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RESEARCH**

APPLICATION NUMBER:

205598Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW (Resubmission)

NDA	205-598; Serials: 0031, 0038
Submission Dates	June 30, 2017; October 19, 2017
Brand Name	MACRILEN
Generic Name	Macimorelin acetate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Jayabharathi Vaidyanathan, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aeterna Zentaris
Formulation; Strength	Granules for oral solution; 0.5 mg/mL
Relevant IND	73,196
Indication	Diagnosis of adult growth hormone deficiency

Table of Contents	Page
1 Executive Summary	1
1.1 Recommendations	1
1.2 Post Marketing Requirement	2
1.3 Summary of Important Clinical Pharmacology Findings	2
2 Question Based Review	
2.1 Regulatory Background	3
2.2 General Clinical Pharmacology	3
2.3 Bioanalytical	11
3 Labeling Recommendations	17

1 Executive Summary

Macimorelin acetate is a new molecular entity and a peptidomimetic ghrelin receptor agonist. NDA 205-598 seeks approval for the indication to diagnose adult growth hormone deficiency (AGHD) (b) (4)

. Other AGHD diagnostics are parenteral products and macimorelin acetate is the 1st oral product seeking this indication. The sponsor received a Complete Response letter for NDA 205-598 on November 5, 2014 because of the need for additional clinical data and a QT prolongation study. On June 30, 2017, the sponsor resubmitted NDA 205-598 thru Serial 0031 to provide a complete response to the Complete Response letter.

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the NDA 205-598 Serials 0031 and 0038's Clinical Pharmacology data and has the following comments:

- The Clinical Pharmacology data for NDA 205-598 Serials 0031 and 0038 are acceptable.
- Labeling recommendations in Section 3 of this review.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

Pharmacokinetics (PK)

Absorption

Macimorelin $C_{\max}$ was observed between 0.5 hour and 1.5 hours upon oral administration of 0.5 mg macimorelin/kg body weight to AGHD patients who fasted for at least 8 hours. The mean plasma macimorelin concentrations are similar between patients with AGHD and healthy subjects for 1.5 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight. The mean macimorelin terminal exponential half-life ($T_{1/2}$) was 4.1 hours for the dose of 0.5 mg macimorelin/kg body weight in healthy subjects fasted for at least 8 hours.

The PK of macimorelin is less than dose proportional for single oral doses from 0.5 mg/kg to 2 mg/kg in healthy volunteers.

The PK of 2 mg macimorelin/kg body weight is consistent between Study AEZS-130-054 (single ascending dose study) and Study AEZS-130-055 (thorough QT study) in healthy subjects.

The dose of 0.5 mg macimorelin/kg for the pivotal Study AEZS-130-052 is acceptable because this is the dose previously examined in Study AEZS-130-047 of the original NDA.

The time for the peak serum growth hormone concentration is 0.75 – 1 hour after oral administration of macimorelin, whereas the time for the peak serum growth hormone concentration is 1 – 1.5 hours after intravenous administration of the insulin tolerance test. Macimorelin stimulation resulted in higher serum growth hormone concentrations than those for the insulin tolerance test.

Formulation

The macimorelin acetate formulation used in the pivotal clinical study (AEZS-130-052) is identical to the to-be-marketed macimorelin acetate formulation.

2 Question-Based Review

Because this is an NDA resubmission for macimorelin acetate, the following Clinical Pharmacology reviews for NDA 205-598 in DARRTS will provide pertinent background information:

- Filing review dated December 9, 2013 and Reference ID 3419292
- Primary review dated July 16, 2014 and Reference ID 3594224
- Addendum due to new data dated August 7, 2014 Reference ID 3606287
- Addendum due to new data dated October 3, 2014 Reference ID 3638847
- Review of the End of Review meeting package dated April 17, 2015 Reference ID 3734495

Thus, this document reviews submissions other than those reviews mentioned above for macimorelin acetate.

2.1 Regulatory Background

The following is the major regulatory events with NDA 205-598 in chronological order:

- On September 25, 2009, the Office of Orphan Products Development granted the orphan drug designation for macimorelin acetate to diagnose AGHD; designation request number 06-2255.
- On November 5, 2013, the sponsor submitted the original NDA for macimorelin acetate to seek the indication to diagnosis AGHD.
- On November 5, 2014, the Office of Drug Evaluation II, Office of New Drugs issued a Complete Response letter because of efficacy issues, statistical issues, and lack of thorough QT study.
- On March 6, 2015, the Division of Metabolism and Endocrinology Products (DMEP) conducted an End of Review meeting with the sponsor to discuss the path forward for macimorelin acetate.
- On June 30, 2017, the sponsor resubmitted NDA 205-598 thru Serial 0031 (Class 2 resubmission) to provide a complete response to the deficiencies outlined in the Complete Response letter dated November 5, 2014.

2.2 General Clinical Pharmacology

2.2.1 What are the submitted clinical studies for macimorelin acetate in NDA 205-598?

Table 1 lists all submitted clinical studies for NDA 205-598. The sponsor conducted the 3 yellow-highlighted Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055 in Table 1 to address the deficiencies outlined in the Complete Response letter. The sponsor submitted the non-highlighted studies of Table 1 with the original submission.

Table 1. Chronological overview of all clinical studies for macimorelin acetate

Study ID	Objective	Design	Route	Dose, mg/kg	N (M/F)
Broglia 2002	Safety, PD	Open, randomized, crossover, SD (+2 nd dose)	IV PO PO PO PO	0.001 0.06 0.125 0.25 0.5	2(2/0)
AEZS-130-IIT-1	Safety, PK/PD	Open, randomized, PC, PG, PD	PO PO PO POPO PO ID ID ID ID	Placebo 0.005 0.05 0.125 0.25 0.5 0.2 0.35 0.5	9(9/0) 27(27/0) in total
ARD-0705-003	Food effect PK/PD	Open randomized, cross-over, SD	PO fasted PO fed	0.5 0.5	16 (8/8) in total

AEZS-130-047	Efficacy, Safety PK/PD	Open, SD	PO	0.5	52 (31/22)
				0.5	48 (30/18)
AEZS-130-052	Efficacy, Safety PK/PD	Open, randomized, cross-over, SD	PO	0.5 ITT (insulin)	154 (90/64) 157 (93/64)
AEZS-130-054	Safety, PK/PD	Open, randomized, PC, PG, SD	PO	Placebo 0.5 1.0 2.0	7 (4/3) 6 (2/4) 6 (3/3) 9 (4/5)
AEZS-130-055	Thorough QT PK/ECG	DB, randomized, PC+AC, 3- cross-over, SD	PO	Placebo 2.0 Moxi	57 (34/23) 57 (33/24) 58 (35/24)

N refers to number of subjects exposed. M=male, F=female. AC=active controlled. ID=intraduodenally. Moxi=moxifloxacin. ITT=insulin tolerance test. PC=placebo controlled. PD=pharmacodynamics. PG= parallel groups. PK= pharmacokinetics. PO=per oral. SD=single dose.

Source: Modified from Module 2.7.2's Table 1.

2.2.2 Does difference exist between the to-be-marketed macimorelin acetate formulation and the clinically-tested macimorelin acetate formulation?

No. The clinically-tested macimorelin acetate formulation is identical to the to-be-marketed macimorelin acetate formulation. Table 2 details the different macimorelin acetate formulations.

Table 2. Macimorelin acetate formulations used in clinical studies and for commercialization^a

Formulation	Formulation 1 ^a	Formulation 2	Formulation 3 ^b	Both Form. 2 + 3
Used in study	Part 1 of AEZS-130-047 (also: ARD-0705-001)	Part 2 of AEZS-130-047	AEZS-130-052 AEZS-130-054 AEZS-130-055	
Macimorelin	50 mg ^{c)}	(b) (4)	(b) (4)	(b) (4)
Lactose monohydrate	(b) (4)			
Crospovidone	(b) (4)			
Saccharin sodium,	(b) (4)			
Colloidal silicon dioxide				
Sodium stearyl fumarate				
Total			1817.2 mg	100%
Volume for reconstitution / Solvent	100 ml water		120 ml water	

(b) (4)

Source: NDA 205-598 Section 2.7.1 Table 1.

2.2.3 Is macimorelin PK dose-proportional upon oral administration?

Background: The November 5, 2014 Complete Response letter states that the sponsor needs to conduct a thorough QT study for macimorelin acetate. According to the ICH E14 guidance's recommendation, a thorough QT study will test a drug at substantial multiples of the anticipated maximum therapeutic exposure of

the drug. Thus, the sponsor conducted Study AEZS-130-054 to check the safety and tolerability of 2-fold and 4-fold higher than the proposed dose of 0.5 mg macimorelin/kg body weight for diagnosis of AGHD before conducting the thorough QT study for macimorelin acetate (Study AEZS-130-055).

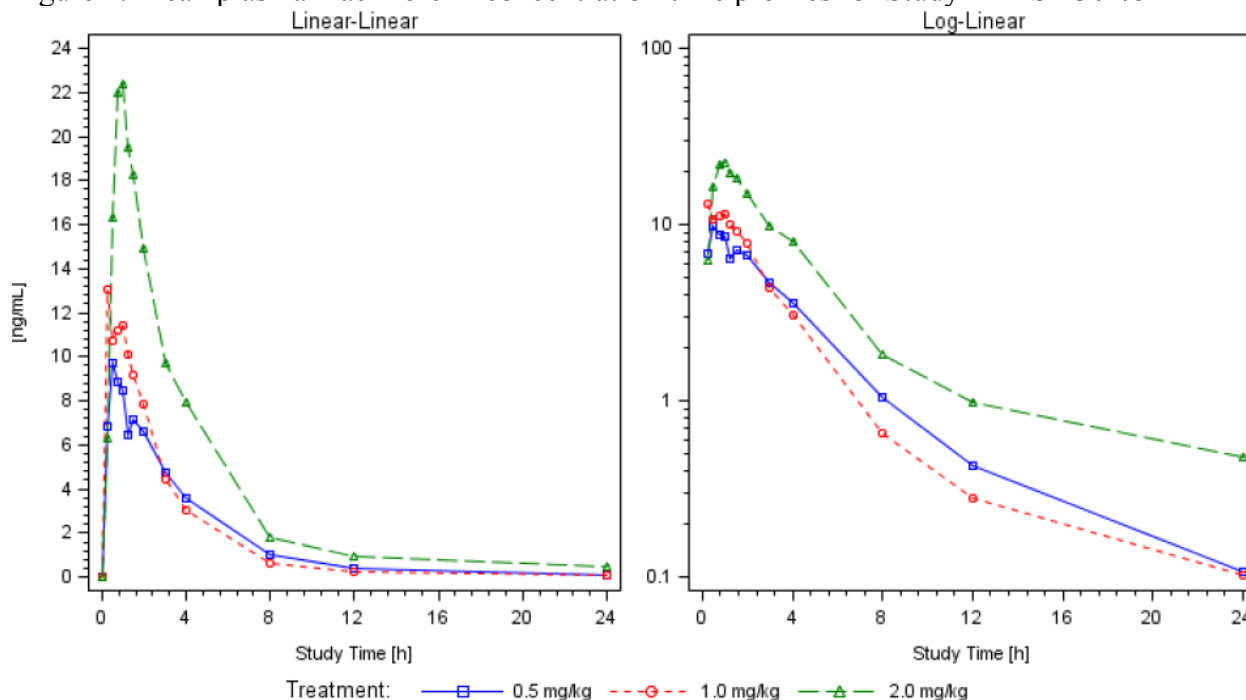
Study AEZS-130-054 assessed the PK of single rising oral doses of macimorelin in a parallel fashion in healthy subjects:

- 0.5 mg macimorelin/kg body weight
- 1 mg macimorelin/kg body weight
- 2 mg macimorelin/kg body weight

Each participant fasted for at least 8 hours predose.

Serial plasma samples at pre-dose, 15, 30, 45, 60, 75, and 90 min as well as 2, 3, 4, 8, 12, and 24 hours after oral administration of the 3 macimorelin doses were collected to determine the macimorelin concentrations via a validated LC-MS/MS bioanalytical method to assess macimorelin pharmacokinetics. Figure 1 shows the mean plasma macimorelin concentration-time profiles for the 3 doses of Study AEZS-130-054. Table 3 shows the macimorelin PK parameters for the 3 doses of Study AEZS-130-054.

Figure 1. Mean plasma macimorelin concentration-time profiles for Study AEZS-130-054



Source: Modified from Study AEZS-130-054's report Figure 1

Table 3. Macimorelin PK parameters for Study AEZS-130-054

Parameter	0.5 mg/kg macimorelin N=6	1.0 mg/kg macimorelin N=6	2.0 mg/kg macimorelin N=9
AUC _{0-t} [h*ng/mL]	36.3 (40.9%)	35.1 (57.6%)	81.9 (38.8%)
AUC _{0-inf} [h*ng/mL]	38.0 (41.6%)	37.0 (58.0%)	84.7 (39.1%) ^a
C _{max} [ng/mL]	9.24 (40.4%)	13.1 (57.1%)	21.3 (49.6%)
t _{1/2} [h]	3.51 (66.7%)	3.51 (106%)	8.29 (17.8%) ^a
λ _z [1/h]	0.198 (66.7%)	0.198 (106%)	0.0837 (17.8%) ^a
t _{max} [h]	0.533 (0.250-0.750)	0.534 (0.250-1.00)	0.750 (0.517-1.50)

Geometric mean and CV are presented, median and range for t_{max}; ^a n=8, due no reliable λ_z in 1 subject

Source: Modified from Study AEZS-130-054's report Table 5

The mean macimorelin terminal half-life is 4.119, 4.929, and 8.397 hours, respectively, for the 0.5, 1, and 2 mg/kg single oral doses.

Per the power model to assess dose-proportionality for macimorelin ($C_{\max}$ or $AUC_{0-\infty} = \alpha \cdot [\text{Oral Dose}]^\beta$; where α depends on the subject and error; β is the dose-proportionality factor; after transformation, $\ln C_{\max}$ or $\ln AUC_{0-\infty} = \ln \alpha + \beta \cdot \ln \text{Oral Dose}$; $\beta = 1$ when dose-proportional) (Gough et al. *Drug Info J* 1995;29:1039-48). The analyses of this power model for macimorelin PK show the following:

- The slope, β , and its (90% CI) for the macimorelin $\ln C_{\max}$ vs. macimorelin $\ln \text{Oral Dose}$ plot was 0.5606 (0.2574 – 0.8638).
- The slope, β , and its (90% CI) for the macimorelin $\ln AUC_{0-\infty}$ vs. macimorelin $\ln \text{Oral Dose}$ plot, was 0.6055 (0.2877 – 0.9233).
- The slope, β , of the power model analyses were 0.5606 and 0.6055; all < 1 .

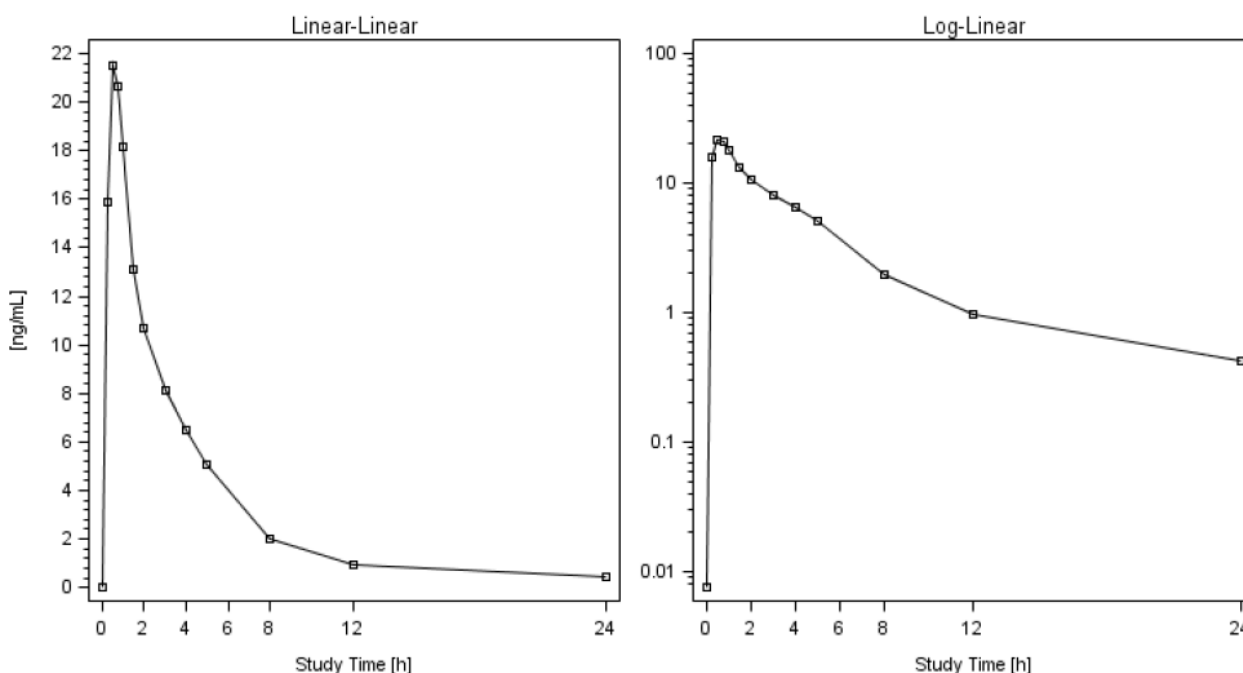
Thus, the PK of macimorelin is less than dose proportional for single oral doses from 0.5 mg/kg to 2 mg/kg in healthy subjects.

Study AEZS-130-055 is a double blind, randomized, single dose, 3-period crossover study in healthy subjects. Study AEZS-130-055 aims to assess the effect of a single oral supra-therapeutic dose of macimorelin with moxifloxacin and placebo as positive and negative control, respectively. Study AEZS-130-055 had the following oral treatments:

- 2 mg macimorelin/kg body weight
- 400 mg moxifloxacin
- placebo of macimorelin

Each subject fasted at least 8 hours before (no food, no beverages, only water was allowed) until 5 hours after drug administration. Ingestion of water was not allowed between 1 hour predose and 1 hour postdose. Five hours postdose, participants received a standard lunch. Food intake may have an effect on the ECG parameters. A washout of at least 3 days separated each treatment. Figure 2 shows the mean plasma macimorelin concentration-time profile of 2 mg macimorelin/kg body weight for Study AEZS-130-055.

Figure 2. Mean plasma macimorelin concentration-time profiles for Study AEZS-130-055



Source: Modified from Study AEZS-130-055's report Figure 4

Table 4. Macimorelin PK parameters for Study AEZS-130-055

Parameter	2.0 mg/kg macimorelin N=57
AUC _{0-t} [h*ng/mL]	71.7 (43.7%)
AUC _{0-inf} [h*ng/mL]	75.7 (43.9%)*
C _{max} [ng/mL]	21.9 (37.9%)
t _{1/2} [h]	7.23 (47.6%)*
λ _z [1/h]	0.0958 (47.6%)*
t _{max} [h]	0.583 (0.300-1.233)

Geometric mean and CV are presented, median and range for t_{max}; * n=54, due no reliable λ_z in 3 participants

Source: Modified from Study AEZS-130-055's report Table 10

According to Tables 3 and 4 as well as Figures 1 and 2, the PK of 2 mg macimorelin/kg body weight appears to be consistent between Study AEZS-130-054 and Study AEZS-130-055 in healthy subjects.

