Clinical trial results:
Confirmatory validation of oral macimorelin as a Growth Hormone (GH) Stimulation Test (ST) for the diagnosis of Adult Growth Hormone Deficiency (AGHD) in comparison with the Insulin Tolerance Test (ITT)

Summary

EudraCT number	2015-002337-22
Trial protocol	GB AT DE PL IT
Global end of trial date	29 November 2016

Results information

Result version number	v1 (current)
This version publication date	15 December 2017
First version publication date	15 December 2017
Summary attachment (see zip file)	AEZS-130-052 Synopsis to E3 Clinical Trial Report (AEZS-130-052_final_synopsis_incl.Titlepage_16Jun2017.pdf)

Trial information

Trial identification

Sponsor protocol code	AEZS-130-052

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02558829
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 073196

Notes:

Sponsors

Sponsor organisation name	Aeterna Zentaris GmbH
Sponsor organisation address	Weismuellerstr. 50, Frankfurt am Main, Germany, 60314
Public contact	Clinical trial information desk, Aeterna Zentaris GmbH, +49 69426023472, clinical.trials@aezsinc.com
Scientific contact	Clinical trial information desk, Aeterna Zentaris GmbH, +49 69426023472, clinical.trials@aezsinc.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2016
Global end of trial reached?	Yes
Global end of trial date	29 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To validate the use of single dose oral macimorelin for the dagnosis of AGHD ('macimorelin GHST'), using the Insulin Tolerance Test (ITT) as comparator (non-reference standard) GHST.

Protection of trial subjects:

The following was applied: selection of trial subjects according to in- and exclusion critieria as defined in the trial protocol; exclusion of subjects e.g., with conditions contraindicated for the conduct of an ITT. Monitoring of subjects by qualified trial site personnel during the conduct of both Growth Hormone Stimulation Tests (GHSTs). Collection of data related to concomitant medication, medical history, adverse events (AEs).
Establishment of a Data Review Committee (DRC): the evaluation of “agreement” in the test outcome of investigational and comparator assay required that in a given subject both assays had been performed and that no critical deviations from the planned test procedure occurred in either assay. Also, the agreement either could not have been determined due to lack of data or would have been questionable with regard to data quality. Therefore, a Data Review Committee (DRC) reviewed the assay performance prior to availability of the data on the stimulated growth hormone levels and qualified a test as “evaluable” or “non-evaluable”.

Background therapy:

Not applicable

Evidence for comparator:

The Insulin Tolerance Test (ITT) is considered as a 'Gold Standard' for diagnosing AGHD

Actual start date of recruitment	15 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 49
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Serbia: 21
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	157
EEA total number of subjects	99

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	154
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study centers: 30 sites in 9 countries were initiated, i.e. 25 sites in Europe (Austria, Germany, Spain, France, Italy, Poland, Serbia, and UK) with 21 of them becoming active, and 5 sites in the USA.
Study period: First subject randomized: 03-Dec-2015, Last subject completed: 29-Nov-2016

Pre-assignment

Screening details:

Screening occurred at D-28 to D-1 (D=Day). Screening procedures included written informed consent procedure, data on vital signs, ECG, clinical laboratory, physical examination, medical history (incl. review for known risk factors for AGHD), prior-/concomitant medication, check of eligibility criteria incl. pre-defined in-and exclusion criteria.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinding for growth hormone (GH) values: serum concentrations of GH for a given subject were provided by the central laboratory to the investigator only after the serum samples for both tests were available and appropriateness of the test performance had been adjudicated by a Data Review Committee (DRC). Adjudications were performed before release of the stimulated GH concentrations from the central laboratory to rule out potential bias if the GHST outcome was known at the time of DRC review.

Arms

Are arms mutually exclusive?	No
Arm title	GHST Sequence A

Arm description:

1st Macimorelin-GHST, 2nd Insulin Tolerance Test.
Drug: Macimorelin
macimorelin acetate, 0.5 mg/kg body weight, drinking solution, single dose
Other Names: Macimorelin-GHST (MAC)
Drug: Insulin
Insulin, 0.10 U/kg (0.15 U/kg if BMI > 30 kg/m2), intravenous injection, single dose
Other Names: Insulin Tolerance Test (ITT)

Arm type	Experimental
Investigational medicinal product name	macimorelin
Investigational medicinal product code	AEZS-130
Other name	macimorelin Growth Hormone Stimulation Test (GHST), macimorelin GHST, MAC
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

macimorelin acetate, 0.5 mg/kg body weight, drinking solution, single dose

Arm title	GHST Sequence B

Arm description:

