability without any TEAEs or SAEs reported in the course of this trial. The PK/PD profiles are in a range expected from the adult development program. The overall characterization of macimorelin in this first pediatric trial supports the choice of a macimorelin dose of 1.0 mg/kg for the investigation in a Phase 3 trial on test validity.

Recommendation

The regulatory requirement according to Article 46 of Regulation (EC) No 1901/2006 which sets out the obligation for marketing-authorisation holders (MAHs) to submit any MAH-sponsored studies involving the use of an authorised medicinal product in the paediatric population to the competent authority, whether or not they are part of a paediatric investigation plan (PIP), has been:

☒ **Fulfilled:**

No further regulatory action required.

4. Additional clarification requested

Not applicable.