2.2.4 What are the pharmacodynamics (PD) effects of macimorelin for Study AEZS-130-054?

Study AEZS-130-054 assessed the PD of single rising oral doses of macimorelin in a parallel fashion in healthy subjects:

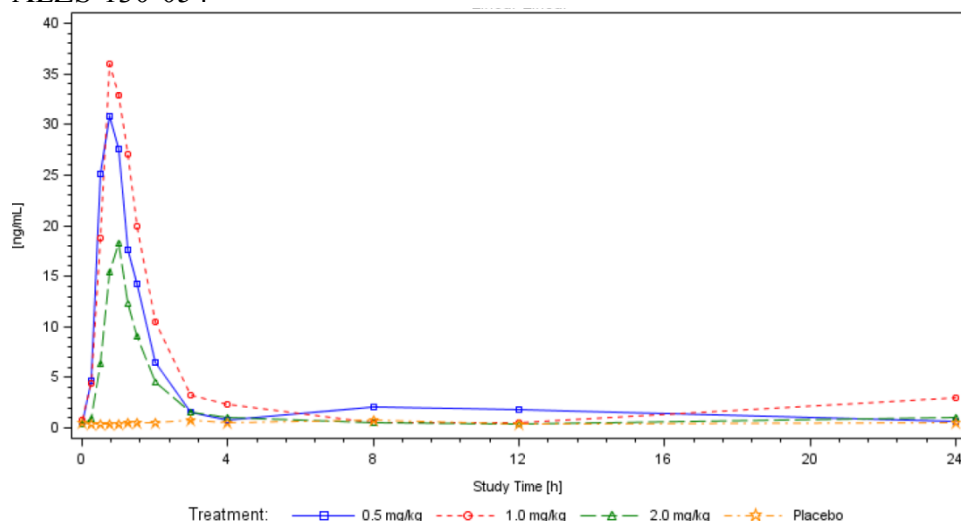
- 0.5 mg macimorelin/kg body weight
- 1 mg macimorelin/kg body weight
- 2 mg macimorelin/kg body weight

Each participant fasted for at least 8 hours predose.

Serial serum samples at pre-dose, 15, 30, 45, 60, 75, and 90 minutes as well as 2, 3, 4, 8, 12, and 24 hours after the oral administration of the 3 macimorelin doses were collected to determine the concentrations of GH, thyroid stimulating hormone (TSH), cortisol, prolactin as PD measures in the clinical laboratory of (b) (4). Serial plasma (K2-EDTA) samples were also collected at the same time as the other PD measures to determine the concentrations of adrenocorticotrophic hormone (ACTH) in the immunological laboratory of (b) (4).

The sponsor did not provide the bioanalytical and validation reports for measuring the concentrations of GH, TSH, cortisol, prolactin, and ACTH. Thus, the results of these PD measures are just for reference purposes. However, this review discusses the mean serum GH concentration-time profile because GH is the marker of interest for the diagnosis of AGHD. Figure 3 shows the mean serum GH concentration-time profiles at 0.5, 1, and 2 mg macimorelin/kg body weight for Study AEZS-130-054.

Figure 3. Mean serum GH concentration-time plots of 0.5, 1, and 2 mg macimorelin/kg body weight for Study AEZS-130-054



Source: Modified from Study AEZS-130-054's report Figure 2

Macimorelin showed dose-related increase in mean serum GH concentration-time profiles from 0.5 mg/kg to 1 mg/kg (Figure 3). Notably, the mean serum GH concentration-time profile resulted from the dose of 2 mg/kg is lower than those from the doses of 0.5 and 1 mg/kg. Upon request, the sponsor explained thru Serial 0038 that the difference in mean serum GH concentrations between 2 mg/kg and 0.5 – 1 mg/kg for Study AEZS-130-054 as the following:

- The maximum GH stimulation is achieved by macimorelin at 0.5 mg/kg in healthy subjects per the results of Study AEZS-130-IIT in the original submission. However, Study AEZS-130-IIT's results may not be reliable because the sponsor did not prepare a bioanalytical report for GH measurements and no validation report for the bioanalytical report is available (see Clinical Pharmacology review dated July 16, 2014 Reference ID: 3594224 Question 2.2.2).
- Study AEZS-130-054's peak serum GH concentrations showed a high inter-individual variability, which is in-line with clinical practice reflecting inter-individual differences as well as circadian fluctuations and fluctuations influenced by intrinsic and extrinsic factors.
- Such differences in peak GH concentration are clinically irrelevant as long as the peak concentration is above a certain limit differentiating healthy subjects from patients with AGHD. In other words, the sponsor claims that the differences in peak GH concentrations among the 3 dose groups do not matter as long as the peak GH concentrations are above the cut-off values for the diagnosis of AGHD.
- Thus, the variability in the mean peak GH concentrations of the different groups can be explained by the high inter-individual variability and the size of the dosing cohorts.

2.2.5 Does the macimorelin PK differ among AGHD patients and healthy subjects upon oral administration?

Study AEZS-130-052 is an open-label, randomized, single-dose, and 2-way crossover in design. Study AEZS-130-052 assessed the single oral dose of 0.5 mg macimorelin/kg as the growth hormone stimulation test (GHST) for the diagnosis of AGHD in the following 4 groups of subjects who fasted for at least 8 hours before receiving macimorelin:

- Group A: high likelihood to be AGHD
- Group B: intermediate likelihood to be AGHD
- Group C: low likelihood to be AGHD
- Group D: healthy control

The definitions of the following 4 Groups are:

- A: High likelihood of GHD:
 - Structural hypothalamic or pituitary lesions and low insulin growth factor -1 (IGF-1), and or
 - 3 or more pituitary hormone deficiencies (PHD) and low IGF-1, or
 - Childhood onset GHD with structural lesions and low IGF-1
- B: Intermediate likelihood of GHD:
 - Eligible subjects not qualifying for either high or low likelihood (Group A or C)
- C: Low likelihood of GHD:
 - 1 risk factor for GHD only, such as history of distant traumatic brain injury or 1 PHD only with otherwise normal pituitary function, or
 - Isolated idiopathic childhood onset GHD without additional pituitary deficits
- D: Healthy control:
 - Healthy subjects matching Group A subjects by sex, age, body mass index (BMI), and estrogen status (females only).

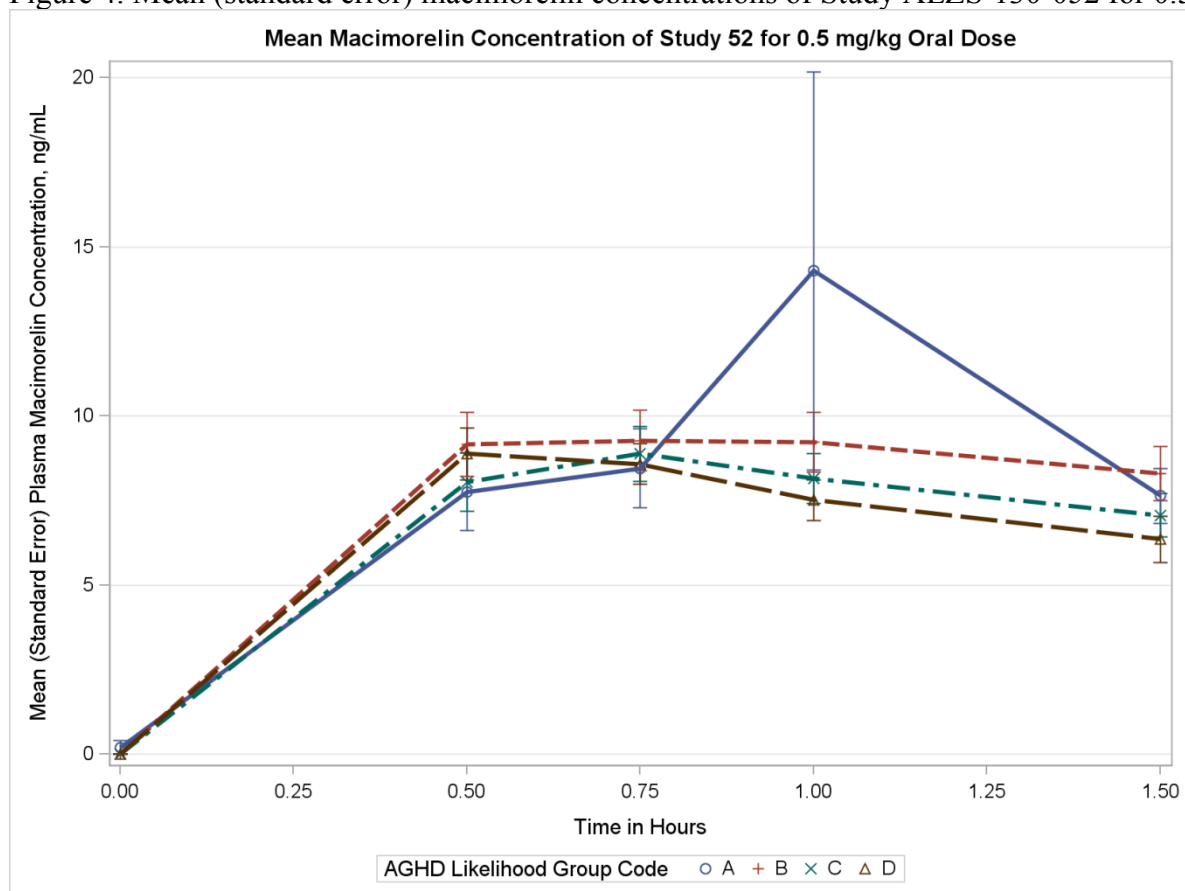
Subjects of these 4 groups also received the insulin tolerance test (ITT) as a crossover comparator to the macimorelin treatment. Subjects fasted for at least 8 hours before intravenously (IV) administered 0.1 U regular human insulin/kg body weight (0.15 U/kg in subjects with a BMI > 30 kg/m²). At the investigator's discretion, individual adaptations with lower or higher doses were allowed as clinically indicated treatment. A 7 days to 1 month washout separated the macimorelin or ITT treatment. The mean macimorelin terminal exponential half-life ($T_{1/2}$) was 4.1 hours for the dose of 0.5 mg macimorelin/kg body weight (Question 2.2.3). The half-life of free GH is 7 minutes and the half-life for bound GH is 27 minutes (Laursen T. Clinical pharmacological aspects of growth hormone administration. *Growth Horm IGF Res.* 2004;14:16-44). Thus, the washout period for Study AEZS-130-052 is acceptable.

The sponsor collected plasma samples at predose, 0.25, 0.5, 0.75, 1, and 1.5 hours postdose to determine the macimorelin concentrations via a validated LC/MS/MS bioanalytical assay. Figure 4 shows the mean (standard error) plasma macimorelin concentration-time profiles of Study AEZS-130-052 for 1.5 hours postdose. Figure 4 shows that the mean (standard error) plasma macimorelin concentration-time profiles for the 4 groups of Study AEZS-130-052 overlap with each other. However, the high likelihood group shows:

- the largest variability of plasma macimorelin concentrations at 1 hour postdose than the other time points
- larger variability of plasma macimorelin concentrations than the other 3 Groups

These observations suggest that the mean plasma macimorelin concentrations are similar between patients with AGHD and healthy subjects for 1.5 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight.

Figure 4. Mean (standard error) macimorelin concentrations of Study AEZS-130-052 for 0.5 mg/kg oral dose



Group A: high likelihood to be AGHD; Group B: intermediate likelihood to be AGHD; Group C: low likelihood to be AGHD; Group D: healthy control

Source: Reviewer's analyses

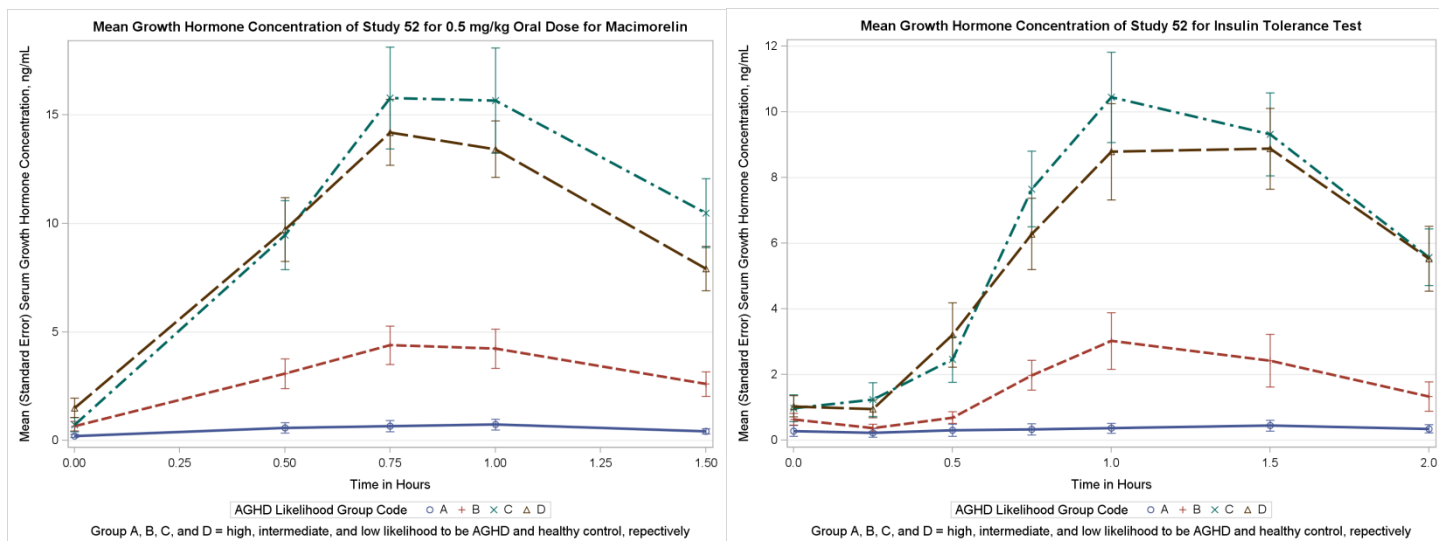
The clinical pharmacology review of NDA 205-598 dated July 16, 2014 in DARRTS, Pages 9 – 10 also recommended that the exposure of macimorelin is not significantly different between patients with AGHD and healthy controls at the single oral dose of 0.5 mg macimorelin/kg body weight. Thus, the analyses above are consistent with the NDA 205-598 clinical pharmacology review dated July 16, 2014.

2.2.6 What is the PD effect of macimorelin for Study AEZS-130-052?

See Question 2.2.5 for details of Study AEZS-130-052. The sponsor collected the following serum samples to measure GH concentrations via the IDS-iSYS diagnostic kit:

- at predose, 0.5, 0.75, 1, and 1.5 hours postdose for the macimorelin GH stimulation test group
- at predose, 0.25, 0.5, 0.75, 1, 1.5, and 2 hours after IV administration of regular human insulin for the ITT group

Figure 5 (left panel) Mean (SE) serum GH concentrations-time profile upon oral administration of macimorelin. Figure 5 (right panel) Mean (SE) serum GH concentrations-time profile upon IV administration of ITT. Note: axes of different scales between the 2 panels.



Source: Reviewer's analyses

Figure 5 shows that the time for the peak serum GH concentration is 0.75 – 1 hour after oral administration of macimorelin, whereas the time for the peak serum GH concentration is 1 – 1.5 hours after IV administration of ITT. Macimorelin stimulation resulted in higher serum GH concentrations than those for the ITT. See Dr. William Lubas' Clinical review in DARRTS for the efficacy of the macimorelin test and the ITT.

2.2.7 Does macimorelin prolong the QT or QTc interval?

The sponsor conducted Study AEZS-130-055 to assess the QT prolongation potential of macimorelin in humans. The sponsor claimed that a single oral dose of 2 mg macimorelin/kg body weight induces a prolongation of QTcF by about 10 milliseconds when compared to placebo at around 4 hours postdose. See the QT-Interdisciplinary Review Team's review dated November 22, 2017 in DARRTS, Reference ID 4184931 for the QT prolongation potential of macimorelin.

2.3 Bioanalytical

2.3.1 Are the bioanalytical methods validated for Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055?

The Clinical Pharmacology review team decided not to recommend inspection for the bioanalytical sites of the pivotal clinical study (AEZS-130-052) for measuring plasma macimorelin concentrations and serum GH concentrations because:

- The sponsor used a validated HPLC-MS/MS bioanalytical assay and (b) (4) site to measure the plasma macimorelin concentrations for Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055 as reported in Serial 0031. The sponsor used the same LC-MS/MS bioanalytical assay and site to measure the plasma macimorelin concentrations for Studies AEZS-130-003 and AEZS-130-047 as reported in Serial 0000. The bioanalytical method for measuring the plasma macimorelin concentrations in Serial 0000 was acceptable. See the clinical pharmacology review dated July 16, 2014 in DARRTS, Reference ID: 3594224.
- The sponsor stated that they used a kit-based assay for measuring GH and followed the Food and Drug Administration's guidance for bioanalytical requirements.
- It is not the usual practice to inspect the bioanalytical site of PD markers such as serum GH for a Phase 3 study.

Macimorelin

Table 5 shows the validation results of the macimorelin bioanalytical method for Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055. Table 6 shows the stability results of macimorelin in plasma samples as assessed in Study AEZS-130-054.

Table 5. Validation of macimorelin bioanalytical method.

	Plasma Samples
Anticoagulant	Na-heparin or Li-heparin
Analyte	macimorelin
Method	HPLC-MS/MS
Sample volume, µL	200
Lower limit of quantitation, ng/mL	0.2
Linear range, ng/mL	0.2 – 200
Calibration Standard (0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 180, 200 ng/mL)	
Interassay accuracy, %	-2.93 to 2.55
Interassay precision, %	1.77 to 6.62
Quality control samples (0.6, 15, 150 ng/mL)	
Interassay accuracy, %	-9.42 to -0.38
Interassay precision, %	3.26 to 8.14

Source: Reviewer's compilation of bioanalytical reports for Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055.

Table 6. Stability of macimorelin in plasma samples as assessed in Study AEZS-130-054

Processed sample stability (autosampler)	68.5 h at 10°C in the autosampler
QC sample short-term stability	4 h at room temperature
QC sample freeze/thaw stability	3 freeze/thaw cycles
Investigation of influence of the dilution factor	1:20 in human plasma
Selectivity and specificity	No interfering peaks were detected in 6 different human blank plasma samples at the retention time of macimorelin and the internal standard.
Carry over	No carry-over peaks were detected in the 2 carry-over samples at the retention time of macimorelin and the internal standard.
QC sample long-term storage stability	12 months at -20°C
Stock solution stability	Working solution (20 ng/mL, 200 ng/mL and 600 ng/mL in solution VD: 8 weeks at +4°C <i>Stock solution (1 mg/mL solution VD) of macimorelin, as well as stock- and working solution stability of the internal standard is ongoing.</i>

Source: Modified from aezs-130-054-e16-1-10-bioanalytical.pdf Page 99/150

The bioanalytical method to measure plasma macimorelin concentrations for Studies AEZS-130-052, AEZS-130-054, and AEZS-130-055 is acceptable.

GH

The sponsor used the IDS-iSYS diagnostic kit that operates on the principle of immunochemiluminescence (ICMA) to measure serum GH concentrations for Study AEZS-130-052. Samples are incubated with a biotinylated anti-human GH monoclonal antibody and streptavidin labelled magnetic particles. The magnetic particles are “captured” by way of a magnet and a wash step are performed. An acridinium labeled anti-human GH monoclonal body is added and following a further incubation step then a 2nd wash step is performed.

Trigger reagents are added and the resulting light emitted by the acridinium label is directly proportional to the concentration of human GH in the original sample.

Table 7's left column summarizes the issues of the IDS-iSYS diagnostic kit to measure serum GH concentrations for Study AEZS-130-052. Per the March 6, 2015 End of Review meeting, the sponsor accepted DMEP's recommendation to develop and validate an assay to measure serum GH concentrations according to the 2013 version of the draft bioanalytical method guidance

(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf>). See the April 1, 2015 meeting minutes, Pages 6 and 7 of 28. However, Study AEZS-130-052's validation report (08-aezs-130-ids-isys-hgh-with-amend-1-7.pdf) for measuring serum GH concentrations is inconsistent with the recommendations of the 2013 version of the draft bioanalytical method guidance and the sponsor seemed to follow the following 2 references instead:

- Analytical Procedures and Methods Validation for Drugs and Biologics for Pharmaceutical Quality/CMC July 2015 at <https://www.fda.gov/downloads/drugs/guidances/ucm386366.pdf>
- Guideline on bioanalytical method validation by EMA 1 February 2012 at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

Upon request, the sponsor responded to these inconsistencies via Serial 0038 on October 19, 2017 as reflected in Table 7's right column. The sponsor also sent an email on November 13, 2017 to further explain the calibrators for the GH standard curve as appeared in Points 2 and 3 of Item 3 in Table 7's right column.