1st Insulin Tolerance Test (ITT), 2nd Macimorelin-GHST (MAC)
Drug: Macimorelin
macimorelin acetate, 0.5 mg/kg body weight, drinking solution, single dose
Other Names:
• Macimorelin-GHST (MAC)
Drug: Insulin
Insulin, 0.10 U/kg (0.15 U/kg if BMI > 30 kg/m2), intravenous injection,
single dose
Other Names:

• Insulin Tolerance Test (ITT)

Arm type	Experimental
Investigational medicinal product name	insulin
Investigational medicinal product code	
Other name	Insulin Tolerance Test; ITT
Pharmaceutical forms	Injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

Insulin, 0.10 U/kg (0.15 U/kg if BMI > 30 kg/m2), intravenous injection, single dose. An additional insulin bolus of 0.05 U/kg was to be administered if glucose did not show a value of less than 2.2 mmol/L (40 mg/dL) AND symptomatic hypoglycemia (e.g., diaphoresis, confusion, sensation of warmth, weakness, or fatigue) had not been achieved within 45 minutes after the initial insulin dose.

Number of subjects in period 1	GHST Sequence A	GHST Sequence B
Started	81	76
Completed	74	66
Not completed	7	10
Protocol deviation	7	10

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

- Safety Population (SAF): included all subjects who received at least 1 dose of the study drug (N=157).
- modified Intent-to-Treat (mITT) Population: is the primary analysis population and included all randomized subjects in whom both GHSTs of the cross-over were evaluable (N=140).
Primary objective: to validate the use of single dose oral macimorelin for the diagnosis of AGHD ('macimorelin GHST'), using the insulin tolerance test as comparator GHST.
The sequential order of the GHSTs for the suspected AGHD subjects was determined by stratified randomization by Group; healthy control subjects (Group D) were tested in the same sequence as the matched Group A subjects. The macimorelin-GHST ('MAC') and the ITT of the core study were to be performed 7 days to 1 month apart. Serum concentrations of growth hormone were measured at pre-defined time points before and after GHST administration of macimorelin or insulin.

Reporting group values	Overall trial	Total	
Number of subjects	157	157	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	40.7		
standard deviation	± 13.1	-	
Gender categorical Units: Subjects			
Female	64	64	
Male	93	93	
BMI			
Body Mass Index			
Units: kg/m²			
arithmetic mean	28.0		
standard deviation	± 4.8	-	

Subject analysis sets

Subject analysis set title	Group A - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

High likelihood of growth hormone deficiency (GHD):
•Structural hypothalamic or pituitary lesions and low insulin-like growth factor 1 (IGF-1), and/or

•Three or more pituitary hormone deficiencies (PHD) and low IGF-1, or
•Childhood onset GHD with structural lesions and low IGF-1.

Subject analysis set title	Group B - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Intermediate likelihood of GHD:
• Eligible subjects not qualifying for either high or low likelihood (Group A/C)

Subject analysis set title	Group C -SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Low likelihood of GHD:
•One risk factor for GHD only, such as history of distant traumatic brain injury (TBI) or one PHD only with otherwise normal pituitary function or
•Isolated idiopathic childhood onset GHD without additional pituitary deficits

Subject analysis set title	Group D - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Healthy control: Healthy subjects matching Group A subjects by sex, age, body mass index (BMI), and estrogen status (females only).

Subject analysis set title	Positive Agreement of MAC with ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Percent positive agreement of MAC with ITT

Subject analysis set title	Negative agreement of MAC with ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Percent negative agreement of MAC with ITT

Subject analysis set title	Sensitivity of MAC
Subject analysis set type	Per protocol

Subject analysis set description:

Group A and Group D subjects

Subject analysis set title	Specificity of MAC
Subject analysis set type	Per protocol

Subject analysis set description:

Group A and Group D subjects

Subject analysis set title	Positive Agreement MAC core and MAC repeatability
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol Amendment 1: had been issued for selected sites in Europe to obtain exploratory data on the repeatability of the MAC in a subset of subjects that had completed the core study. Primary efficacy variable: comparison of peak GH levels following repeated treatments with macimorelin. MAC repeatability was evaluated for overall agreement only. Pre-defined MAC cut-off point GH: 2.8 ng/mL. Data presented: percent positive agreement of MAC core study with MAC repeatability extension.