Table 7. Issues of bioanalytical assay to measure GH in serum samples and the sponsor's response to these issues

	Study AEZS-130-052 did	2013 FDA Draft Bioanalytical Method Validation Guidance Recommends	Sponsor's Responses on 10/19/2017
1	Sparse calibrators of 2 concentrations (0.185 and 19.662 ng/mL)	6 non-zero calibrators	Cut-off values in the range of 2.8 – 5.1 ng/mL for both GHST and ITT are covered by the calibrators concentrations of 0.185 and 19.662 ng/mL.
2	No duplicate calibrators	Duplicate calibrators	Triplicate per manufacturer manual
3	Standard curve not include LLOQ (< 0.05 ng/mL) and the measured serum GH concentration up to 60 ng/mL	Standard curve includes the LLOQ covering the entire measured concentration range	• Reportable range of assay is 0.05 – 100 ng/mL per manufacturer's validation information. • The calibration of the hGH assay is based on a lot-specific master calibration curve provided with the kit. This master calibration is performed by the manufacturer for each lot of assay reagents using a total of 9 samples covering reportable range of the assay (0.05 - 100 ng/mL). The calibration is provided on a computer disc and is loaded onto the IDS analyzer system. The calibration using the two calibrators (Cal A and Cal B, 0.185 and 19.662 ng/mL, resp.) provided with the assay, is a two-point re-calibration conducted in triplicate to generate a calibration curve using a 4-parameter logistic regression. • This approach, using a master calibration and re-calibration with sparse calibrators is current standard practice for automated immune-assays.

4	Calibrators in horse serum; absence of justification for the use of horse serum for biological matrix	Calibrators in human serum to match sample matrix	• Clemmons et al. stated that “...it may be necessary to use serum from another species that maintains optimal linearity and recovery of known quantities of the hormone” for standardization and evaluation of GH assays. <i>Clin Chem.</i> 2011;57:555-9. • Excellent linearity and recovery of known quantities of human GH has been demonstrated for the IDS-iSYS hGH assay (Manolopoulou et al. <i>Clin Chem.</i> 2012;58:1446-56). • This approach is also used for other commercial assay kits (Siemens Immulite 2000 hGH; Delfia hGH) use horse or bovine serum as matrix.
5	Absence of information on calibrators show no measurable endogenous human GH	The biological matrix of calibrators shows no measurable endogenous human GH.	Due to the absence of a reference measurement procedure for GH, the demonstration of absence of the analyte in human serum might be challenging.
6	Absence of information on the analyte-free biological matrix should have no matrix effect or interference when compared to the biological matrix of calibrators	The analyte-free biological matrix should have no matrix effect or interference when compared to the biological matrix of calibrators.	See responses to Item 4 “Calibrators in horse serum” above.
7	QC samples, at 2.59, 6.74, and 12.4 ng/mL, do not cover the entire concentration range observed in the study.	QC at low, mid, and high concentrations: low QC should be within 3 times the LLOQ, midrange QC, and QC at high end of the expected study sample concentrations	The QC samples (2.59, 6.74, and 12.4 ng/mL) covered the critical concentration range for Study AEZS-130-052.

Source: Reviewer’s compilation of facts.

This reviewer recommends accepting the results of serum GH concentrations for Study AEZS-130-052 because:

- Most of the measured serum GH concentrations for Study AEZS-130-052 are below 20 ng/mL. (b) (4) cut-off values for the diagnosis of AGHD are 2.8 – 5.1 ng/mL for serum GH concentrations. The 2 calibrators concentrations of 0.185 and 19.662 ng/mL as well as the 3 quality control concentrations of 2.59, 6.74, and 12.4 ng/mL cover the cut-off range of 2.8 – 5.1 ng/mL and serum GH concentrations of less than 20 ng/mL. Thus, Items 1, 3, and 7 of Table 7 appear acceptable.
- The Clemmons article does point out the challenges of developing GH assay such as GH standardization and matrix requirements (Consensus statement on the standardization and evaluation of growth hormone and insulin-like growth factor assays. *Clin Chem.* 2011;57:555-9). The Clemmons article is the recommendations of an expert workshop conducted by the Growth Hormone Research Society in collaboration with the IFCC, the International Society for IGF Research, and the Pituitary Society. No authors of the Clemmons article declared any potential conflict of interest. Thus, Items 4 – 6 of Table 7 appear acceptable.
- This reviewer later confirmed that calibration was carried out in triplicate per bioanalytical report “02-aezs-130-analytical-report-hgh.pdf” Page 6. Thus, Item 2 of Table 7 is acceptable.
- Table 8 and Figure 6 show the comparison between the IDS Isys-hGH and the hGH Siemens Immulite 2000 Xpi to measure serum GH concentrations. The results are comparable between

these 2 bioanalytical methods. The Siemens Immulite 2000 Xpi is a commercially available continuous random-access instrument that performs chemiluminescent immunoassays for diagnosis of growth hormone disorders (<https://usa.healthcare.siemens.com/growth-disorders/growth-diagnostics/assay-menu>).

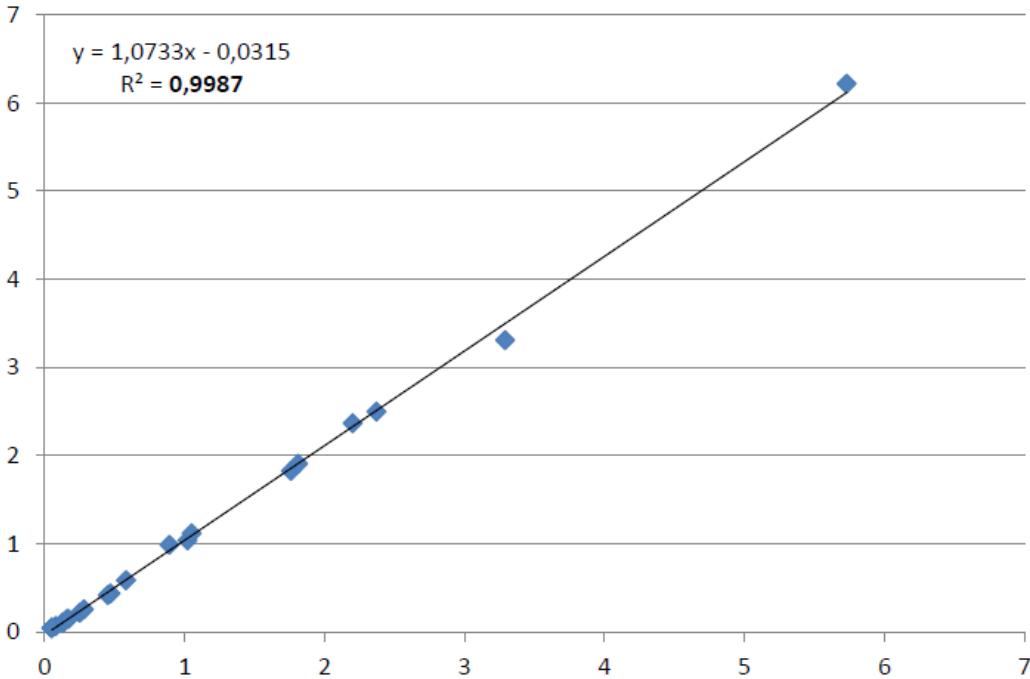
- The ITT is the positive control of Study AEZS-130-052 for GH secretion. Results of the ITT can help verify the results of the macimorelin stimulated release of GH.
- Acceptability of the serum GH concentrations was discussed at the DMEP Clinical Pharmacology team meeting on October 23, 2017 and the Division of Clinical Pharmacology 2 Advisory Council on November 15, 2017. Majority of the discussants voted to accept the serum GH concentrations data.
- The serum GH concentrations are not used for dose adjustment purpose because the dose is fixed at 0.5 mg macimorelin/kg body weight. Overall, the serum GH concentrations appear to be fit for the purpose of diagnosing AGHD with reference to the cut-off values.

Table 8. Results of serum GH concentration measurements via IDS Isys-hGH and hGH Siemens Immulite 2000 Xpi

	IDS Isys-hGH	hGH Siemens Immulite 2000 Xpi
Sample No.	hGH concentration (ng/mL)	hGH concentration (ng/mL)
1	1.02	1.04
2	0.58	0.59
3	0.08	0.07
4	2.37	2.5
5	0.05	0.05
6	0.05	0.05
7	0.89	0.99
8	0.13	0.11
9	0.47	0.44
10	0.25	0.22
11	0.28	0.26
12	0.16	0.15
13	0.13	0.11
14	2.2	2.37
15	1.76	1.83
16	0.05	0.05
17	0.17	0.15
18	1.05	1.12
19	0.45	0.42
20	1.81	1.91
21	3.29	3.31
22	5.73	6.22

Source: 08-aezs-130-ids-isys-hgh-with-amend-1-7.pdf, Page 10, Table 4

Figure 6. Linear correlation of the results of comparing IDS Isys-hGH and hGH Siemens Immulite 2000 Xpi



X axis: hGH concentrations measured with IDS iSYS method (ng/mL)
Y axis: hGH concentration measured with Siemens Immulite method (ng/mL)
IDS: X Mean= 1.04; Min.=0.05; Max.=5.73
Siemens: X Mean= 1.09; Min.=0.05; Max.=6.22
Linear correlation coefficient: R=0.9987.

Source: 08-aezs-130-ids-isys-hgh-with-amend-1-7.pdf, Page 11, Figure 11

Table 9 shows the validation results of the GH bioanalytical method for Study AEZS-130-052.

Table 9. Validation of GH bioanalytical method for Study AEZS-130-052.

	Serum Samples
Analyte	GH
Method	Immunochemiluminescence (ICMA)
Sample size, µL	300
Lower limit of quantitation, ng/mL	0.05
Dynamic range, ng/mL	0.05 – 100
Precision	
Intraassay, % (3 QCs)	2.77 – 5.24
Interassay, % (2 calibrators)	3.6 – 4.5

Source: Reviewer's compilation of Report 08-aezs-130-ids-isys-hgh-with-amend-1-7.pdf and 02-aezs-130-analytical-report-hgh.pdf

The sponsor did not provide bioanalytical and validation reports for PD markers such as GH, ACTH, TSH, cortisol, and prolactin for Study AEZS-130-054. Study AEZS-130-055 is a thorough QT study and did not measure any PD marker.

3. Labeling Recommendations

Strikethrough text means deletion of the sponsor's proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

(b) (4)

Editorial changes

FULL PRESCRIBING INFORMATION: CONTENTS*

- 1 INDICATIONS AND USAGE
- 2 DOSAGE AND ADMINISTRATION
 - 2.1 Recommended Dose
 - 2.2 Directions for Preparation (b) (4)
- 3 DOSAGE FORMS AND STRENGTHS
- 4 CONTRAINDICATIONS
- 5 WARNINGS AND PRECAUTIONS
- 6 ADVERSE REACTIONS
 - 6.1 Clinical Studies Experience
- 7 DRUG INTERACTIONS
 - 7.1 CYP 3A4 Inducers

7 DRUG INTERACTIONS

(b) (4)

7.1 Cytochrome P450 (CYP) 3A4 Inducers

- (b) (4) Coadministration of a CYP3A4 inducer ((b) (4)), carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort, bosentan, efavirenz, etravirine, modafinil, (b) (4) armodafinil, (b) (4) rufinamide (b) (4)) (b) (4) affect the diagnostic performance of the test lead to false positive test results. Avoid concomitant use with CYP3A4 inducers. (b) (4)

Cardiac eElectrophysiology:

The effects of macimorelin on ECG parameters were investigated in a dedicated Thorough QT study that investigated in a 3-way cross-over design with 60 healthy subjects the effects of a supra-therapeutic dose of macimorelin (2.0 mg/kg) in comparison with placebo and with moxifloxacin. (b) (4)

12.3 Pharmacokinetics

(b) (4)

The mean plasma macimorelin concentrations are similar between patients with AGHD and healthy subjects for 1.5 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight.

Absorption

The maximum plasma macimorelin concentrations (C_{max}) were observed between 0.5 hour and 1.5 hours upon oral administration of 0.5 mg macimorelin/kg body weight to patients with AGHD under fasting for at least 8 hours. A liquid meal decreased the macimorelin C_{max} and AUC by 55% and 49%, respectively.

Elimination

An in vitro human liver microsomes study showed that CYP3A4 is the major enzyme to metabolize macimorelin.

Macimorelin was eliminated with a mean terminal half-life ($T_{1/2}$) of 4.1 hours following administration of a single oral dose of 0.5 mg macimorelin/kg body weight in healthy subjects.

According to the Clinical Pharmacology Labeling guidance

<https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm109739.pdf>

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
11/22/2017

JAYABHARATHI VAIDYANATHAN
11/22/2017

CLINICAL PHARMACOLOGY REVIEW

(Addendum to the original review dated July 16, 2014 and Addendum dated August 7, 2014)

NDA	205-598; 0022; 0023
Submission Dates	September 2, 2014; September 8, 2014
Brand Name	MACRILEN [®]
Generic Name	Macimorelin acetate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aeterna Zentaris
Formulation; Strength	Granules for oral solution; 0.5 mg/mL
Relevant IND	73,196
Indication	Diagnosis of adult growth hormone deficiency

Background

The purpose of this addendum is to review the sponsor's additional response particularly to the growth hormone (GH) concentrations measurement issue communicated to the sponsor with letter dated July 14, 2014, further discussed in the Late Cycle Meeting on July 23, 2014, and specified in the Late-Cycle Meeting Minutes. Also, refer to the following in DARRTS:

- Clinical Pharmacology review for macimorelin dated July 16, 2014
- Late Cycle Review Meeting's minutes dated August 15, 2014
- Addendum to the Clinical Pharmacology review dated August 7, 2014

Findings and Recommendations

In the Late-Cycle Meeting, the sponsor claimed that all GH concentrations were measured in serum samples for Study AEZS-130-047 (see Addendum to the Clinical Pharmacology review dated August 7, 2014). (b) (4)

(b) (4) reviewed the database of Study AEZS-130-047 and found that the sponsor's claim is incorrect.

Study AEZS-130-047 has 4 subjects that do not have serum samples for GH measurement for Visit 2 and Visit 3.

Thus, (b) (4) recommended the following statement for the bioanalytical report VR07-(b) (4) 018:

"Due to deviations from the protocol, serum samples are not available for either a Visit 2 or 3 on four subjects."

The sponsor clarified that Report VR07-(b) (4) 018 does not identify the 4 subjects who had missing serum samples and confirmed that the missing serum samples are not for Subjects 0105, 0306, 0304, and 0609 but for Subjects 0802, 0801, 0604, and 0603 instead (see Attachment below). The sponsor also confirmed that the GH concentrations for Subjects 0105, 0306, 0304, and 0609 in Visits 2 and 3 are measured in serum. However, the sponsor used Report VR07-(b) (4) -018 to justify the substitution of plasma pharmacokinetic backup samples for the missed serum samples via the bioanalytical analyses of serum and plasma samples of Subjects 0105, 0306, 0304, and 0609 in Visit 3. Again, this substitution is not acceptable due to the bias between the serum GH concentration and plasma GH concentration ranges from -27.4% to 26.19% (see Clinical Pharmacology review for macimorelin dated July 16, 2014). This reviewer recommends the following:

The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for Subjects 0802 and 0603 and Visit 3 for

Subjects 0801 and 0604 per Report VR07-(b) (4) 018 is not acceptable due to the range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples is -27.4% to 26.19%. Thus, the reported serum growth hormone concentration results on Visit 2 for Subjects 0802 and 0603 and Visit 3 for Subjects 0801 and 0604 of Study AEZS-130-047 are not reliable.

Attachment starts here

Please find below a response to the identified and not yet resolved review issues communicated to Aeterna Zentaris with letter dated July 14, 2014 and further discussed in the Late Cycle Meeting on July 23, 2014.

Clinical Pharmacology

Late-Cycle Meeting Background package dated July 14, 2014:

The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit

2 for 4 subjects per Report VR07-(b) (4) 018 is not acceptable due to the wide range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples. Thus, the reported serum growth hormone concentration results on Visit 2 for 4 subjects of Study AEZS-130-047 are not reliable.

Late-Cycle Meeting Minutes, received Aug 27, 2014:

The applicant claimed that serum samples for the measurement of growth hormone for all patients were available from Study AEZS-130-047. The applicant also claimed that there was a mistake in the bioanalytical report (VR07-(b) (4) 018) when it stated that the serum samples were not available due to a protocol deviation for Visit 2 from 4 subjects and that instead backup plasma samples had been used to replace the missing serum samples for growth hormone measurement. The Agency asked the applicant to specifically confirm that the growth hormone concentration measurement for Subject 0609 was indeed determined from serum samples.

Response

On 01Aug2014, we have provided the FDA a statement issued by (b) (4) documenting that all values for GH measurements in the database were done with serum samples (see [Appendix 1](#)).

Upon completion of a database review by (b) (4), the above statement is incorrect. The database review has brought up the following clarifications pertaining to the validation report VR07-(b) (4) 018.

- 1) Section 2 (entitled Summary), the 2nd sentence should read (change highlighted in bold):

*Due to deviations from the protocol, serum samples are not available for Visit 2 **or Visit 3** on four subjects.*

The rationale for this change is a typographical error, as indicated in the 29Aug2014 note to file provided by (b) (4) (see [Appendix 2](#)).

- 2) The four subjects with no serum samples available for Visit 2 or Visit 3 had not been identified in the validation report. They are 0603 (at Visit 2), 0604 (at Visit 3), 0801 (at Visit 3) and 0802 (at Visit 2), as indicated in [Appendix 2](#). At those visits, the four patients had received AEZS-130 treatment. Due to the importance of knowing the GH concentrations following AEZS-130 treatment (the primary endpoint is derived from this concentration), the GH concentrations were determined in plasma samples that had been taken at the same time as scheduled for the serum samples, however, for the purpose of pharmacokinetic analysis. [Appendix 3](#) shows, for each of the 4 subjects in question, the laboratory reports on the GH measurements as provided in the listing 16.2.6.1 of the clinical study report AEZS-130-047. Each laboratory

report is preceded by a 28Aug2014 note to file (provided by [REDACTED] (b) (4)) indicating the matrix analyzed (plasma or serum) at Visit 2 or Visit 3.

For all four subjects, the highest GH values obtained from analysis of plasma samples after dosing with AEZS-130 are in line with the values obtained from serum samples after L-ARG+GHRH test done during study, thus indicating GH deficiency for the 4 subjects.

3) The four subjects where GH was assayed in plasma at Visit 2 or Visit 3 are not to be confounded with the four subjects listed in section 4.3 and 4.4 of the validation report, namely 0105, 0306, 0304 and 0609. Visit 3 plasma samples from these latter 4 subjects were used to validate the assay of IGF-1 and GH in lithium heparin plasma samples, by comparing the concentrations of IGF-1 and GH when measured in both, serum and plasma samples collected at the same time. The Visit 3 plasma samples were available for this purpose since they had not been used (as originally planned) as back-up samples for the pharmacokinetic analyses. [Appendix 4](#) shows, for each of these 4 other subjects, the laboratory reports on the GH measurements provided in the listing [16.2.6.1](#) of the clinical study report AEZS-130-047. The laboratory reports are preceded by notes to file (provided by [REDACTED] (b) (4)) confirming that for subjects 0105, 0306, 0304 and 0609 the GH concentrations used in the evaluation of study AEZS-130-047 were measured in serum samples.

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/s/

SZE W LAU
10/02/2014

IMMO ZADEZENSKY
10/03/2014

CLINICAL PHARMACOLOGY REVIEW
(Addendum to the original review dated July 16, 2014)

NDA	205-598; 0017; 0018
Submission Dates	July 31, 2014; August 1, 2014
Brand Name	MACRILEN®
Generic Name	Macimorelin acetate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aeterna Zentaris
Formulation; Strength	Granules for oral solution; 0.5 mg/mL
Relevant IND	73,196
Indication	Diagnosis of adult growth hormone deficiency

Background

The purpose of this addendum is to review the following:

- The sponsor's response to the Division of Metabolism and Endocrinology Products' labeling recommendations (submitted on July 31, 2014).
- New information that the sponsor submitted in response to the Clinical Pharmacology issues discussed during the Late Cycle Review Meeting on July 23, 2014 (submitted on August 1, 2014).
- Three new bioanalytical reports for plasma macimorelin concentrations after intraduodenal administration for Study AEZS-130-IIT-1 (submitted on August 1, 2014).

Refer to Clinical Pharmacology review dated July 16, 2014 in DARRTS for the Clinical Pharmacology information of macimorelin and the meeting minutes of the Late Cycle Review Meeting dated August 15, 2014 in DARRTS.

Findings and Recommendations

For the July 31, 2014 submission, Points A13, A15, and Justifications for only partially implementing FDA proposals 1 pertain to Clinical Pharmacology.