Subject analysis set title	Negative Agreement MAC core and MAC repeatability
Subject analysis set type	Per protocol

Subject analysis set description:

Protocol Amendment 1: had been issued for selected sites in Europe to obtain exploratory data on the repeatability of the MAC in a subset of subjects that had completed the core study. Primary efficacy variable: comparison of peak GH levels following repeated treatments with macimorelin. MAC repeatability was evaluated for overall agreement only. Pre-defined MAC cut-off point GH: 2.8 ng/mL. Data presented: percent negative agreement of MAC core study with MAC repeatability extension.

Reporting group values	Group A - SAF	Group B - SAF	Group C -SAF
Number of subjects	42	42	44

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	42.3	45.8	34.9
standard deviation	± 15.0	± 11.8	± 10.5
Gender categorical Units: Subjects			
Female	17	24	9
Male	25	18	35
BMI			
Body Mass Index			
Units: kg/m²			
arithmetic mean	27.6	29.8	27.9
standard deviation	± 4.6	± 4.5	± 5.7

Reporting group values	Group D - SAF	Positive Agreement of MAC with ITT	Negative agreement of MAC with ITT
Number of subjects	29	140	140
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	40.0		
standard deviation	± 12.4	±	±
Gender categorical Units: Subjects			
Female	14		
Male	15		

BMI			
Body Mass Index			
Units: kg/m²			
arithmetic mean	26.1		
standard deviation	± 3.2	±	±

Reporting group values	Sensitivity of MAC	Specificity of MAC	Positive Agreement MAC core and MAC repeatability
Number of subjects	63	63	34
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	±
Gender categorical			
Units: Subjects			
Female			
Male			
BMI			
Body Mass Index			
Units: kg/m²			
arithmetic mean			
standard deviation	±	±	±

Reporting group values	Negative Agreement MAC core and MAC repeatability		
Number of subjects	34		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			

Age continuous Units: years arithmetic mean standard deviation	±		
Gender categorical Units: Subjects			
Female Male			
BMI			
Body Mass Index			
Units: kg/m²			
arithmetic mean standard deviation	±		

End points

End points reporting groups

Reporting group title	GHST Sequence A

Reporting group description:

1st Macimorelin-GHST, 2nd Insulin Tolerance Test.
Drug: Macimorelin
macimorelin acetate, 0.5 mg/kg body weight, drinking solution, single dose
Other Names: Macimorelin-GHST (MAC)
Drug: Insulin
Insulin, 0.10 U/kg (0.15 U/kg if BMI > 30 kg/m2), intravenous injection, single dose
Other Names: Insulin Tolerance Test (ITT)

Reporting group title	GHST Sequence B

Reporting group description:

1st Insulin Tolerance Test (ITT), 2nd Macimorelin-GHST (MAC)
Drug: Macimorelin
macimorelin acetate, 0.5 mg/kg body weight, drinking solution, single dose
Other Names:
• Macimorelin-GHST (MAC)
Drug: Insulin
Insulin, 0.10 U/kg (0.15 U/kg if BMI > 30 kg/m2), intravenous injection,
single dose
Other Names:
• Insulin Tolerance Test (ITT)

Subject analysis set title	Group A - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

High likelihood of growth hormone deficiency (GHD):
•Structural hypothalamic or pituitary lesions and low insulin-like growth factor 1 (IGF-1), and/or
•Three or more pituitary hormone deficiencies (PHD) and low IGF-1, or
•Childhood onset GHD with structural lesions and low IGF-1.

Subject analysis set title	Group B - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Intermediate likelihood of GHD:
• Eligible subjects not qualifying for either high or low likelihood (Group A/C)

Subject analysis set title	Group C -SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Low likelihood of GHD:
•One risk factor for GHD only, such as history of distant traumatic brain injury (TBI) or one PHD only with otherwise normal pituitary function or
•Isolated idiopathic childhood onset GHD without additional pituitary deficits

Subject analysis set title	Group D - SAF
Subject analysis set type	Safety analysis

Subject analysis set description:

Healthy control: Healthy subjects matching Group A subjects by sex, age, body mass index (BMI), and estrogen status (females only).