[REDACTED] (b) (4)

Sponsor's Response

[REDACTED] (b) (4)

Reviewer's comment: no action necessary now

A15 See previous comment on [REDACTED] (b) (4)
Sponsor's Response

Reviewer's comment: This reviewer recommends to present Study AEZS-130-047's results (b) (4) because Study AEZS-130-047 assessed the macimorelin pharmacokinetics of the target patients with adult growth hormone deficiency (b) (4)

Justifications for only partially implementing FDA proposals / recommendations or are subject to ongoing discussions in the revised Prescribing Information

1 Section 12.3 Pharmacokinetics, first paragraph: Per study ARD-0705-003 clinical study report, based on the AUC_(0-∞), the proposed sentence should read (changes are highlighted in bold): A liquid meal decreased the macimorelin C_{max} and AUC_{(b) (4)}% and AUC_{(b) (4)}%, respectively.

Reviewer's comment: The sponsor seems to compare the arithmetic mean of macimorelin C_{max} and AUC_(0-∞) (b) (4)

However, the sponsor should use the Geometric Mean Ratio (With food/Without food) of the 2-sided paired t-test of log-transformed outcomes in Table 5 Page 42 (82) of Study ARD-0705-003's report for the 55% and 47% decreases in macimorelin C_{max} and AUC_(0-∞), respectively.

The August 1, 2014 submission pertains to the following 5 discussed topics below. See the Attachment for details.

- 1) Plasma samples were measured twice for macimorelin concentration in Study AEZS-130-IIT-1.

Reviewer's comment: The sponsor basically repeated the information that they submitted in the original submissions on November 5, 2013 and April 11, 2014.

- 2) A lapse of more than 10 months exists between the 2 measurements. Thus, stability of macimorelin in the plasma samples under storage is questionable. Your substantiation for the stability of the plasma samples under storage as submitted on April 11, 2014, for Study AEZS-130-IIT-1 is not acceptable.

Reviewer's comment: The sponsor performed statistical tests for the data between the 1st and 2nd bioanalytical analyses and concluded that the 2 bioanalytical analyses are statistically not different and that there was no trend observed when comparing the 2 datasets. These statistical tests are not acceptable because comparing the 1st and 2nd bioanalytical analyses is improper to show sample stability under long term storage as discussed before.

Anyhow, the sponsor has initiated a long-term stability study per the Bioanalytical Guidance for method validation. The sponsor will inform the Division of Metabolism and Endocrinology Products on any relevant information in the course of the stability study. Thus, no further action is necessary now.

- 3) Also, there are no validation report and bioanalytical report for the measurement of growth hormone in serum samples for Study AEZS-130-IIT-1.

Reviewer's comment: This reviewer acknowledges that the laboratory that performed the growth hormone measurement in serum samples of Study AEZS-130-IIT-1 was then accredited by the (b) (4). The English translation of the German document verified the standardization of the old and new human growth hormone measurements. See Attachment for details. This verification for the bioanalytical assay to measure serum growth hormone concentrations of Study AEZS-130-IIT-1 is not acceptable because this verification does not provide the information for the lower limit of quantitation, dynamic range, precision, and accuracy of the serum

growth hormone concentrations that are necessary for validating a bioanalytical assay per the Bioanalytical Guidance.

- 4) Without acceptable plasma macimorelin concentration and serum growth hormone concentration data for Study AEZS-130-IIT-1, the following data will be unacceptable:
- macimorelin pharmacokinetic dose proportionality data
 - macimorelin exposure-response data
 - macimorelin dose-response data
 - optimal macimorelin dose data

Reviewer's comment: (b) (4)
(b) (4) *compliance to all formal requirements including long-term stability data is missing. Thus, no further action is necessary now.*

- 5) The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for 4 subjects per Report VR07 (b) (4) 018 is not acceptable due to the wide range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples. Thus, the reported serum growth hormone concentration results on Visit 2 for 4 subjects of Study AEZS-130-047 are not reliable.

Reviewer's comment: The sponsor claimed that the statement in the validation Report VR07- (b) (4) -018 is wrong and that the clinical study report (CSR) as well as (b) (4) (bioanalytical laboratory) database showed no values for measurements of heparin plasma sample for growth hormone are included in the CSR. See Attachment for the e-mail for proof. The laboratory is currently rechecking their database and will come up with a formal statement in due course. The sponsor will submit the respective document for further clarification as soon as they have received it. Thus, no further action is necessary now.

Another August 1, 2014 submission pertains to 3 bioanalytical reports for plasma macimorelin concentrations after intraduodenal administration for Study AEZS-130-IIT-1

The sponsor submitted the following 3 bioanalytical reports for plasma macimorelin concentrations determination:

- Report no. EP01572/050016002, Date 05 April 2005
- Report no. EP01572/050016003, Date 29 June 2005
- Report no. EP01572/050016004, Date 18 Nov 2005

However, these 3 reports did not identify which clinical study that they pertain to.

Reviewer's comment: This reviewer identified that these 3 bioanalytical reports pertain to Study AEZS-130-IIT-1 because of the following:

- The sponsor placed these reports under the "Healthy Subjects PD and PK/PD Study Reports [Study ID – Study Title]" folder in the August 1, 2014 submission, which is consistent with the location and name of folder for Study AEZS-130-IIT-1 in the original submission.
- The sponsor conducted only 1 macimorelin PK/PD study, which is Study AEZS-130-IIT-1.
- The subject ID number and plasma macimorelin concentrations are consistent with the subject ID, dose, and intraduodenal route of administration in the electronic data file (SAS xpt file) for Study AEZS-130-IIT-1.
- Report no. EP01572/050016001, Date 19 Jan 2005 pertains to the 1st bioanalytical analysis for the plasma macimorelin concentrations and Report no. EP01572/050016005, Date 18 Nov 2005 pertains to the 2nd

bioanalytical analysis for the plasma macimorelin concentrations after oral administration for Study AEZS-130-IIT-1. These 5 bioanalytical reports seem to be in sequence.

The key issue is the stability of macimorelin in the plasma samples stored for more than 10 months for the oral administration part of Study AEZS-130-IIT-1. The plasma macimorelin concentrations after intraduodenal administration are for reference. Until the sponsor provides the stability data of macimorelin in plasma samples for long term storage per the bioanalytical guidance, this reviewer recommends no further action is necessary now.

Internal comments NOT to be sent to the sponsor

This reviewer notices that the sponsor tends to provide more information that was not submitted in the original NDA submission when questioned by the Division of Metabolism and Endocrinology Products. Also, the sponsor tends to submit report amendments when questioned by the Division for Clinical Pharmacology issues (see the April 11, 2014 and June 30, 2014 submissions). These behaviors make it difficult for the review of NDA 205-598 since this seems to be a “progressive submission” NDA.

Attachment starts here

Please find below a response to the identified and not yet resolved review issues communicated to Aeterna Zentaris with letter dated July 14, 2014 and further discussed in the Late Cycle Meeting on July 23, 2014.

Clinical Pharmacology

Plasma samples were measured twice for macimorelin concentration in Study AEZS-130-IIT-1.

Response

All data for the measurements of macimorelin concentration in plasma have been reported. As stated in our response to clinical pharmacology issues submitted on April 11, 2014, the plasma concentration data for samples which were measured twice were reported in the following bioanalytical reports:

- First analysis (15 Dec 2004 - 05 Jan 2005) performed utilizing a bioanalytical method with an LOQ of 5 ng/ml are presented in the bioanalytical report EP01572/050016001 in CTD section 5.3.4.1.2.1.

In summary, a total of 351 samples were analyzed for the cohorts (n = 9 subjects per dose group, 13 time points each) after oral administration of macimorelin with 0.005, 0.05 and 0.5 mg/kg. Out of the 351 samples analyzed, 29 samples were above the LOQ.

- Second analysis (“reanalysis”, 03 Nov 2005 - 09 Nov 2005) performed utilizing an improved bioanalytical method with an LOQ of 0.2 ng/ml are presented in the bioanalytical report EP01572/050016005 in CTD section 5.3.4.1.3.1.

Reanalysis was performed on 234 samples for the cohorts (n = 9 subjects per dose group, 13 time points each) after oral administration of macimorelin with 0.05 and 0.5 mg/kg. The samples from the cohort dosed with the lowest dose (0.005 mg/kg) were not reanalyzed, since most if not all of the samples were expected to fall below the LOQ of the method.

- All other samples, i.e. after oral administration of macimorelin with 0.125 and 0.25 mg/kg as well as after intraduodenal dosing with 0.2, 0.35 and 0.5 mg/kg were measured once utilizing an improved bioanalytical method with a LOQ of 0.2 ng/ml. These results are presented in the bioanalytical reports EP01572/050016002 (CTD section 5.3.4.1.2.2), EP01572/050016003 (CTD section 5.3.4.1.2.3) and EP01572/050016004 (CTD section 5.3.4.1.2.4).

Please refer to section 16.2.5.1 in the clinical study report for study AEZS-130-IIT-1-01 for a table provided to facilitate subjects identification (ID) in the original data sheets.

A lapse of more than 10 months exists between the 2 measurements. Thus, stability of macimorelin in the plasma samples under storage is questionable. Your substantiation for the stability of the plasma samples under storage as submitted on April 11, 2014, for Study AEZS-130-IIT-1 is not acceptable.

Response

As discussed during the late cycle review meeting, we have conducted a more thorough analysis of the data used to support the stability of plasma samples. The analysis conducted was an ANOVA analysis in order to assess potential statistical differences between the two data sets (first measurement = series 1, second measurement = series 2). The analysis demonstrated that both data sets are statistically not different, and that there was no trend observed when comparing the two data sets. Therefore, we believe that the plasma macimorelin concentration data is acceptable. Please find the statistical analysis in CTD section 1.11.3.

Further, for FDA's convenience, please find a tabulated side by side comparison of all samples generated after oral administration of macimorelin with 0.005, 0.05 and 0.5 mg/kg in CTD section 1.11.3. (Please note, that the samples from the cohort dosed with the lowest dose (0.005 mg/kg) were not reanalyzed, since most if not all of the samples were expected to fall below the LOQ of the method.).

We acknowledge the concerns expressed by the FDA that individual values showed a substantial difference between both measurements. However, it should be noted that the measured values are close to the LOQ of the analytical method and analytical variability at the LOQ is accepted to be higher as compared to the variability at higher concentrations.

To comply with formal requirements and as proposed during the late cycle review meeting, AEZS has initiated a long-term stability study according to the guidance for bioanalytical method validation. We will inform the FDA on any relevant information in the course of the stability study.

Also, there are no validation report and bioanalytical report for the measurement of growth hormone in serum samples for Study AEZS-130-IIT-1.

Response

As stated in our response to clinical pharmacology issues submitted on April 11, 2014, the plasma growth hormone concentrations were measured at the central laboratory at the (b) (4). This laboratory has an established quality management system, and is certified according to ISO/IEC standards (i.e. ISO/IEC 17025 and ISO 15189 for medical laboratories). Please find the certificate issued by the (b) (4) in CTD section 1.11.3.

The laboratory routinely participates in ring trials across laboratories. Validation of the assays and quality checks are routinely performed. AEZS has recently received documents (in German language) verifying the assay performance of the GH bioassay. These documents describe the verification of the assay performance ("restandardization") using the Nichols Advantage HGH (human Growth Hormone) Assay according to the quality control ranges provided by the manufacturer of the assay. This restandardization was performed April / May 2004, which correlates with the start of the clinical study AEZS-130-IIT-1-01. Please find the original and translated documents in CTD section 1.11.3.

However, we acknowledge that a bioanalytical report for GH measurements was not prepared. Instead the raw data of the growth hormone measurements were provided to the investigator in electronic format. The raw data were archived for a period of 1 year after transfer of the data to the investigator (Dr. Beglinger).

Without acceptable plasma macimorelin concentration and serum growth hormone concentration data for Study AEZS-130-IIT-1, the following data will be unacceptable:

- macimorelin pharmacokinetic dose proportionality data
- macimorelin exposure-response data
- macimorelin dose-response data

- optimal macimorelin dose data

Response

We acknowledge FDA's concerns regarding quality issues related to study data and documentation. Nevertheless, AEZS believes that the study AEZS-130-IIT-1-01 justifies our clinical development program. As suggested by the FDA, AEZS will not use this study to derive any label claims as long as compliance to all formal requirements incl. long-term stability data is missing.

The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for 4 subjects per Report VR07-(b) (4)-018 is not acceptable due to the wide range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples. Thus, the reported serum growth hormone concentration results on Visit 2 for 4 subjects of Study AEZS-130-047 are not reliable.

Response

We acknowledge the statement in the validation report VR07 (b) (4)-018 that for some subjects no serum samples for GH measurements have been taken. However, according to the CSR listings and (b) (4) database no values for measurements of heparin plasma sample are included in the CSR.

Attached please find an e-mail dated 17 May 2011 and issued by (b) (4) (see CTD section 1.11.3) documenting that all values for GH measurements in the database were done with serum samples. In addition, the laboratory is currently rechecking their database and will come up with a formal statement in due course. We will submit the respective document for further clarification as soon as we have received it.

According to our understanding, the statement regarding missing serum samples for 4 subjects at visit 2 was partly based on (incorrect) notes on the original CRFs regarding unavailability of serum samples.

For example for subject 0609, at visit 2 on 8 Nov 2007 the tick boxes for inadvertent omission of blood sampling were marked. On 10 Jan 2008 corrections were made on the sampling sheets indicating that samples had been taken.

For subject 0304, at visits 2 (2 Nov 2007) and 3 (16 Nov 2007) the tick boxes for inadvertent omission of blood sampling were marked. On 15 Feb 2008 a data query form was issued in order to clarify whether blood samples were taken or not. Finally, on 3 Mar 2008 it was stated by the investigator that the boxes were marked in error.

Since the validation report VR07 (b) (4)-018 was signed on 10 Jan 2008, the validation for GH measurements in plasma samples was conducted at a time when it was assumed that samples were not available.

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08/07/2014

IMMO ZADEZENSKY
08/07/2014

CLINICAL PHARMACOLOGY REVIEW

NDA	205-598; original; 005; 008; 0014; 0015
Submission Dates	November 5, 2013; February 14, 2014; April 11, 2014; June 30, 2014; July 3, 2014
Brand Name	MACRILEN [®]
Generic Name	Macimorelin acetate
Reviewer	S.W. Johnny Lau, R.Ph., Ph.D.
Team Leader	Immo Zadezensky, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Aeterna Zentaris
Formulation; Strength	Granules for oral solution; 0.5 mg/mL
Relevant IND	73,196
Indication	Diagnosis of adult growth hormone deficiency

Table of Contents	Page
1 Executive Summary	1
1.1 Recommendations	2
1.2 Post Marketing Requirement	2
1.3 Summary of Important Clinical Pharmacology Findings	2
2 Question Based Review	
2.1 General Attributes	4
2.2 General Clinical Pharmacology	5
2.3 Intrinsic Factors	11
2.4 Extrinsic Factors	13
2.5 General Biopharmaceutics	15
2.6 Bioanalytical	15
3 Labeling Recommendations	24
4 Appendix	
4.1 Proposed Labeling	25

1 Executive Summary

Macimorelin acetate is a new molecular entity and is a peptidomimetic ghrelin receptor agonist. The sponsor seeks approval for the use of single oral dose of macimorelin acetate to diagnose adult growth hormone deficiency (AGHD) via NDA 205-598. Macimorelin is the 1st oral product that its sponsor is seeking this indication and other AGHD diagnostics are parenteral products. The Office of Orphan Products Development granted the orphan-drug designation for macimorelin acetate to diagnose ADHD on September 25, 2009 (designation request number 06-2255).

1.1 Recommendations

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 205-598's Clinical Pharmacology data and recommends the following:

- The Clinical Pharmacology data for NDA 205-598 is acceptable.
- The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for Subjects 0105, 0306, 0304, and 0609 per Report VR07 (b) (4) 018 is not acceptable due to the range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples is -27.4% to 26.19%. Thus, the reported serum growth hormone concentration results on Visit 2 for Subjects 0105, 0306, 0304, and 0609 of Study AEZS-130-047 are not reliable.

1.2 Post Marketing Requirement

None.

1.3 Summary of Important Clinical Pharmacology Findings

Pharmacokinetics (PK)

Absorption

Macimorelin C_{max} s were observed between 0.5 and 4 hours after oral administration of 0.5 mg/kg macimorelin to AGHD patients who fasted for at least 6 hours. The mean C_{max} was 10.25 ng/mL and the mean terminal exponential half-life ($T_{1/2}$) was 3.56 hours in AGHD patients. In vitro study shows that the mean Caco-2 permeability for macimorelin is 1.33 cm/s $\times 10^{-6}$ for the apical to basolateral direction and 2.37 cm/s $\times 10^{-6}$ for the basolateral to apical direction. With concomitant administration of a liquid meal, macimorelin C_{max} and AUC_t decreased 54% and 49%, respectively, in healthy volunteers.

Distribution

In vitro study shows that macimorelin does not inhibit Pgp ATPase activity.

Metabolism

In vitro human biomaterials studies show that:

- CYP3A4 is a major enzyme to metabolize macimorelin in the liver.
- Macimorelin does not undergo conjugation type of biotransformation.
- Macimorelin does not inhibit CYPs 1A2, 2A6, 2C8, 2C9, 2C19, and 2D6.
- Macimorelin may be a CYP3A4 direct inhibitor.

The sponsor did not submit information on macimorelin's excretion, intrinsic and extrinsic factors, QT prolongation potential, pharmacogenomics, and biopharmaceutics classification system.

The macimorelin dose-response relationship cannot be determined due to lack of bioanalytical and validation documentation for the determination of GH concentrations.

The pharmacokinetics of macimorelin upon oral administration is not different between AGHD patients and matched healthy controls. Also, the pharmacokinetics of macimorelin is not different between females and males in both AGHD patients as well as healthy volunteers.

Formulation

Refer to the review by the Office of New Drugs, Quality Assurance Biopharmaceutics for the biowaiver of the clinically-tested formulation and the to-be-marketed formulation of macimorelin acetate.

S.W. Johnny Lau, R.Ph., Ph.D.
OCP/DCP2

FT signed by, Immo Zadezensky, Ph.D., Team Leader _____ 7/ /14

An Optional Intra-Division Level Clinical Pharmacology Briefing for NDA 205-598 was conducted on July 8, 2014; participants included N. Zhang, I. Melas, A. Noory, P. Balimane, J. Vaidyanathan, S. Sista, W. Lubas, D. Roman, S. Doddapaneni, C. Sahajwalla, I. Zadezensky, and J. Lau in person; D. Volpe, A. Adeolu via Adobe Connect.

APPEARS THIS WAY ON ORIGINAL

2 Question-Based Review

AEZS-130, ARD07, EP01572, SP001572 are synonyms of macimorelin acetate.

2.1 General Attributes

2.1.1 What are macimorelin acetate’s key physicochemical properties?

Figure 1 shows the chemical structure of macimorelin acetate.

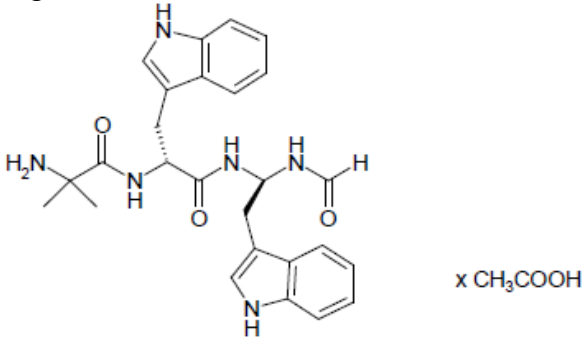


Figure 1. Macimorelin acetate ’s molecular structure. Source: CTD Reference 3.2.S.1.2

Macimorelin acetate has a molecular formula of C₂₆H₃₀N₆O₃ x C₂H₄O₂ and molecular weight of 474.5 g/mol (base); 535.6 g/mole (acetate salt). Macimorelin acetate is amorphous and has the following solubility:

- Water: 300 g/L (pH 1 – 8)
- Ethanol: 260 g/L
- Acetonitrile: 40 g/L

The pH value of a 1% aqueous solution is 6.1. Macimorelin has 2 chiral carbon centers in D,D (R,R) configuration. This subsection’s information originates from CTD 2.3.S.1.

2.1.2 What is the formulation for the to-be-marketed oral macimorelin acetate?

Macimorelin acetate’s dosage form is granules for oral solution. Table 1 details the composition of a unit dose in an aluminum (b) (4) which contains (b) (4) mg granules for reconstituting the granules in 120 mL of water, 1 mL of the solution will contain 0.5 mg macimorelin. The patient will receive the dose per bodyweight adjusted aliquot of the solution.

Table 1. Composition of macimorelin acetate per (b) (4) Source: CTD Reference 3.2.P.1

Composition	Function	Standard	Mass / (b) (4)
Macimorelin (as acetate)	API	Internal	(b) (4)
Lactose monohydrate, (b) (4)	(b) (4)	USP-NF	(b) (4)
Crospovidone, (b) (4)		USP-NF	
Colloidal silicon dioxide		USP-NF	
Sodium stearyl fumarate		USP-NF	
Saccharin sodium, (b) (4)		USP-NF	
Total			1817.2 mg

(b) (4)

2.1.3 How does macimorelin work?

Ghrelin is a 28-amino-acid peptide reported in 1999 (Howard et al. A receptor in pituitary and hypothalamus that functions in growth hormone release. *Science* 1996;273:974-7; Kojima et al. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. *Nature* 1999;402:656-60). Upon intravenous administration, ghrelin shows a dose-dependent stimulation of growth hormone (GH) release in the pituitary. Macimorelin is a peptidomimetic ghrelin receptor agonist with GH secretagogue activity.

2.1.4 What are the sponsor's proposed indication and dosage regimen for macimorelin acetate?

Macimorelin acetate's proposed indication is for the diagnosis of AGHD (b) (4). The macimorelin acetate dose must be calculated based on each patient's body weight. Patients should receive a single oral dose of 1 mL/kg by bodyweight of the prepared 0.5 mg/mL macimorelin acetate solution, after fasting for at least (b) (4) hours. Of note, macimorelin is the 1st oral product that its sponsor is seeking this indication and other AGHD diagnostics are parenteral products.

2.2 General Clinical Pharmacology

The following publications have clinical pharmacology information of growth hormone releasing hormone analogs:

- Prakash A, Goa KL. Sermorelin: a review of its use in the diagnosis and treatment of children with idiopathic growth hormone deficiency. *BioDrugs* 1999;12:139-57.
- Wang Y, Tomlinson B. Tesamorelin, a human growth hormone releasing factor analogue. *Expert Opin Investig Drugs* 2009;18:303-10.

For information on the diagnosis of AGHD:

- Glynn N, Agha A. Diagnosing growth hormone deficiency in adults. *Int J Endocrinol* 2012;2012:972617.

2.2.1 What is macimorelin's clinical pharmacokinetic (PK) characteristics?

Absorption

Study 8100-2013-950 assessed the in vitro Caco-2 permeability of macimorelin acetate 21 days after seeding of Caco-2 cells in transwell plates. The sponsor made the measurements in duplicate at 120 min after addition of macimorelin acetate in the donor compartment. Bovine serum albumin concentrations were 0.25% in the donor and 1% in the acceptor compartments. The sponsor used Lucifer Yellow and Rhodamine 123 as controls to verify monolayer integrity and expression of the P-glycoprotein (Pgp)-efflux pump. They measured permeability over the macimorelin concentration range of 2.5 – 1000 μ M (0.0013 – 0.534 mg/mL). Table 2 shows that the apparent permeability (Papp) values for macimorelin are roughly similar over the studied concentration range. Mean (SD) Papp values over the entire concentration range were 1.33 (0.19) cm/s $\times 10^{-6}$ for the apical to basolateral (a→b) direction, and 2.37 (0.36) cm/s $\times 10^{-6}$ for the basolateral to apical (b→a) direction. The mean (SD) efflux ratio of Papp values (efflux/influx) is 1.8 (0.3).

Table 2. Caco-2 permeability of macimorelin 2.5 – 1000 μ M (Source: Study 8100-2013-950's Table 3)

Concentration [μ M]	2.5	5	10	20	30	40	50	75	100	1000	Mean (SD)
Papp (a→b) [cm/s] $\times 10^{-6}$	1.38	1.10	1.15	1.17	1.33	1.38	1.53	1.41	1.10	1.73	1.33 (0.19)
Papp (b→a) [cm/s] $\times 10^{-6}$	2.08	1.78	2.00	2.47	2.75	2.82	2.66	2.79	2.28	2.11	2.37 (0.36)
Efflux ratio	1.5	1.6	1.7	2.1	2.1	2.0	1.7	2.0	2.1	1.2	1.8 (0.3)

Reviewer's comment: Rhodamine 123 is a P-gp substrate but Study 8100-2013-950 did not report the Rhodamine 123 transport characteristics. This makes it difficult for this reviewer to interpret Study 8100-2013-950's results to determine macimorelin's P-gp substrate status. Also, Study 8100-2013-950 lacks a positive control and thus makes it difficult to evaluate the degree of macimorelin permeability, which is test system dependent. Nevertheless, this study can serve as a reference for macimorelin permeability across the Caco-2 cells in vitro.

Distribution

Study AEZS-130 (D-87575) assessed the potential of macimorelin to inhibit the ATPase activity of Pgp via membrane preparations of Pgp over-expressing SF9 cells in the presence of ATP and the Pgp substrate verapamil. The sponsor measured ATP consumption via a luciferase based reporter system. The positive controls, cyclosporin A and ritonavir, confirmed the validity of the test system. Macimorelin did not inhibit Pgp ATPase activity up to 88.8 μ M.

The sponsor did not investigate the plasma protein binding of macimorelin in humans.

Metabolism

Metabolism of macimorelin

Study ADME-2012-01 assessed the metabolic stability of macimorelin in pooled male and female human liver microsomes via an HPLC-based assay. After 1 hour of incubation at 37°C, 52.8% of macimorelin was metabolized in a NADPH-dependent manner. In vitro hepatic intrinsic clearances (Cl_{int}) calculated per fitted half-lives were 11.9 μ L/min/mg microsomal protein.

Reaction phenotyping (CYP profiling) was conducted via 2 independent methods (chemical inhibition and recombinant CYPs). Incubation of macimorelin with the recombinant isozymes CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, and 2E1 over 60 min showed no significant metabolism (less than 10% metabolized). Recombinant CYP3A4 metabolized about 40% macimorelin within the same time period. Chemical inhibition experiments via specific inhibitors for the same CYP isozymes showed only a significant reduction in metabolism from about 40 – 90% if ketoconazole (inhibitor of CYP3A4) was used. These results suggest that CYP3A4 is a major enzyme to metabolize macimorelin in the liver.

Phase II metabolism was investigated via human liver S9 fraction (macimorelin 8.9 μ M) in the presence and absence of cofactors required for cytochrome P450 enzymes (Phase I; NADPH) or transferases (Phase II; GSH, PAPS, UDPGA) with 10 μ M testosterone and 10 μ M umbelliferone as positive controls for Phases I and II metabolism, respectively. Study ADME-2012-01 did not show conjugation type of biotransformation for macimorelin.

Cytochrome P450 inhibition in human liver microsomes

Study ADME-2012-01 also assessed the ability of macimorelin to inhibit the enzymatic function of 7 CYP isozymes (CYPs 1A2, 2A6, 2C8, 2C9, 2C19, 2D6, and 3A4/5) in human liver microsomes in vitro. The tested macimorelin concentrations were 0.01 – 200 μ M. The sponsor used marker substrate at a concentration in the range of the k_m of the respective CYP isozyme. Macimorelin showed inhibition of CYP2C19 with an IC_{50} value of 78 μ M. For all other CYP isozymes, IC_{50} values were set to > 25 – 30 μ M due to incomplete inhibition profiles. The sponsor only measured time-dependent inhibition for CYP3A4 and did not observe significant time-dependent CYP3A4 inhibition versus direct inhibition. The sponsor set the IC_{50} for time-dependent inhibition for CYP3A4 to > 30 μ M. An IC_{50} value of > 30 μ M corresponds to a plasma macimorelin concentration of > 16 μ g/mL and, for reference, macimorelin C_{max} values are about 11 ng/mL per the phase III clinical study.

For the direct inhibition potential of macimorelin, other CYPs besides CYP2C19 have the smallest IC_{50} value of 25 μ M. Thus, this reviewer used it to estimate the direct inhibition potential for CYPs 1A2, 2A6, 2C8, 2C9, 2C19,

and 2D6. [I] is 11 ng/mL, which is the C_{max} upon single dose of 0.5 mg/kg macimorelin oral administration. The K_i is 12.5 μ M ($IC_{50}/2$). The $R_1 = 1 + [I]/K_i$ value practically equals to 1. Thus, macimorelin is not a direct inhibitor for CYPs 1A2, 2A6, 2C8, 2C9, 2C19, and 2D6 ($R_1 < 1.1$).

For macimorelin's inhibition of CYP3A4 via oral administration, $R_{alternate} = 1 + I_{gut}/K_i$. I_{gut} is $0.5 \times 60 \times 1000 / 474.5$ μ moles/250 mL. $K_i = 15$ μ M (30 μ M/2). Macimorelin $R_{alternate}$ for CYP3A4 is 17.86 ($R_{alternate} > 11$). Thus, macimorelin may likely be a CYP3A4 direct inhibitor and needs to conduct a clinical study with an appropriate probe substrate to confirm macimorelin's CYP3A4 inhibition potential per the draft drug interaction guidance. *However, this reviewer sees that a clinical drug interaction study for macimorelin may be unnecessary since it is for single dose use and the drug interaction potential may be managed via respective statements in the product label.*

In vitro Cytochrome P450 Induction

Study ADME-2013-01 assessed the ability of macimorelin to induce increases in the mRNA of the CYPs 1A2, 2B6, and 3A4/5 isozymes via primary cultures of cryopreserved human hepatocytes from a donor. The sponsor treated cultures once daily for 2 consecutive days with DMSO, known human CYP inducers (omeprazole, phenobarbital and rifampicin) as positive controls, an internal negative control (D-81050), and 3 concentrations of macimorelin (3.16, 10 and 31.6 μ M).

For CYP1A2, macimorelin showed negligible induction over the 3 concentrations, with maximum induction values being below 2-fold of DMSO control. For CYPs 2B6 and 3A4, a concentration dependency and fold induction values up to 4.4 and 3.7 were observed at 31.6 μ M, respectively. These values were lower than the positive control inducers (18.3% for CYP2B6 compared to phenobarbital and 12.5% for CYP3A4 compared to rifampicin). The induction values at macimorelin 3.16 μ M were below 2-fold (1.9 and 1.3). Macimorelin 3.16 μ M is about 150 times the mean macimorelin C_{max} observed in the clinical phase III trial. (b) (4)

Reviewer's comment: *Macimorelin's CYP isozyme induction potential information may not be relevant for NDA 205-598 because macimorelin is intended for single dose administration to diagnose AGHD. If macimorelin were to have CYP isozyme induction potential, a single dose of macimorelin may not significantly induce CYP isozymes. Moreover, the draft drug interaction guidance recommends the following*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>):

- *Assess cultured human hepatocytes from ≥ 3 donors, whereas Study ADME-2013-01 assessed 1 donor's hepatocytes.*
- *Use sufficient numbers of clinical inducers and non-inducers to determine a cutoff value; Study ADME-2013-01 assessed 1 known inducer per CYP isozyme and 1 negative control but did not prospectively determine a cutoff value.*

This reviewer does not recommend macimorelin's label to contain Study ADME-2013-01's results. Nevertheless, the sponsor did not claim that macimorelin does not have induction potential of CYP isozymes in the label.

Excretion

The sponsor intended to study the of excretion macimorelin in Study ARD-0705-003. Due to missed collection of urine volume, the sponsor cannot quantify the urine excretion of macimorelin in Study ARD-0705-003. See Question 2.4.1 for details.

Chiral Conversion

Per the Clinical Pharmacology review dated June 18, 2007 for IND 73,196 Serial 004 in DARRTS, chiral conversion does not occur in vivo for peptides.

2.2.2 Is macimorelin PK dose-proportional upon intraduodenal and oral administrations?

Study AEZS-130-IIT-1 assesses the PK and PD of single rising doses of macimorelin acetate via the following 2 routes of administration in healthy volunteers:

- Oral: placebo, 0.005, 0.05, 0.125, 0.25, or 0.5 mg/kg
- Intraduodenal as a bolus infusion: placebo, 0.2, 0.35, or 0.5 mg/kg

Serial plasma samples were collected to determine the macimorelin concentrations via LC-MS/MS method as PK measure. Serial plasma samples were collected to determine GH concentrations via radioimmunoassay as PD measure. Study AEZS-130-IIT-1's results are published in the Piccoli et al.'s article (Pharmacokinetics and pharmacodynamic effects of an oral ghrelin agonist in healthy subjects. *J Clin Endocrinol Metab* 2007;92:1814-20).

The sponsor measured the plasma samples for macimorelin concentration twice with at least 10 months between the 2 analyses. Piccoli et al.'s article (*J Clin Endocrinol Metab* 2007;92:1814-20) contains only the results of the 2nd analysis and the sponsor also submitted only the results of the 2nd analysis in the original NDA. This reviewer has concern for the long-term stability of plasma samples for macimorelin determination in storage for at least 10 months and requested the sponsor to provide proof of the sample stability on March 31, 2014. *This reviewer recommends that the sponsor's substantiation for the stability of the plasma samples under storage as submitted on April 11, 2014 is not acceptable (see Question 2.6.1 for further details).*

Also, the sponsor stated in their April 11, 2014 response that they did not prepare a bioanalytical report for GH measurements and no validation report for the bioanalytical report is available.

Study AEZS-130-IIT-1's results of both plasma macimorelin concentrations and plasma GH concentrations may not be reliable. Thus, this reviewer did not review Study AEZS-130-IIT-1's results. **These findings also nullify this reviewer's conclusion that macimorelin PK is dose-proportional for oral single doses of 0.05 – 0.5 mg/kg (Clinical Pharmacology review for IND 73,196 dated March 1, 2013 in DARRTS).** This March 1, 2013 conclusion was based on the assumption that the bioanalytical methods and validation for macimorelin and GH are acceptable.

2.2.3 Does the macimorelin PK differ among AGHD patients and healthy volunteers upon oral administration?

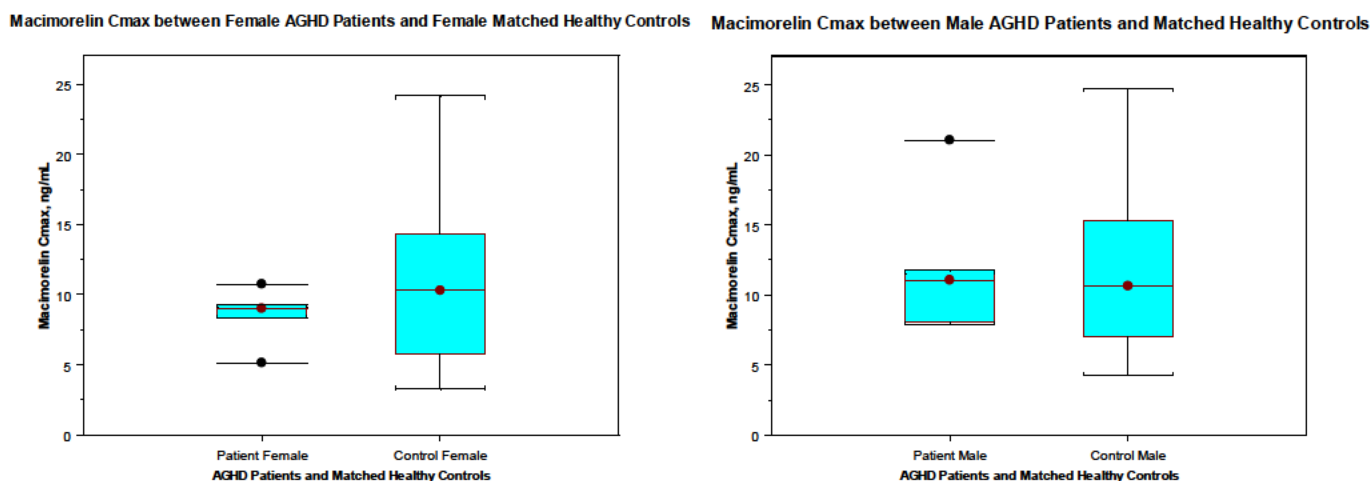
Study AEZS-130-047 assesses the efficacy and safety of single oral 0.5 mg macimorelin/kg dose to diagnose AGHD. Towards the latter part of the study, the sponsor collected plasma samples to determine macimorelin concentrations for 10 AGHD patients (5 female and 5 male) and 38 matched controls (16 female and 22 male). The matched controls are healthy volunteers matched with sex, age (± 5 years), BMI (± 2 kg/m²), and estrogen status (women only) to the AGHD patients. Table 3 details the PK of macimorelin.

Table 3. Summary of PK parameters after oral administration of 0.5 mg/kg macimorelin. Source: Study AEZS-130-047's report Table 12 Page 50 of 68.

		n	Mean	SD	Min	Median	Max
AGHD Patients	C_{max} (ng/mL)	10	10.25	4.24	5.14	9.17	21.04
	t_{max} (hour)	10	1.20	1.03	0.50	0.88	4.00
	AUC _{0-t} (ng/mL*h)	10	28.64	17.56	9.80	26.09	65.69
	AUC _{0-∞} (ng/mL*h)	9	52.19	24.50	17.83	59.45	84.17
	$t_{1/2}$ (hour)	9	3.56	1.73	1.16	3.76	6.03
Matched Controls	C_{max} (ng/mL)	38	11.50	5.88	3.25	10.65	24.71
	t_{max} (hour)	38	0.82	0.41	0.50	0.75	2.50
	AUC _{0-t} (ng/mL*h)	38	21.78	17.51	4.95	19.60	105.67
	AUC _{0-∞} (ng/mL*h)	37	46.80	58.42	9.79	31.48	316.71
	$t_{1/2}$ (hour)	37	2.77	3.57	0.86	2.02	22.52

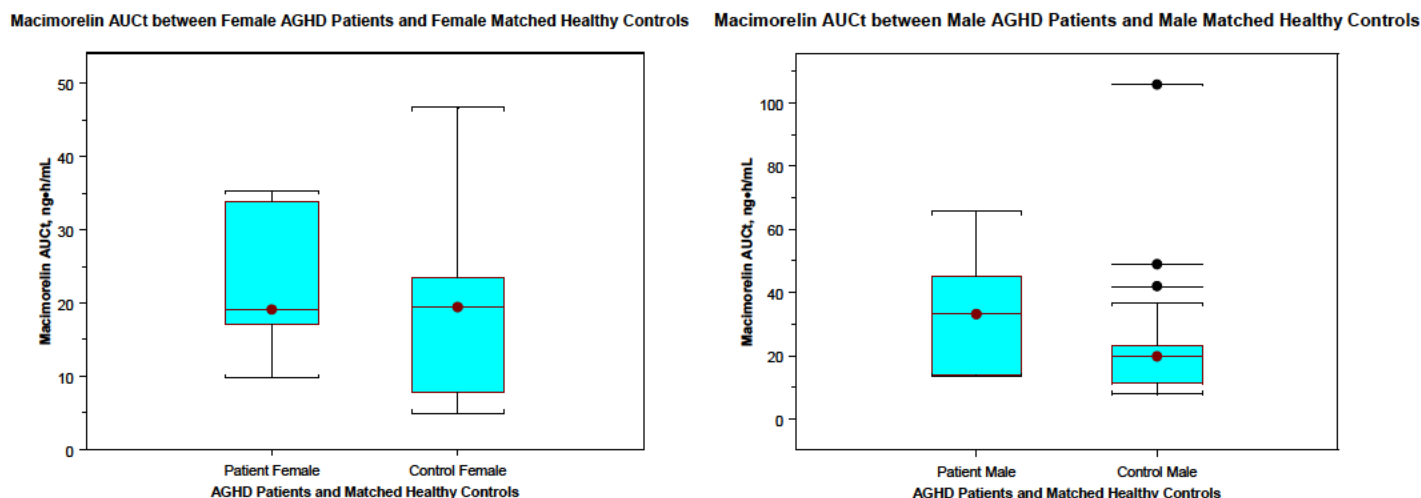
Figures 2 and 3 show the box plots for macimorelin C_{max} between female AGHD patients and female matched healthy controls as well as macimorelin C_{max} between male AGHD patients and male matched healthy controls. The 25th, median, and 75th percentile values for macimorelin C_{max} of female AGHD patients and macimorelin C_{max} of male AGHD patients are all within those of female matched healthy controls and of male matched healthy controls, respectively. The p values of the 2-sided t-test assuming unequal variance for macimorelin C_{max} between female AGHD patients and female matched healthy controls as well as macimorelin C_{max} between male AGHD patients and male matched healthy controls are 0.4544 and 0.9447, respectively. Thus, the macimorelin C_{max} is not significantly different between female AGHD patients and female matched healthy controls as well as the macimorelin C_{max} is not significantly different between male AGHD patients and male matched healthy controls.