Subject analysis set title	Positive Agreement of MAC with ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Percent positive agreement of MAC with ITT

Subject analysis set title	Negative agreement of MAC with ITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Percent negative agreement of MAC with ITT

Subject analysis set title	Sensitivity of MAC

Subject analysis set type	Per protocol
Subject analysis set description: Group A and Group D subjects	
Subject analysis set title	Specificity of MAC
Subject analysis set type	Per protocol
Subject analysis set description: Group A and Group D subjects	
Subject analysis set title	Positive Agreement MAC core and MAC repeatability
Subject analysis set type	Per protocol
Subject analysis set description: Protocol Amendment 1: had been issued for selected sites in Europe to obtain exploratory data on the repeatability of the MAC in a subset of subjects that had completed the core study. Primary efficacy variable: comparison of peak GH levels following repeated treatments with macimorelin. MAC repeatability was evaluated for overall agreement only. Pre-defined MAC cut-off point GH: 2.8 ng/mL. Data presented: percent positive agreement of MAC core study with MAC repeatability extension.	
Subject analysis set title	Negative Agreement MAC core and MAC repeatability
Subject analysis set type	Per protocol
Subject analysis set description: Protocol Amendment 1: had been issued for selected sites in Europe to obtain exploratory data on the repeatability of the MAC in a subset of subjects that had completed the core study. Primary efficacy variable: comparison of peak GH levels following repeated treatments with macimorelin. MAC repeatability was evaluated for overall agreement only. Pre-defined MAC cut-off point GH: 2.8 ng/mL. Data presented: percent negative agreement of MAC core study with MAC repeatability extension.	

Primary: Percent Positive/ Percent Negative Agreement of Macimorelin-GHST (MAC) With ITT

End point title	Percent Positive/ Percent Negative Agreement of Macimorelin-GHST (MAC) With ITT[1]
End point description: Percent positive agreement (upper limit for crossover interval between both GHSTs); percent negative agreement of Macimorelin-GHST (MAC) with ITT. Pre-defined cut-off point for the Macimorelin GHST (MAC): GH 2.8 ng/mL; cut-off point for the ITT: GH 5.1 mg/mL. Percent positive and negative agreement are defined as co-primary outcome measures. The probability for a "Negative Agreement" equals the sum of the probability of both tests being correct (negative test results for both tests for subjects with "true non-AGHD") and the probability of both tests being wrong (negative test results for both tests for subjects with "true AGHD").	
End point type	Primary
End point timeframe: 8-28 days (time frame between two GHSTs)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: A short statistical analysis description is provided in the End point definition. No statistical testing for a p-value was performed in this test validation study. Therefore, no p-value related information can be entered in the Statistical Analysis section - but without entering a value here, an error message occurs. Furthermore, the trial has a cross-over design: unfortunately, a wrong number of subjects is automatically calculated (280 instead of 140 subjects).

End point values	Positive Agreement of MAC with ITT	Negative agreement of MAC with ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	140[2]	140[3]		
Units: percent				
number (confidence interval 95%)	74.32 (62.84 to 83.78)	93.94 (85.20 to 98.32)		

Notes:

[2] - modified Intention-to-Treat (mITT)

[3] - modified Intention-to-Treat (mITT)

Statistical analyses

No statistical analyses for this end point

Secondary: Sensitivity and Specificity of the MAC, GH: 2.8 ng/mL

End point title	Sensitivity and Specificity of the MAC, GH: 2.8 ng/mL

End point description:

Exploratory evaluation of sensitivity and specificity of the MAC based on GH Peak Levels in Group A and Group D subjects.

End point type	Secondary

End point timeframe:

90 minutes

End point values	Sensitivity of MAC	Specificity of MAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63[4]	63[5]		
Units: percent				
number (not applicable)	87	96		

Notes:

[4] - Group A and Group D subjects

[5] - Group A and Group D subjects

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Agreement MAC Core Study and MAC Repeatability Extension

End point title	Overall Agreement MAC Core Study and MAC Repeatability Extension

End point description:

Amendment no 1 (repeatability extension) had been issued for selected sites in Europe to obtain exploratory data on the repeatability of the MAC in a subset of subjects that had completed the core study. Primary efficacy variable: comparison of peak GH levels following repeated treatments with macimorelin. MAC repeatability was evaluated for overall agreement only. Pre-defined MAC cut-off point GH: 2.8 ng/mL.

End point type	Other pre-specified

End point timeframe:

90 minutes

End point values	Positive Agreement MAC core and MAC repeatability	Negative Agreement MAC core and MAC repeatability		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	34[6]	34[7]		
Units: percent				
number (confidence interval 95%)	88.89 (65.29 to 98.62)	100.00 (79.41 to 100.00)		

Notes:

[6] - All subjects included in the mITT analysis who also participated in the repeatability extension.