Figure 2. Box plot of macimorelin C_{max} for female AGHD patient and matched healthy controls for Study AEZS-130-047 (left panel). Figure 3. Box plot of macimorelin C_{max} for male AGHD patient and matched healthy controls for Study AEZS-130-047 (right panel). Source: Reviewer's analyses.



Figures 4 and 5 show the box plots for macimorelin AUC_t between female AGHD patients and female matched healthy controls as well as macimorelin AUC_t between male AGHD patients and male matched healthy controls. The p values of the 2-sided t-test assuming unequal variance for macimorelin AUC_t between female AGHD patients and female matched healthy controls as well as macimorelin AUC_t between male AGHD patients and male matched healthy controls are 0.3716 and 0.4181, respectively. Thus, the macimorelin AUC_t is not significantly different between female AGHD patients and female matched healthy controls as well as the macimorelin AUC_t is not significantly different between male AGHD patients and male matched healthy controls.

Figure 4. Box plot of macimorelin AUC_t for female AGHD patient and matched healthy controls for Study AEZS-130-047 (left panel). Figure 5. Box plot of macimorelin AUC_t for male AGHD patient and matched healthy controls for Study AEZS-130-047 (right panel). Source: Reviewer's analyses.



This reviewer used the Shapiro-Wilk procedure to test the macimorelin C_{max} and AUC_t data for AGHD patients and matched healthy controls of both female and male gender and found that these data are normally distributed. Thus, the applied t-tests above are appropriate (satisfying t-test's assumption of normal distribution). This reviewer chose to analyze macimorelin AUC_t because some of the extrapolated AUC from time t to infinity are more than 20% of the AUC from time zero to infinity.

2.2.4 How is the proposed oral macimorelin acetate dose determined?

GH is macimorelin's PD (response) measure. The sponsor proposed the 0.5 mg macimorelin/kg dose to be studied in the clinical efficacy and safety study (AEZS-130-047) based on Study AEZS-130-IIT-1's results and another published article (Broglia et al. EP1572: a novel peptido-mimetic GH secretagogue with potent and selective GH-releasing activity in man. *J Endocrinol Invest* 2002;25:RC26-8).

Study AEZS-130-IIT-1 also serves as a dose finding study for macimorelin besides a single rising dose study of macimorelin acetate (see Question 2.2.2). However, its plasma GH concentrations results may not be reliable. Thus, it is not reliable to establish the dose-response relationship for macimorelin after both oral and intraduodenal administrations.

The Broglia article shows that macimorelin induces GH release upon 0.06, 0.125, 0.25, and 0.5 mg/kg macimorelin oral and 1 µg/kg macimorelin intravenous administrations in 2 healthy men. Broglia et al. did not measure systemic macimorelin concentrations in this study. Neither the Broglia article nor this NDA provided the bioanalytical validation for the assay used to measure plasma GH concentrations. The published plasma GH concentrations may not be reliable. Thus, this reviewer did not review the Broglia article.

2.2.5 Exposure-Response

2.2.5.1 Is there evidence of a dose-response for effectiveness?

Dose-response for efficacy cannot be established see Question 2.2.2. The sponsor conducted an efficacy and safety study (AEZS-130-047 formerly ARD-0705-001) for macimorelin. Study AEZS-130-047's results are published in Garcia et al.'s article (Macimorelin (AEZS-130)-stimulated growth hormone (GH) test: validation of a novel oral stimulation test for the diagnosis of adult GH deficiency. *J Clin Endocrinol Metab* 2013;98:2422-9).

2.2.5.2 Is there evidence of a dose-response for safety?

Dose-response for safety cannot be established see Question 2.2.2. See Dr. Lan Huang's statistical review for the efficacy analysis of macimorelin dated July 9, 2014 in DARRTS.

2.2.6 What would be the recommended optimal oral macimorelin acetate dose?

Without a valid dose-response relationship for macimorelin, one can only depend on the dose studied in the pivotal clinical efficacy and safety study (AEZS-130-047), which is 0.5 mg/kg.

2.2.7 Does macimorelin acetate prolong the QT or QTc interval?

The sponsor did not conduct thorough QT prolongation study for macimorelin in humans.

2.3 Intrinsic Factors

2.3.1 How does hepatic impairment affect macimorelin PK?

The sponsor did not conduct dedicated hepatic impairment study for macimorelin in humans.

2.3.2 How does renal impairment affect macimorelin PK?

The sponsor did not conduct dedicated renal impairment study for macimorelin in humans and renal excretion data is unavailable (see Question 2.2.1).

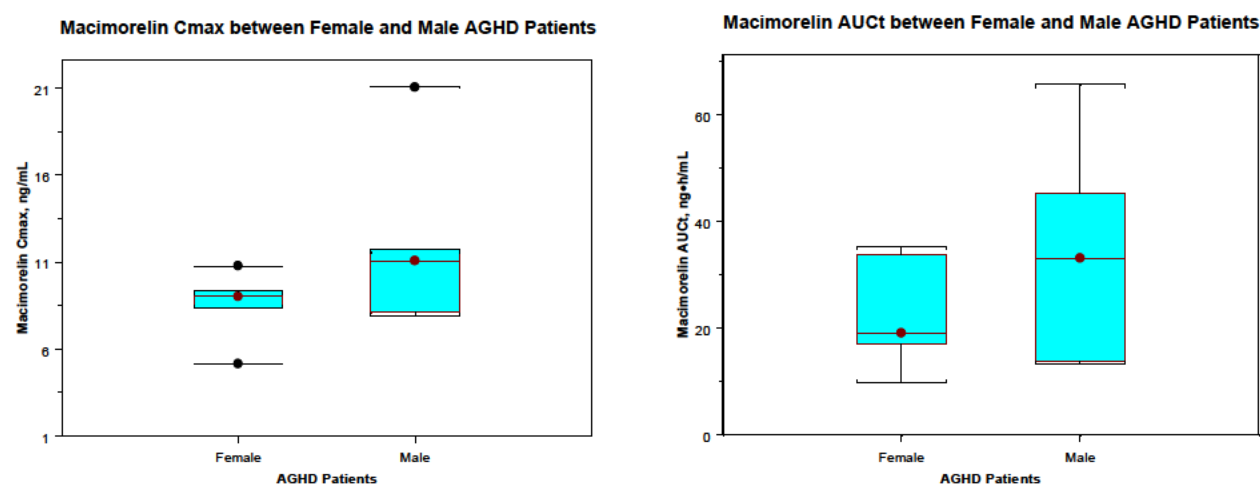
2.3.3 Do the intrinsic factors such as age, body mass index, gender, and race affect macimorelin PK?

The sponsor conducted neither dedicated study nor population approach study for analysis of covariate intrinsic factors that may affect macimorelin PK in humans. Dr Jeffrey A. Quinn's Pharmacology/Toxicology review dated June 5, 2014 in DARRTS has the following comment for macimorelin:

Gender-related differences in drug exposures were noted during the pivotal toxicity studies and may represent a complication when using this compound as a diagnostic agent in human subjects.

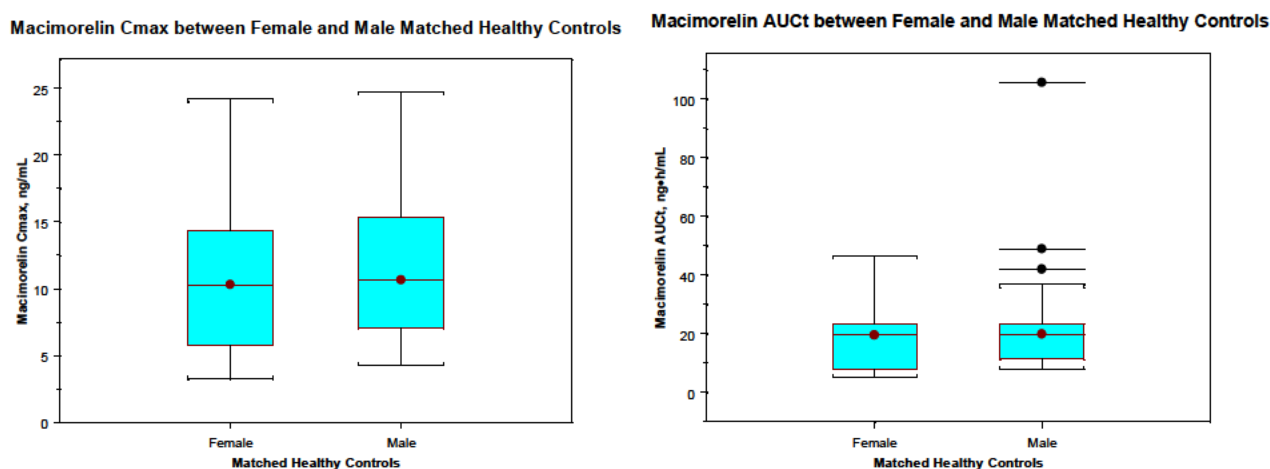
This reviewer analyzed the clinical pivotal Study AEZS-130-047's macimorelin PK data for potential gender difference. Figure 6 shows the box plots for macimorelin C_{max} between female and male AGHD patients. Similarly, Figure 7 shows the box plots for macimorelin AUC_t between female and male AGHD patients. Median values for both macimorelin C_{max} and AUC_t appear to differ between female and male but the 25th and 75th percentile values of macimorelin C_{max} and AUC_t for the female patients are within the range of those for the male patients. Moreover, the p value for the 2-sided t-test assuming unequal variance for macimorelin C_{max} and AUC_t among female and male patients are 0.2372 and 0.3511, respectively. Thus, the macimorelin C_{max} and AUC_t for the AGHD female patients are not significantly different from the macimorelin C_{max} and AUC_t for the male AGHD patients.

Figure 6. Box plot of macimorelin C_{max} and AGHD patient's gender for Study AEZS-130-047 (left panel). Figure 7. Box plot of macimorelin AUC_t and AGHD patient's gender for Study AEZS-130-047 (right panel). Source: Reviewer's analyses.



Figures 8 and 9 show the box plots for macimorelin C_{max} and AUC_t between female and male matched controls. The 25th, median, and 75th percentile values for both macimorelin C_{max} and AUC_t appear to be similar between female and male matched controls. The p value for the 2-sided t-test assuming unequal variance for macimorelin C_{max} and AUC_t among female and male patients are 0.4156 and 0.4181, respectively. Thus, the macimorelin C_{max} and AUC_t for the female matched controls are not significantly different from the macimorelin C_{max} and AUC_t for the male matched controls.

Figure 8. Box plot of macimorelin C_{max} and matched control's gender for Study AEZS-130-047 (left panel). Figure 9. Box plot of macimorelin AUC_t and AGHD patient's gender for Study AEZS-130-047 (right panel). Source: Reviewer's analyses.



This reviewer used the Shapiro-Wilk procedure to test the macimorelin C_{max} and AUC_t data for AGHD patients and matched healthy controls of both female and male gender and found that these data are normally distributed. Thus, the applied t-tests above are appropriate (satisfying t-test's assumption of normal distribution). This reviewer chose to analyze macimorelin AUC_t because some of the extrapolated AUC from time t to infinity are more than 20% of the AUC from time zero to infinity.

2.3.4 What pharmacogenomic information is in the application?
Pharmacogenomic information is not available in this submission.

2.4 Extrinsic Factors

2.4.1 How does food affect macimorelin's bioavailability (BA)?

Study ARD-0705-003 assessed the effect of food on the bioavailability of macimorelin acetate. Sixteen more-than-10-hours-fasted healthy participants either received a single oral 0.5 mg macimorelin/kg dose alone or received the dose with a concomitant liquid meal on Day 1. In the same way, all participants orally received the treatment on Day 4 that they did not receive on Day 1. Serial plasma samples for the determination of macimorelin as well as serial serum samples for the determination of GH and insulin growth factor-1 (IGF-1) were collected. A single urine sample for the determination of macimorelin was collected within 6 hours postdose. The sponsor used a validated bioanalytical method to determine the plasma macimorelin concentrations.

The sponsor did not submit bioanalytical and validation reports for both GH and IGF-1 measurements to substantiate the validity of serum GH and IGF-1 concentration data. However, both GH and IGF-1 data are unnecessary to assess the effect of food on the pharmacokinetics of macimorelin. Thus, this reviewer did not request the sponsor to submit Study ARD-0705-003's GH and IGF-1 results.

Table 4. Macimorelin PK parameters in the presence and absence of the liquid meal.

Characteristic	Variable	With food Total N=16	Without food Total N=16
AUC _(0-t) (h x ng/mL)	Mean (SD)	14.07 (5.545)	29.52 (17.172)
	Median	13.16	22.79
	Min, max	7.71, 24.89	10.27, 76.21
AUC _(0-inf) (h x ng/mL)	Mean (SD)	15.90 (6.442)	31.95 (17.952)
	Median	15.09	24.69
	Min, max	8.42, 29.30	11.36, 80.14
C _{max} (ng/mL)	Mean (SD)	4.41 (1.912)	10.58 (6.249)
	Median	3.89	7.58
	Min, max	2.18, 9.66	3.32, 21.90
T _{max} (h)	Mean (SD)	1.09 (0.576)	0.78 (0.417)
	Median	0.88	0.75
	Min, max	0.25, 2.00	0.25, 2.00
t _{1/2} (h)	Mean (SD)	3.80 (2.111)	3.87 (2.032)
	Median	3.10	3.54
	Min, max	1.34, 9.12	1.82, 8.25

Source: Study ARD-0705-003's report's Table 4.

Table 5. Ratio of macimorelin PK parameters in the presence and absence of the liquid meal.

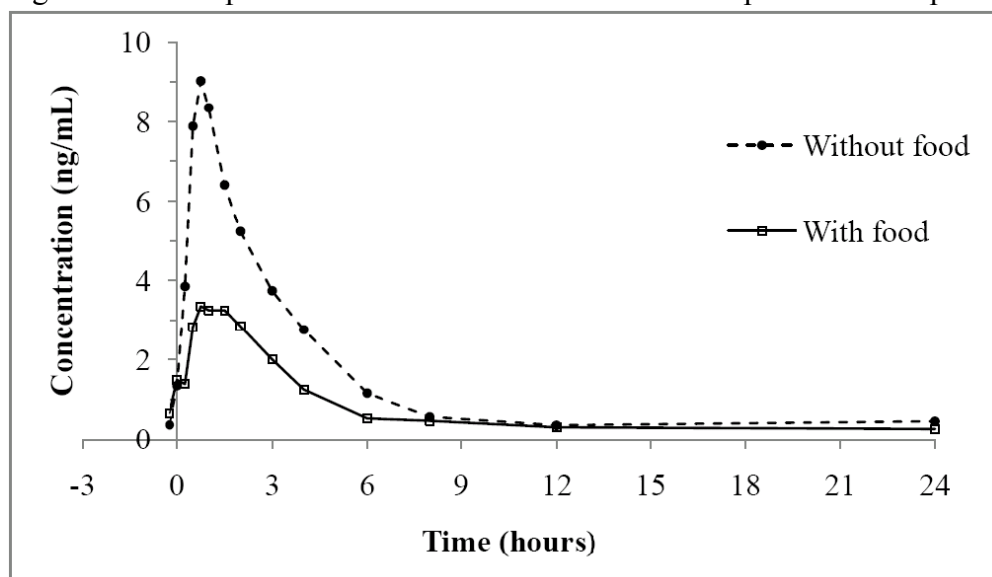
Outcome	N	Ratio (With food/ Without food)					
		Min	Median	Max	Mean	Geometric mean	90% CI*
AUC _(0-t)	16	0.288	0.475	0.970	0.542	0.510	0.436, 0.596
AUC _(0-inf)	16	0.321	0.496	0.992	0.556	0.526	0.454, 0.610
C _{max}	16	0.216	0.461	1.163	0.486	0.453	0.386, 0.533

* Based on two-sided paired t-test of log-transformed outcomes

Source: Study ARD-0705-003's report's Table 5.

Per the results in Table 5, macimorelin C_{max} and AUC_t decreased 54% and 49%, respectively, with concomitant administration of a liquid meal. Figure 10 shows the mean plasma macimorelin concentration – time profile upon oral administration of macimorelin acetate with and without a liquid meal.

Figure 10. Mean plasma macimorelin concentration-time profiles in the presence and absence of the liquid meal.



Source: Amendment to Study ARD-0705-003's report's Change #1.

On NDA 205-598's January 15, 2014 filing review letter, the Division of Metabolism and Endocrinology Products asked the sponsor for the content of the test "standard liquid meal" used in Study ARD-0705-003. The sponsor responded on February 14, 2014 that the standard liquid meal consisted of 200 mL "Resource 2.0 Fibre" (Novartis) containing 18 g protein, 17 g fat, and 43 g carbohydrates per portion. The sponsor asserted that the test meal (400 calories) is different from the food effect guidance's recommended meal (800 to 1000 calories). *Despite the tested liquid meal is different from the food-effect guidance's recommended high-fat meal, this reviewer recommends acceptance of Study ARD-0705-003's results because:*

- *The study already shows that macimorelin C_{max} and AUC_1 both decreased 55% and 49%, respectively, in the presence of the tested liquid meal. The food-effect guidance's recommended meal will likely further decrease the macimorelin exposure.*
- *Because the tested liquid meal significantly decreased the bioavailability of macimorelin, the sponsor conducted the subsequent efficacy and safety study (AEZS-130-047) in participants fasted for at least 6 hours before receiving macimorelin acetate.*
- *The proposed administration of macimorelin acetate in the label is after fasting for at least (b) (4) hours.*
- *The proposed use of macimorelin acetate is for a single dose to diagnose AGHD.*

This reviewer found the following discrepancy:

- Summary of Biopharmaceutic Studies, Module 2.7.1 page 6 states: "A single urine sample approximately 4 hours post-dosing was collected. Macimorelin urine concentration (mean $\pm$ SD) was 182 ± 132 ng/mL (median = 154 ng/mL, range = 11 to 517 ng/mL) when administered without food and 82 ± 41 ng/mL (median = 77 ng/mL, range = 16 to 180 ng/mL) when administered with food."
- Study ARD-0705-003's report Page 42 (82) states "A single urine sample approx. 4 hours post-dosing was collected and ARD-07 was measured in it. Measurable amounts were detected in urine but could not be quantified in this study." ARD-07 is macimorelin acetate.

The sponsor responded on June 30, 2014 that the macimorelin concentrations could not be quantified because the volume of each pre-dose and post-dose urine sample was not collected by the site. Thus, it is not possible to quantify urinary excretion in Study ARD-0705-003.

2.4.2 What are the potential drug-drug interactions for macimorelin?

The sponsor did not conduct dedicated study to assess the effect of coadministered drugs on macimorelin PK and macimorelin's effect on coadministered drugs' PK. However, the label of sermorelin acetate (Geref[®]), another synthetic analog of growth hormone-releasing hormone approved for evaluating the ability of the somatotroph of the pituitary gland to secrete GH, has the following language for drug interactions:

The Geref[®] Diagnostic test should not be conducted in the presence of drugs that directly affect the pituitary secretion of somatotropin. These include preparations that contain or release somatostatin, insulin, glucocorticoids, or cyclooxygenase inhibitors such as aspirin or indomethacin. Somatotropin levels may be transiently elevated by clonidine, levodopa, and insulin-induced hypoglycemia. Response to Geref[®] Diagnostic may be blunted in patients who are receiving muscarinic antagonists (atropine) or who are hypothyroid or being treated with antithyroid medication such as propylthiouracil. Obesity, hyperglycemia, and elevated plasma fatty acids generally are associated with subnormal GH responses to Geref[®] Diagnostic. Exogenous growth hormone therapy should be discontinued at least one week before administering the Geref[®] Diagnostic test.

Thus, this reviewer recommends using the drug interaction statements from Geref[®]'s label to convey a similar message about drugs that may affect the pituitary secretion of somatotropin for macimorelin's label. Geref[®] (NDA20-443) is discontinued from marketing per the Drugs@FDA database.

2.5 General Biopharmaceutics

2.5.1 What biopharmaceutics classification system (BCS) class does macimorelin acetate belong?

This submission did not address the BCS classification of macimorelin acetate.

2.5.2 Does difference exist between the to-be-marketed macimorelin acetate formulations and the clinically-studied macimorelin acetate formulations? If so, has the sponsor addressed it satisfactorily?

See Dr. Assadollah Noory's review of the Office of New Drugs, Quality Assurance, Division of Biopharmaceutics dated June 17, 2014 in DARRTS.

2.6 Bioanalytical

2.6.1 Are the bioanalytical methods properly validated?

Measuring plasma macimorelin concentration

The sponsor used an HPLC-MS/MS bioanalytical method to measure the macimorelin concentration in plasma samples for the 3 clinical studies. This assay has 2 versions, namely the October 2003 and July 2005 versions. Briefly, the July 2005 version is an improved October 2003 version with the following partial assay validation (Table 6):

Version	Intraassay CV, %	Interassay CV, %	LLOQ, ng/mL
October 2003	4 – 10	8 – 13	5
July 2005	6 – 10	2 – 8	0.2

CV = coefficient of variation; LLOQ = lower limit of quantitation

The sponsor used the following assay to measure macimorelin in 3 clinical studies' plasma samples (Table 7):

Study	Version of macimorelin bioanalytical assay
AEZS-130-IIT-1 (single dose PK)	Initially with October 2003 and reanalyzed with July 2005
ARD-0705-003 (food effect)	July 2005
AEZS-130-047 (efficacy and safety)	July 2005

The sponsor analyzed Study AEZS-130-IIT-1's plasma samples for macimorelin twice with at least 10 months apart. Per the sponsor's April 11, 2014 response, the sponsor justified the stability of macimorelin in the plasma samples thru reanalysis and compared the results with the 1st analysis. Table 8 below details the results of the 2 bioanalyses:

LOQ of bioanalytical method			5 ng/ml	0.2 ng/ml	
Date of analysis			15. Dec 2004 - 05. Jan 2005	03. Nov 2005 - 09. Nov 2005	
Subject no.	Period	Time [min]	AEZS-130 [ng/ml]	AEZS-130 [ng/ml]	Deviation [%]
26	2	30	5.70	6.98	22.46
26	2	45	6.53	7.88	20.67
26	2	60	6.60	7.56	14.55
27	2	30	9.28	8.53	-8.08
27	2	45	11.29	10.14	-10.19
27	2	75	5.94	6.09	2.53
28	2	30	7.63	7.00	-8.26
28	2	45	7.96	7.37	-7.41
28	2	60	7.04	6.99	-0.71
28	2	75	5.76	6.57	14.06
28	2	90	5.16	5.78	12.02
29	1	60	5.78	6.17	6.75
29	1	75	5.83	4.67	-19.90
29	1	105	5.13	4.51	-12.09
29	1	120	5.87	4.57	-22.15
30	1	60	6.46	7.90	22.29
30	1	75	8.38	9.96	18.85
30	1	90	9.74	11.44	17.45
30	1	105	11.63	12.76	9.72
30	1	120	13.62	10.54	-22.61
30	1	150	10.63	11.69	9.97
30	1	180	5.97	8.95	49.92
31	2	60	7.08	6.25	-11.72
31	2	75	5.97	6.50	8.88
31	2	90	5.03	5.90	17.30
32	2	45	9.56	6.03	-36.92
32	2	60	5.58	4.71	-15.59
33	1	15	7.44	7.06	-5.11
33	1	45	5.79	5.43	-6.22
Mean_{ar} (n = 29)					2.08

The sponsor's justification for the macimorelin stability in Study AEZS-130-IIT-1's plasma samples is not acceptable because:

- Analyzing Study AEZS-130-IIT-1's plasma samples the 2nd time after storage cannot establish the long term stability of macimorelin in the plasma samples because there is no storage sample with known macimorelin concentration to compare with the samples of unknown macimorelin concentrations after long-term storage and the results may be confounded with factors such as variability of the 2 analyses.
- The sponsor did not spike blank plasma samples with different known amount of macimorelin and then store the samples under the same condition and time as Study AEZS-130-IIT-1's plasma samples so as to compare the spiked samples with Study AEZS-130-IIT-1's samples after analyses. See the bioanalytical method validation guidance (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm#>).

- The mean deviation of 2.08% cannot justify the long-term stability either since the deviation ranges from -36.92 to 49.92%.

See Table 9 below for the validation of the macimorelin bioanalytical method.

Table 9. Validation of macimorelin bioanalytical method. Source: This reviewer's compilation.

	Plasma Samples	Urine Samples
Analyte	macimorelin	macimorelin
Method	HPLC-MS/MS	HPLC-MS/MS
Sample size, µL	500	500
Lower limit of quantitation, ng/mL	0.2	0.2
Linear range, ng/mL	0.2 – 500	0.2 – 500
Calibration Standard:		
Interassay accuracy, %	-9.51 to +6.14	-10 to +5.48
Interassay precision, %	±2.45 to ±7.77	±2.11 to ±9.91
Quality control samples:		
Intraassay accuracy, %	-2.53 to +0.73	-0.24 to -8.80
Interassay precision, %	±6.43 to ±10.3	±4.45 to ±7.95

Accuracy is defined as the deviation of the observed from the theoretical concentration related to the theoretical concentration in [%]: $(C_{\text{obs}} - C_{\text{theor}})/C_{\text{theor}} \times 100$.

For Study ARD-0705-003's macimorelin analysis in plasma samples (Report EP01572/070016034 Tabs III.5 and III.7): The 11 calibration standards (0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200, and 500 ng/mL) on 7 analysis days have at least 82% of calibration standards achieving accuracy < 15%. The 3 quality control standards (0.75, 15, and 150 ng/mL) on 7 analysis days have at least 67% of quality control standards achieving accuracy < 15%.

For Study ARD-0705-003's macimorelin analysis in urine samples (Report EP01572/070016034 Tabs III.6 and III.8): The 11 calibration standards (0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200, and 500 ng/mL) on an analysis day have accuracy < 15%. The 3 quality control standards (0.75, 15, and 150 ng/mL) on an analysis day all have accuracy < 6%.

For Study AEZS-130-047's macimorelin analysis in plasma samples (Report AEZS-130/110002181 Tabs3 and 4): The 11 calibration standards (0.2, 0.5, 1, 2, 5, 10, 20, 50, 100, 200, and 500 ng/mL) on all analysis days have accuracy < 15%. The 3 quality control standards (0.75, 15, and 150 ng/mL) on all analysis days have accuracy < 15%.

Thus, Study ARD-0705-003 and Study AEZS-130-047's bioanalytical method for the determination of plasma macimorelin concentrations as well as Study ARD-0705-003's bioanalytical method for the determination of urine macimorelin concentrations appear acceptable.

Requested information on macimorelin bioanalytical reports for Studies ARD-0705-003 and AEZS-130-047 on June 20, 2014 and June 25, 2014

Study ARD-0705-003's bioanalytical report's (EP10572/070016034) Pages 2 and 3 show the following inconsistencies in comparison with Tab III.9 and Tab III.10 (Pages 24 and 25):

- a) 476 plasma samples vs. 960 plasma samples**
- b) 12 subjects vs. 16 subjects**

- c) peak plasma macimorelin concentrations range of 2.9 – 21.9 ng/mL vs. 2.18 – 9.66 ng/mL when administered with food
- d) peak plasma macimorelin concentrations range of 2.2 – 20.1 ng/mL vs. 3.32 – 21.9 ng/mL when administered without food
- e) The concentration vs. time plots of Pages 2 and 33 for Day 1 (with food) are inconsistent with Tab III.9 since the Day 1 plot shows plasma macimorelin concentrations above 10 ng/mL, whereas the highest is 9.66 ng/mL.
- f) The concentration vs. time plots of Pages 3 and 33 for Day 4 (without food) are inconsistent with Tab III.10 since the Day 4 plot shows peak plasma macimorelin concentrations below 20 ng/mL, whereas the highest is 21.9 ng/mL.
- g) Summary of Biopharmaceutic Studies, Module 2.7.1 page 6 states: “A single urine sample approximately 4 hours post-dosing was collected. Macimorelin urine concentration (mean $\pm$ SD) was 182 ± 132 ng/mL (median = 154 ng/mL, range = 11 to 517 ng/mL) when administered without food and 82 ± 41 ng/mL (median = 77 ng/mL, range = 16 to 180 ng/mL) when administered with food.” Also Study ARD-0705-003’s bioanalytical report’s (EP10572/070016034) Pages 26 Tab III.11 shows the postdose urine macimorelin concentrations. However, Study ARD-0705-003’s report Page 42 (82) states “A single urine sample approx. 4 hours post-dosing was collected and ARD-07 was measured in it. Measurable amounts were detected in urine but could not be quantified in this study.”

The sponsor responded on June 30, 2014 that b) to f) are their mistakes and this reviewer’s assessment is correct and submitted the corresponding report amendment for Report EP10572/070016034. However, this reviewer made a mistake in counting the number of plasma samples as 960. Report EP10572/070016034 has the correct number of plasma samples as 476.

Measurable amounts of macimorelin were detected in urine. However, macimorelin urine concentrations could not be quantified because the volume of each pre-dose and post-dose urine sample was not collected by the (clinical) site. Thus, it is not possible to quantify urinary excretion in this study.

Reviewer’s comment: *The sponsor’s response is acceptable. Per the sponsor’s request, this reviewer responded to the sponsor that the correct number of plasma samples is 476 per Report EP10572/070016034 on July 8, 2014.*

Bioanalytical Report EP01572/070016034 for Study ARD-0705-003’s Tab III.9 (with meal; Page 24) shows that Participant 3 has quantifiable plasma macimorelin concentration at 0 hour and Participant 4 has quantifiable plasma macimorelin concentration at -0.25 hour. These predose plasma macimorelin concentrations are > than 5 percent of the macimorelin $C_{\max}$ value for Participants 3 and 4. Justify these predose plasma macimorelin concentrations.

Bioanalytical Report EP01572/070016034 for Study ARD-0705-003’s Tab III.10 (without meal; Page 25) shows that Participants 8 and 12 have quantifiable plasma macimorelin concentration at -0.25 hour. Also, Participants 3, 6, and 8 have quantifiable plasma macimorelin concentration at 0 hour. Justify the predose

plasma macimorelin concentration at 0 hour is > than 5 percent of the macimorelin C_{max} value for Participant 6.

The sponsor responded on June 30, 2014 that “We are pursuing our investigation for an explanation and will inform the agency of any significant findings.”

Reviewer’s comment: *This reviewer chose Participant 6’s macimorelin data (without meal) since this participant’s time zero sample has the highest plasma macimorelin concentration (42.1% of C_{max}). The predose plasma macimorelin concentrations will not affect the macimorelin C_{max} assessment but may affect macimorelin AUC_t assessment. This reviewer calculated the macimorelin AUC_t via plasma macimorelin concentration of 2.49 ng/mL at time zero versus 0 ng/mL at time zero and 2.49 ng/mL at 5 minutes. The difference of AUC_t is < 1% between these 2 approaches. This reviewer recommends accepting the sponsor’s original macimorelin AUC_t calculations (with predose quantifiable concentration).*

Bioanalytical Report AEZS-130/110002181 for Study AEZS 130-047’s Tab 5 (Page 15 of 24) shows that the -0.25 and 0 hours plasma samples have quantifiable macimorelin concentrations for the following patients:

- **Patient 1029 at -0.25 hour**
- **Patients 1032, 1142, 1702, 1703, 1704, 1705, 1706, 1714, and 1715 at 0 hour**

These predose plasma macimorelin concentrations are > than 5 percent of the macimorelin C_{max} value in the corresponding patient’s data except Patient 1032. Justify these predose plasma macimorelin concentrations.

The sponsor responded on June 30, 2014 that:

- In general, there is a ± 2 minutes window for sampling plasma after dose administration.
- There may be a mixed up of -0.25 hour sample with the zero hour sample for Patient 1029.
- The 0 hour plasma macimorelin concentration of Patient 1032 is < 5% of the macimorelin C_{max} and thus is needless for explanation.
- Patient 1142’s 0 hour plasma sample was collected 5 minutes postdose.
- Patients 1702, 1703, and 1704’s 0 hour plasma samples were collected 7 – 10 minutes postdose.
- Patients 1705, 1706, 1714, and 1715’s 0 hour plasma samples have no additional information.

Reviewer’s comment: *The predose plasma macimorelin concentrations will not affect the macimorelin C_{max} assessment but may affect macimorelin AUC_t assessment. This reviewer recommends accepting the sponsor’s original macimorelin AUC_t calculations (with predose quantifiable concentration) with the same reason as that for Study ARD-0705-003 above.*

Measuring serum growth hormone concentration

The sponsor used the following studies to substantiate the release of GH upon oral administration of macimorelin:

- Broglio et al. *J Endocrinol Invest* 2002;25:RC26-8
- AEZS-130-IIT-1 (single dose PK)
- ARD-0705-003 (food effect)
- AEZS-130-047 (efficacy and safety)

Neither the Broglio article nor this NDA provided the bioanalytical validation for the assay used to measure plasma GH concentrations. Per the sponsor’s April 11, 2014 response for Study AEZS-130-IIT-1, the sponsor did not prepare a bioanalytical report for GH measurements and no validation report for the bioanalytical report is

available. The sponsor did not submit bioanalytical and validation reports for GH measurements in serum samples for Study ARD-0705-003.

The primary endpoint for Study AEZS-130-047 is the peak GH concentration following macimorelin treatment. Thus, this reviewer checked for the validation report and bioanalytical report for the determination of serum GH concentrations per the draft bioanalytical guidance’s recommendation for biomarkers (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm121568.htm>). The sponsor submitted the validation report for the development of bioanalytical assay used to measure serum GH concentrations for Study AEZS-130-047’s samples (of Report GH-RS-ICMA V1.2). However, in the June 30, 2014 response, the sponsor claimed that there is no bioanalytical report for the determination of serum GH concentration for Study AEZS-130-047’s samples. (b) (4) measured the serum GH concentrations and provided the results to the central data management group for Study AEZS-130-047. During the conduct of the study, (b) (4) was licensed under the Clinical Laboratory Improvement Amendments and was accredited by the College of American Pathology.

The sponsor used the 2-site immunochemiluminometric (ICMA) method to measure GH in Study AEZS-130-047’s serum samples. The GH-regular sensitive (RS)-ICMA assay uses 2 monoclonal antibodies reactive to human GH (hGH), 1 immobilized on polystyrene bead binding the N terminal and the other labeled with acridinium ester binding the C terminal of hGH. The hGH in serum samples or control is complexed between the bead-bound antibody and the liquid-phase labeled antibody. After final washing, the bound complexes are measured in a luminometer. The amount of signal (light) generated is directly proportional to the GH concentration. Absolute concentrations for unknown and control sera are determined via comparison with hGH standard data generated with each assay run.

This 2-site method measures only intact 22 kD hGH. GH-RS-ICMA does not cross react with structural variants of hGH such as the 20 kD splice variant, hGH 44-191 fragment or hGH 1-43 fragment, with other pituitary hormones (prolactin, luteinizing hormone, follicle-stimulating hormone, or adrenocorticotrophic hormone) or with related growth factors like human placental lactogen. See Table 10 below for the validation of the GH bioanalytical method used to measure in serum GH concentrations for Study AEZS-130-047’s samples.

Table 10. Validation of growth hormone bioanalytical method. Source: This reviewer’s compilation of Report GH-RS-ICMA V1.2.

	Serum Samples
Analyte	Growth Hormone
Method	GH-RS-ICMA
Sample size, µL	50
Lower limit of quantitation, ng/mL	0.06
Dynamic range, ng/mL	0.05 – 50
Precision	
Intraassay, %	3.8 – 14 with a mean of 7.4
Interassay, %	7 at 0.3 ng/mL, 8 at 1.9 ng/mL, 9 at 3.6 ng/mL, 9 at 9.2 ng/mL, 12 at 11.7 ng/mL, and 14 at 41 ng/mL
Accuracy, %	4.2 at 0.4 ng/mL, 6.7 at 2 ng/mL, 1.3 at 4 ng/mL, and 10.3 at 20 ng/mL

The accuracy of this GH bioanalytical assay is actually a measure of the accuracy of the recovery of the added known GH concentration (Report GH-RS-ICMA V1.2 Table 8 Page 17 of 39). Since GH is an endogenous substance, there is no true blank serum sample to spike known concentration of GH to serve as reference for the measured GH concentration of serum samples. This reviewer consulted with the OCP’s Division of Applied Regulatory Science (OCP/DARS) and Center for Biologics Evaluation and Research’s Office of Biologic Products (CBER/OBP) and learned that it is a challenge to strip serum samples of GH even with today’s technology. Thus,

the sponsor's approach to measure the accuracy of the recovery of the added known GH concentration is appropriate. Table 11 details the accuracy/recovery of the bioanalytical assay used for Study AEZS-130-047.

Table 11. Accuracy/Recovery of the GH bioanalytical assay used for Study AEZS-130-047. Source: Modified from Report GH-RS-ICMA V1.2 Table 8 Page 17 of 39.

Sample	GH Added	GH Measured (ng/	GH Recovered (ng/	%Recovery	%Bias	Average Bias	Average Bias Reviewer
1	0	0.52	NA	NA	NA		
2	0	0.06	NA	NA	NA		
3	0	0.64	NA	NA	NA	NA	NA
1	0.4	0.89	0.37	92.5	-7.5		
2	0.4	0.47	0.41	102.5	2.5		
3	0.4	1.11	0.47	117.5	17.5	4.2	4.2
1	2.0	2.26	1.74	87.0	-13.0		
2	2.0	2.60	2.54	127.0	27.0		
3	2.0	2.76	2.12	106.0	6.0	6.7	6.7
1	4.0	3.81	3.29	82.3	-17.7		
2	4.0	4.12	4.06	101.5	1.5		
3	4.0	5.45	4.81	120.2	20.2	1.3	1.3
1	20.0	17.85	17.33	86.7	-13.3		
2	20.0	21.01	20.95	104.8	4.8		
3	20.0	28.51	27.87	139.3	39.3	-10.3	10.3

Samples 1, 2, and 3 are from 3 sources. GH Recovered = GH Measured minus GH Measured at 0 GH Added

The sponsor's calculated average of the average bias is 0.43%, whereas this reviewer's calculated average of the average bias is 5.6% for Table 11. This discrepancy stems from the sponsor's error of -10.3% for the average bias for the 20 ng/mL GH added group, which should be 10.3% instead.

The sponsor analyzed 10 random serum samples with quadruplicate determination for GH concentrations to establish the intraassay variability. Table 12 details the intraassay results to show the precision of the assay.

Table 12. Intraassay precision for the assay used to determine serum GH concentrations for Study AEZS-130-047.

Source: Report GH-RS-ICMA V1.2 Table 6 Page 15 of 39

Replicate	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6	Sample 7	Sample 8	Sample 9	Sample 10
	0.090	0.22	0.48	0.88	2.6	3.3	7.5	12	18	38
2	0.078	0.24	0.51	0.94	2.5	3.0	7.9	12	19	42
3	0.063	0.26	0.47	1.0	2.6	3.0	8.3	13	21	35
4	0.081	0.24	0.42	0.95	2.4	3.1	7.3	11	22	34
Mean	0.08	0.24	0.47	0.94	2.5	3.1	7.8	12	20	37
SD	0.011	0.016	0.037	0.049	0.096	0.14	0.44	0.82	1.8	3.6
%CV	14	6.8	8.0	5.2	3.8	4.6	5.7	6.8	9.1	9.7

The sponsor determined the interassay variability at target serum GH concentrations of 0.33, 1.9, 3.9, 9, 11, and 38 ng/mL (see Table 13).

Table 13. Interassay precision for the assay used to determine serum GH concentrations for Study AEZS-130-047.

Source: Report GH-RS-ICMA V1.2 Table 7 Page 16 of 39

GH (ng/mL)	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
1	0.31	1.9	3.5	10	9.8	42
2	0.27	1.5	3.5	9.0	11	40
3	0.29	2.1	3.7	9.4	12	43
4	0.32	1.9	4.1	9.2	13	49
5	0.30	1.9	3.3	8.9	9.8	34
6	0.28	1.8	3.1	10	11	40
7	0.31	2.1	3.6	10	12	32
8	0.29	1.9	3.9	9.0	11	50
9	0.33	1.8	3.7	9.9	9.8	36
10	0.28	2.1	3.8	8.1	12	36
11	0.33	1.8	3.9	9.5	14	51
12	0.32	1.8	3.9	7.0	13	44
13	0.28	1.7	3.0	8.9	11	42
14	0.33	2.0	3.5	9.6	12	46
15	0.31	2.0	3.8	8.4	13	35
16	0.28	1.9	3.6	10	10	40
17	0.28	2.1	4.1	10	14	
Mean	0.30	1.9	3.6	9.2	11.7	41
SD	0.02	0.2	0.3	0.82	1.4	5.8
%CV	7	8	9	9	12	14
n	17	17	17	17	17	16

Both intraassay and interassay precision for the GH determination are reasonably good because the CV% is less than 15% for a ligand binding assay like ICMA per the draft bioanalytical guidance.

The sponsor claimed that hemolysis or three freeze-thaw cycles did not alter GH-RS-ICMA results significantly, nor did storage at 4°C or at room temperature up to 24 hours.

This reviewer recommends accepting the results of serum GH concentrations results of Study AEZS-130-047 even in the absence of a bioanalytical report because of the following:

- *The ICMA assay has reasonably good intraassay and interassay precision per the validation report.*
- *The ICMA assay is reproducible per the validation report.*
- *The ICMA assay has acceptable accuracy (recovery) per the validation report.*
- *The ICMA assay is selective that it does not cross react with structurally similar or dissimilar hormones per the validation report.*
- *The ICMA assay has a lower limit of quantitation of 0.06 ng/mL per the validation report that is sensitive as compared to a human ELISA kit that is for research use (minimal sensitivity of the kit is 0.5 ng/mL (b) (4)).*

- The ICMA assay has a dynamic range of 0.05 – 50 ng/mL per the validation report that is in the expected range of serum GH concentrations for the clinical study.
- The ICMA assay showed that GH appears to be stable in the serum samples per the validation report.
- The bioanalytical laboratory was licensed under the Clinical Laboratory Improvement Amendments and was accredited by the College of American Pathology during the study.
- The sponsor conducted Study AEZS-130-047 between July 12, 2007 and July 11, 2011. The draft bioanalytical guidance issued on September 2013 recommends the validation of biomarkers, whereas the original bioanalytical guidance issued on May 2001 does not recommend the validation of biomarkers. It would be unreasonable to retrospectively evaluate this ICMA assay to a higher standard of the draft bioanalytical guidance.
- Five of 7 persons whom this reviewer or his Team Leader had informal discussions from the following groups recommended acceptance of this ICMA assay:
 - OCP/DARS' 2 members on June 20, 2014
 - CBER/OBP's member on June 26, 2014
 - Office of Scientific Investigation's ex-member now in the Office of Generic Drugs on June 23, 2014, also this reviewer's Team Leader had informal discussion with a member of the Office of Scientific Investigation on June 30, 2014
 - OCP's Bioanalytical Scientific Interest Group's 2 members on July 1, 2014
- Bidlingmaier and Strasburger recognize that the invention of immunoassays for the measurement of peptide hormones was a major breakthrough, enabling the routine analysis of GH concentrations in larger series of samples (Growth hormone assays: current methodologies and their limitations. Pituitary 2007;10:115-9).
- Taking the above as a whole, this reviewer believes this ICMA assay is likely to measure serum GH concentrations for the purpose of Study AEZS-130-047.

During the process of reviewing the bioanalytical assay of serum GH concentration for Study AEZS-130-047, this reviewer discovered Report VR07- (b) (4) 018. This report is to substantiate a protocol deviation that is neither recorded in Study AEZS-130-047's core report nor in the protocol deviation listing (Listing 16.2.2.1). The deviation is that serum samples are unavailable for Visit 2 on 4 subjects for the determination of GH. The protocol corrective action was to test the PK backup samples that were collected as lithium-heparinized plasma. The sponsor used the ICMA assay to analyze the remaining serum samples from Visit 3 for Subjects 0105, 0306, 0304, and 0609 as well as the plasma PK backup samples from Visit 3 for Subjects 0105, 0306, 0304, and 0609 for GH determination of Study AEZS-130-047 so as to justify the substitution of plasma PK backup samples for the missed serum samples.

Table 14. Comparison of serum vs. lithium heparin plasma for GH determination in Study AEZS-130-047. Source: Report VR07- (b) (4) 018 Table 7.2 Page 7 of 12.

Sample	Time points	Serum	Li Hep Plasma	%Bias**	%Bias Reviewer
A	10:45	6.2	4.5	-27.2	-27.4
	11:00	4.2	5.3*	28.5	26.19
B	10:30	2.8	3.0	7.4	7.14
	10:45	2.7	2.5*	-9.5	-7.41
C	10:40	5.7	6.2*	8.3	8.77
	10:55	5.1	5.0*	-3.1	-1.96
D	12:15	7.9*	8.1	3.3	2.53
	12:45	QNS	2.0	NA	

** % Bias = [(plasma-serum)/serum] x 100 ; *Duplicate CV ranges= >15% to < 27%

The sponsor calculated the average bias between the serum GH concentration and plasma GH concentration

and claimed that average bias of $\leq 20\%$ is considered acceptable. However, the range of the bias between the serum GH concentration and plasma GH concentration ranges from -27.4% to 26.19%. Moreover, the samples with “*” in Table 13 are results of duplicates with coefficient of variation ranges between 15% and 27%. Together with the variability of the corresponding samples without “*”, the true bias may be larger than the sponsor’s calculations. *Thus, this reviewer recommends the following:*

The substantiation to use lithium-heparinized plasma pharmacokinetic backup samples to substitute for the missed serum samples of Study AEZS-130-047 on Visit 2 for Subjects 0105, 0306, 0304, and 0609 per Report VR07-(b) (4) 018 is not acceptable due to the range of the percent difference between plasma growth hormone concentration and serum growth hormone concentration for the tested samples is -27.4% to 26.19%. Thus, the reported serum growth hormone concentration results on Visit 2 for Subjects 0105, 0306, 0304, and 0609 of Study AEZS-130-047 are not reliable.

Labeling Recommendations

Strikethrough text means deletion of the sponsor’s proposed text. Underscored text means recommended addition. *Italicized text means internal notes and not to be communicated with the sponsor.*

7 DRUG INTERACTIONS

- Co-administration of a CYP3A4 inducer (b) (4) may reduce the (b) (4) plasma macimorelin concentrations, and (b) (4).

The MACRILEN® Diagnostic test should not be conducted in the presence of drugs that directly affect the pituitary secretion of somatotropin. These include preparations that contain or release somatostatin, insulin, glucocorticoids, or cyclooxygenase inhibitors such as aspirin or indomethacin. Somatotropin concentrations may be transiently elevated by clonidine, levodopa, and insulin-induced hypoglycemia. Response to MACRILEN® Diagnostic test may be blunted in patients who are receiving muscarinic antagonists (atropine) or who are hypothyroid or being treated with antithyroid medication such as propylthiouracil. Obesity, hyperglycemia, and elevated plasma fatty acids generally are associated with subnormal growth hormone responses to MACRILEN® Diagnostic. Exogenous growth hormone therapy should be discontinued at least one week before administering the MACRILEN® Diagnostic test. *Modified from Geref® Diagnostic test’s label.*

Should we add “Response to MACRILEN® Diagnostic test may be augmented in patients who are receiving drugs (such as metformin) that increase ghrelin secretion, which in turn may increase the release of GH from the pituitary.” to the MACRILEN® label? (Doogue MP et al. Metformin increases plasma ghrelin in Type 2 diabetes. Br J Clin Pharmacol 2009;68:875-82).

8.5 Geriatric Use

(b) (4)
(b) (4)

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

(b) (4) stimulates GH release, (b) (4) present in the
pituitary and hypothalamus. (b) (4)

12.2 Pharmacodynamics

(b) (4)

12.3 Pharmacokinetics

(b) (4)

A liquid meal decreased the macimorelin C_{max} and AUC 55% and 49%, respectively. See Question 2.4.1 Study ARD-0705-003's discussion in this review.

No significant difference in macimorelin pharmacokinetics is observable between adult growth hormone deficient patients and matched healthy volunteers. See Question 2.2.3 Study AEZS-130-047's discussion in this review.

Neither adult growth hormone deficient patients nor matched healthy volunteers show significant gender difference in macimorelin pharmacokinetics. See Question 2.3.3 Study AEZS-130-047's discussion in this review.

4 Appendix

4.1 Proposed Labeling

9 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SZE W LAU
07/16/2014

IMMO ZADEZENSKY
07/16/2014

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

NDA Number: 205-598

**Applicant: Aeterna Zentaris
Pharmaceuticals**

**Stamp Date: November 4,
2013**

**Drug Name: Macimorelin
acetate**

NDA Type: Standard

On **initial** overview of the NDA application for RTF:

	Content Parameter	Yes	No	Comment
Criteria for Refusal to File (RTF)				
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		No	Submitted bioequivalence study waiver request
2	Has the applicant provided metabolism and drug-drug interaction information?	Yes		In vitro data only
Criteria for Assessing Quality of an NDA				
Data				
3	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g. CDISC)?			Not applicable
4	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			Not applicable
Studies and Analyses				
5	Has the applicant made an appropriate attempt to determine the reasonable dose individualization strategy for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	Yes		
6	Did the applicant follow the scientific advice provided regarding matters related to dose selection?			Not applicable
7	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted in a format as described in the Exposure-Response guidance?			Not applicable
8	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			Not applicable
9	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		No	Exempt, orphan drug designation
10	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		No	Exempt, orphan drug designation
11	Is the appropriate pharmacokinetic information submitted?	Yes		
12	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	Yes		
General				
13	On its face, is the clinical pharmacology and	Yes		

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

	biopharmaceutical section of the NDA organized in a manner to allow substantive review to begin?			
14	Is the clinical pharmacology and biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	Yes		
15	On its face, is the clinical pharmacology and biopharmaceutical section of the NDA legible so that a substantive review can begin?	Yes		
16	Are the clinical pharmacology and biopharmaceutical studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	Yes		
17	Was the translation from another language important or needed for publication?		No	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILABLE?

___ Yes ___

If the NDA/BLA is not filable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

S. W. Johnny Lau, R.Ph., Ph.D.

Reviewing Pharmacologist

Date

Immo Zadezensky, Ph.D.

Team Leader/Supervisor

Date

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

Office of Clinical Pharmacology <i>New Drug Application Filing and Review Form</i>				
General Information about the Submission				
	Information		Information	
NDA	205-598	Brand Name	MACRILEN®	
OCP Division	2	Generic Name	Macimorelin acetate	
Medical Division	DMEP	Drug Class	Growth hormone secretagogue	
OCP Reviewer	S.W. Johnny Lau	Indication(s)	Diagnosis adult growth hormone deficiency	
OCP Team Leader	Immo Zadezensky	Dosage Form	Granules for oral solution	
Date of Submission	5-NOV-2013	Dosing Regimen	1 mL/kg of 0.5 mg/mL solution after ≥ ^(b) ₍₄₎ hours fasting	
Estimated Due Date of OCP Review	5-SEPT-2014	Route of Administration	Oral	
PDUFA Due Date	5-NOV-2014	Sponsor	Aeterna Zentaris	
Division Due Date	5-OCT-2014	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Comments (Study number)
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
In vivo mass balance:				
In vitro isozyme characterization				
In vitro metabolite Identity				
In vitro metabolism inhibition	X	1		ADME-2012-01
In vitro metabolism induction				
In vitro efflux and uptake transporters inhibition:				
P-gp substrate assessment				
In vitro mechanism of uptake in human liver				
In vitro plasma protein binding:				
Blood/plasma ratio:				
Pharmacokinetics (e.g., Phase I) -	X	1		AEZS-130-IIT-1
Dose proportionality, healthy volunteers – fasting & non-fasting single and multiple doses:				
Drug-drug interaction studies -				
In-vivo effects <u>on</u> primary drug:				
In-vivo effects <u>of</u> primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

pediatrics:				
gender & geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 1:	X	1		Broglia
Phase 3:				
PK/PD:				
Phase 2, dose ranging studies:				
Phase 3 clinical STUDIES (matched controlled):	X	1		AEZS-130-047
Phase 3 clinical STUDIES (cancer cachexia):	X	1		H-27747
Population Analyses -				
Meta-analysis:				
NONMEM:				
II. Biopharmaceutics				
Absolute bioavailability:				
Bioequivalence studies – traditional design				
Relative bioavailability				
alternate formulation as reference:				
Food-drug interaction studies:	X	1		ARD-0705-003
Absorption site				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Phenotype studies:				
Chronopharmacodynamics				
Pediatric development plan				
Literature References				
QT prolongation assessment				
Total Number of Studies		6		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable?	X			
Comments to be sent to firm?	X	State Study ARD-0705-003's "standard liquid meal" content per the food-effect study guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070241.pdf). Inform the location or send the datasets of macimorelin, growth hormone, and insulin growth factor-1 for Study ARD-0705-003.		
QBR questions (key issues to be considered)		- Macimorelin pharmacokinetics and pharmacodynamics as related to efficacy and safety - Study ARD-0705-03-25 does not follow the food effect guidance's recommendations for meal and drug administration as well as the test meal. - Bioanalytical validations for macimorelin, insulin growth factor-11BL, and growth hormone.		

**CLINICAL PHARMACOLOGY
FILING CHECKLIST FOR NDA 205-598**

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

Filing Memo

CLINICAL PHARMACOLOGY

NDA: 205-598
Compound: Macimorelin acetate (MACRILEN®)
Sponsor: Aeterna Zentaris
Submission Date: November 5, 2014
Relevant IND: 73,196
From: S.W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submits a 505(b)(1) New Drug Application (NDA 205-598) to seek marketing approval for macimorelin acetate to diagnose adult growth hormone (GH) deficiency (AGHD) (b) (4)

Findings

To support NDA 205-598's Clinical Pharmacology sections, the sponsor submitted studies' results as indicated in the table above. Findings' highlights follow:

- The sponsor used the former ARDANA formulation and the later AEZS formulation to conduct the pivotal clinical trial for AEZS-130-047. Both of these clinically-tested formulations differ slightly from the AEZS to-be-marketed formulation. The sponsor opted not to conduct bioequivalence study between the clinically-tested formulation and the to-be-marketed formulation but submitted a bioequivalence study waiver with this NDA submission.
- The sponsor provided annotated labeling and supportive documents, which allow substantive review for the clinical pharmacology information.
- The sponsor provided bioanalytical validation reports of macimorelin, insulin growth factor-1BL, and GH for the clinical pharmacology studies.
- Briefly, the sponsor submitted 6 clinical pharmacology-related studies:
 - ADME-2012-01 is an in vitro study to identify the cytochrome P450 (CYP) isozyme(s) that metabolize macimorelin and its inhibition potential on the CYP isozymes.
 - ARD-0705-003 is a food effect study to assess the effect of a standard liquid meal on macimorelin exposure.
 - Broglia 2002 study compared the pharmacodynamics of intravenous ghrelin to intravenous and oral macimorelin acetate. The sponsor did not provide study report but a publication as Broglia et al. *J Endocrinol Invest* 2002;25:RC26-RC28.
 - AEZS-130-ITT-1 is a single ascending dose study to assess the pharmacokinetics and pharmacodynamics of macimorelin via oral and intraduodenal administrations. Besides the study report, the sponsor also published the study as Piccoli et al. *J Clin Endocrinol Metab* 2007;92:1814-20.
 - AEZA-130-047 is the pivotal clinical study for macimorelin acetate.
 - H-27747 is a clinical study to assess the safety and efficacy of repeated oral administration of macimorelin to treat cachexia. This reviewer will not review this study since it does not measure macimorelin exposure and is for a different usage (not AGHD).
- The sponsor labeled the electronic datasets just as "dataset" for different files of each clinical pharmacology study, which made this reviewer difficult to discern the categories of those files.

Attachment starts here.

CLINICAL PHARMACOLOGY FILING CHECKLIST FOR NDA 205-598

Table 1: Tabular Listing of all clinical studies

Type of study	Study identifier	Location of study report	Objective of study	Study design and type of control	Test product ^a , Dosage regimen ^b , Route of administration	Number of subjects	Type of subjects	Duration of treatment	Study status, Report type
PD	Broglio (2002)	5.4	Define PD	Cross-over	Macimorelin 1.0 µg/kg, IV 0.06, 125 and 0.25 mg/kg Oral solution ^c 0.5 mg/kg Oral solution ^c	2	Healthy volunteers	SD SD 2 doses, 24 hours apart	Completed, Publication
BA	ARD-0705-003	5.3.1.1.1	Food-effect	Cross-over	Macimorelin 0.5 mg/kg Oral solution ^d	16	Healthy volunteers	2 doses, 3 days apart	Completed, Full
PK/PD	AEZS-130-IIT-1	5.3.4.1.1	Define PK/PD	Cross-over	Macimorelin 0.005, 0.05, 0.125, 0.25 and 0.5 mg/kg Oral solution ^e Macimorelin 0.2, 0.35 and 0.5 mg/kg ID solution ^f	36	Healthy volunteers	SD	Completed, Full
Efficacy	AEZS-130-047	5.3.5.1.1	Diagnostic efficacy	Open	Macimorelin 0.5 mg/kg, Oral solution ^g	52 ^h 48	AGHD patients Matched controls	SD	Completed, Full
Type of study	Study identifier	Location of study report	Objective of study	Study design and type of control	Test product ^a , Dosage regimen ^b , Route of administration	Number of subjects	Type of subjects	Duration of treatment	Study status, Report type
Safety and efficacy	H-27747	5.3.5.4.1	Efficacy (cancer cachexia)	Double-blind placebo-controlled	Macimorelin ⁱ 0.25, 0.5, 1 mg/kg or placebo ^j QD Oral solution	9	Solid tumor cancer patients	7 days	Ongoing, Synopsis

AGHD = adult growth hormone deficiency, BA = bioavailability, ID = intraduodenal, IV = intravenous, PD = pharmacodynamic, PK = pharmacokinetic, PO = per os (oral), QD = once a day, SD = single dose

^a: Macimorelin was administered as the trifluoroacetate salt in the first-in-man study (published by Broglio et al, 2002) and administered as the acetate salt in all subsequent studies.

^b: All numbers refer to the amount of macimorelin free peptide base.

^c: No information is available regarding the concentration of macimorelin in the solution administered.

^d: 0.5 mg/mL prepared as 50 mg macimorelin in 100 mL sterile water for irrigation.

^e: The required amount of macimorelin to be administered (calculated based on the subject's body weight) was dissolved in 40 mL of distilled water. Therefore, the concentration of the solution increased proportionally to the dose, e.g., for a 70-kg subject, the concentration of the solution increased from 0.0088 mg/mL for the dose of 0.005 mg/kg to 0.875 mg/mL for the dose of 0.5 mg/kg. For doses > 0.05 mg/kg, 40 µL of HCl (1 N) was added to aid in solubilization.

^f: The required amount of macimorelin to be administered (calculated based on the subject's body weight) was dissolved in 20 mL of distilled water (supplemented with 40 µL 1 N HCl) and administered via a polyvinyl feeding tube. The tube was then flushed with an additional 20 mL of distilled water, thus leading to a final administration volume of 40 mL. Therefore, the concentration of the solution increased proportionally to the dose, e.g., for a 70-kg subject, the concentration of the solution increased from 0.35 mg/mL for the dose of 0.2 mg/kg to 0.875 mg/mL for the dose of 0.5 mg/kg.

^g: 0.5 mg/mL prepared as 50 mg macimorelin granules in 100 mL water (and referred to as the "Ardana clinically-tested formulation" in the biowaiver document (see CTD Section 1.12.15)) for the 42 AGHD patients and the 10 matched controls enrolled in the study sponsored by Ardana. The remainder of the patients (n = 10) and of the matched controls (n = 38) received a solution of (b) (4) (and referred to as the

"AEZS clinically-tested formulation" in the biowaiver document see CTD Section 1.12.15).

^h: A total of 53 AGHD patients were enrolled in study but only 52 were exposed to macimorelin.

ⁱ: 0.5 mg/mL prepared as 60 mg macimorelin granules in 120 mL Powerade.

^j: Powerade given at the same volume as if calculated for macimorelin on the basis of body weight.

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/s/

SZE W LAU
12/09/2013

IMMO ZADEZENSKY
12/09/2013