[7] - All subjects included in the mITT analysis who also participated in the repeatability extension.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Agreement between MAC and ITT at MAC cut-off point 5.1 ng/mL

End point title	Agreement between MAC and ITT at MAC cut-off point 5.1 ng/mL

End point description:

After this study was found not to have met one of two co-primary endpoints of the confirmatory efficacy analyses, encouraging preliminary results from exploratory analysis suggesting superior performance of the MAC if evaluated at a higher GH cut-off point were discussed with the FDA. It was considered acceptable by the Agency, to include results from exploratory analyses supporting the validity of the MAC at a recommended GH cut-off point.

The exploratory analyses applied the same methodology as used for the planned primary efficacy analyses (incl. agreement between MAC and ITT, estimated sensitivity and specificity for both GHSTs, explored in hierarchical testing). A value of 5.1 ng/mL was finally concluded to be the recommended optimal GH cut-off point for the MAC, with collection of blood samples for GH measurements 45 and 60 minutes after intake of the macimorelin test dose.

End point type	Post-hoc

End point timeframe:

28 days

End point values	Positive Agreement of MAC with ITT	Negative agreement of MAC with ITT		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	139[8]	139[9]		
Units: percent				
number (confidence interval 95%)	83.78 (73.39 to 91.33)	90.77 (80.98 to 96.54)		

Notes:

[8] - Exclusion of data from one subject with suspected non-compliance or dosing error from the mITT.

[9] - Exclusion of data from one subject with suspected non-compliance or dosing error from the mITT.

Statistical analyses

No statistical analyses for this end point

Post-hoc: Sensitivity and Specificity of the MAC, cut-off GH: 5.1 ng/mL

End point title	Sensitivity and Specificity of the MAC, cut-off GH: 5.1 ng/mL

End point description:

Within exploratory post-hoc analyses to determine an optimal GH cut-off point, the same values for sensitivity and specificity in the subset of Group A and Group D subjects were obtained for the recommended new GH cut-off point of 5.1 ng/mL as for the planned analyses at the value of 2.8 ng/mL.

End point type	Post-hoc

End point timeframe:

90 minutes

End point values	Sensitivity of MAC	Specificity of MAC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	63[10]	63[11]		
Units: percent				
number (not applicable)	92	96		

Notes:

[10] - Assuming Group A as 'true' AGHD subjects and Group D as 'true' AGHD negative subjects.

[11] - Assuming Group A as 'true' AGHD subjects and Group D subjects as 'true' AGHD negative subjects.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Throughout the trial, i.e. over a period of ca. 15 months, the subjects were questioned and/or examined by the Investigators or his/her designee for evidence of adverse events. Per subject, the time frame for collection of such data was up to 70 days.

Adverse event reporting additional description:

GHST emergent adverse events (TEAEs): various untoward effects were anticipated to be associated with the GHSTs. For the ITT, this included signs and symptoms associated with the hypoglycemia, which is prerequisite for an appropriate ITT performance. All untowards effects during or after a GHST were documented as an AE.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Macimorelin GHST (MAC) SAF population

Reporting group description:

Macimorelin GHST (MAC): combined safety data from core study and repeatability extension (Amendment 1, European sites only)).
All subjects with at least one macimorelin GHST performed: N=154 (subjects in the repeatability extension: N=34)
All subjects valid for safety (SAF) analysis: N=157 (three subjects were exposed to the ITT only).

Reporting group title	ITT, SAF Population

Reporting group description:

Insulin Tolerance Test (ITT)
All subjects with at least one ITT performed: N=157
All subjects valid for safety (SAF) analysis: N=157

Serious adverse events	Macimorelin GHST (MAC) SAF population	ITT, SAF Population	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 154 (0.65%)	1 / 157 (0.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Upper limp fracture	Additional description: The patient had underwent an ITT on July 5 and the macimorelin GHST on July 12, 2016. On July 13, the patient fell of a ladder accidentally and broke his left arm. Causality reported: unrelated to study treatment.		
subjects affected / exposed	1 / 154 (0.65%)	1 / 157 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Macimorelin GHST (MAC) SAF population	ITT, SAF Population	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 154 (25.32%)	151 / 157 (96.18%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 154 (0.65%)	17 / 157 (10.83%)	
occurrences (all)	1	18	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 154 (3.90%)	43 / 157 (27.39%)	
occurrences (all)	7	48	
Dysgeusia			
subjects affected / exposed	7 / 154 (4.55%)	5 / 157 (3.18%)	
occurrences (all)	7	7	
Headache			
subjects affected / exposed	6 / 154 (3.90%)	15 / 157 (9.55%)	
occurrences (all)	6	16	
Somnolence			
subjects affected / exposed	1 / 154 (0.65%)	57 / 157 (36.31%)	
occurrences (all)	1	62	
Tremor			
subjects affected / exposed	1 / 154 (0.65%)	25 / 157 (15.92%)	
occurrences (all)	1	28	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	6 / 154 (3.90%)	43 / 157 (27.39%)	
occurrences (all)	6	49	
Hunger			
subjects affected / exposed	5 / 154 (3.25%)	46 / 157 (29.30%)	
occurrences (all)	5	51	
Asthenia			
subjects affected / exposed	1 / 154 (0.65%)	30 / 157 (19.11%)	
occurrences (all)	1	32	
Chills			

subjects affected / exposed	1 / 154 (0.65%)	9 / 157 (5.73%)	
occurrences (all)	1	12	
Feeling cold			
subjects affected / exposed	1 / 154 (0.65%)	6 / 157 (3.82%)	
occurrences (all)	1	6	
Feeling hot			
subjects affected / exposed	2 / 154 (1.30%)	44 / 157 (28.03%)	
occurrences (all)	2	50	
Thirst			
subjects affected / exposed	1 / 154 (0.65%)	12 / 157 (7.64%)	
occurrences (all)	1	13	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 154 (3.25%)	21 / 157 (13.38%)	
occurrences (all)	5	22	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	2 / 154 (1.30%)	105 / 157 (66.88%)	
occurrences (all)	2	120	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2015	Amendment 1 - Repeatability Extension This amendment implements a suggestion from a Scientific Advice Procedure with EMA (Procedure No. EMEA/H/SA/FU1/2015/SME/III) on the planned Phase III Trial of macimorelin. In the Final Advice Letter (EMA/CHMP/SAWP/295316/2015, dated 21 May 2015), the Scientific Advice Working Party (SAWP) suggested to assess the reproducibility of the macimorelin GHST, and a "three-way cross-over with two repeat macimorelin tests and one ITT per participant" was suggested, leaving open the choice of other trial design option. The amendment describes the performance of a second macimorelin GHST in subjects that have completed the trial procedures according to the core protocol AEZS-130-052 (furtheron referred to as "core trial") and was implemented at selected trial sites in Europe. A subset of 30 participants who have completed the core trial, 10 subjects each from Group A, B, and C (subjects with high, intermediate, and low AGHD likelihood, respectively) was planned to be retested with macimorelin. No healthy control subjects (Group D) were retested, as a sufficient number of "true test-negative" subjects was included in the retested Group B and C subjects to assess the repeatability of the macimorelin GHST in subjects without AGHD. The additional macimorelin GHST was performed at or after the End-of-trial visit of the core trial to minimize the impact of the amendment on the analysis and reporting of the core trial.
18 February 2016	Amendment 2 was implemented in a Protocol Version 2. The main reason for this Amendment 2 was a refinement of the rules for the inclusion of GHST results in the primary analysis and an extension in the scope of the Data Review Committee (DRC). Like the new task of verifying an investigator's Group assignment of a trial subject, the adjudication of the GHST performance by the DRC had to be done before GH concentration data were available to prevent bias in the qualification of a GHST as "evaluable" or "not evaluable". However, if potentially critical deviations in a GHST procedure would lead to the conservative adjudication of a GHST as "not evaluable", subsequently available GH concentration data would re-qualify a GHST as "evaluable". Under specific conditions, missing values would reasonably be imputed and also allow to re-qualify a GHST as "evaluable", so that the repetition of that GHST would finally not be needed and justifiable. Additional changes related to clarifications of DRC-related procedures, IMP dosage, and three exclusion criteria, as well as the affiliation of the coordinating investigator. Amendment 2 was based on clinical trial protocol version 1.0 and CTP version 2.0 was applicable for all sites participating in the trial. Amendment 2 did not affect Amendment 1 ('Exploratory evaluation of the repeatability of the macimorelin GHST') that remained in place unchanged at all sites participating in that trial extension. For trial sites in France, Amendment 2 replaced the local amendment 1 (19-Nov-2015) which covered Change 4 of Amendment 2. For trial sites in Germany, Amendment 2 replaced a note to file (17-Dec-2015) which covered the clarification provided in Change 7 of Amendment 2.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported