15 November 2018
EMA/CHMP/845216/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Macimorelin Aeterna Zentaris

International non-proprietary name: macimorelin

Procedure No. EMEA/H/C/004660/0000

Note

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

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List of abbreviations

ACTH	adrenocorticotropic hormone
AE	adverse event
AGHD	adult growth hormone deficiency
ALAT	alanine amino transferase (= serum glutamate pyruvate transaminase, SGPT)
ASAT	aspartate amino transferase (= serum glutamate oxalo-acetate transaminase, SGOT)
AUC	area under the curve
AVP	arginine vasopressin (synonyms: antidiuretic hormone / vasopressin)
BMI	Body Mass Index
CI	confidence interval
Cmax	maximum concentration
CRL	Complete Response Letter
CRO	Contract Research Organization
CYP	cytochrome
dL	deciliter [100 mL]
DRC	Data Review Committee
eCRF	electronic Case Report Form(s)
ECG	electrocardiogram
EMA	European Medicines Agency
EOS	End-of-Study
EU	Europe, or European Union, dependent on the context
FDA	Food and Drug Administration
FN	false negative
FP	false positive
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GH	growth hormone
GHD	growth hormone deficiency
GHST	growth hormone stimulation test
GMP	good manufacturing practice
GnRH	gonadotropin releasing hormone
GST	glucagon stimulation test
ICH	International Conference on Harmonization
ICMA	immunochemiluminometric assay
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor 1
IMP	investigational medicinal product
IRB	Institutional Review Board
ITT	insulin tolerance test
ITT RS	insulin tolerance test rescheduled
IUD	intra-uterine device
i.v.	intravenous
IWRS	interactive web-based randomization system
Kg	kilogram
L	liter
LCMS/MS	liquid chromatography-mass spectrometry
LLN	lower limit of normal range
MAC	macimorelin GHST
MAC RS	macimorelin GHST rescheduled
Max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
Mg	milligram
mITT	modified intention-to-treat (population)
mL	milliliter
mmol	millimol
min	minimum
N	number
no.	number

PD	pharmacodynamics
PHD	pituitary hormone deficiencies
PK	pharmacokinetics
PT	preferred term (PT)
Q1, Q3	first quartile, third quartile
ROC	receiver operator characteristics
RS	rescheduled
SAE	Serious Adverse Event
SAF	Safety Population
SAP	statistical analysis plan
Std	Standard Deviation
SOC	system organ class
SOP	standard operating procedures
ST	stimulation test
Tab.	table
TEAE	treatment ('test') emergent adverse event
TBI	traumatic brain injury
Tmax	time of maximum measured concentration
TN	true negative
TP	true positive
TSH	thyroid stimulating hormone
ULN	upper limit of normal range
U	Unit
US/USA	United States of America
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Aeterna Zentaris GmbH submitted on 26 October 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Macimorelin Aeterna Zentaris, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 September 2016.

The applicant applied for the following indication:

Adult growth hormone deficiency (AGHD)
This medicinal product is for diagnostic use only.
Macimorelin Aeterna Zentaris is indicated in adults for evaluating the pituitary gland secretion of growth hormone (GH) in response to an oral dose of the product.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is

composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0105/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0105/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

New active Substance status

The applicant requested the active substance macimorelin acetate contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received Scientific advice from the CHMP:

Scientific advice	date	Area
EMA/CHMP/SAWP/295316/2015	21 May 2015	Quality, Non-Clinical, Clinical
EMEA/CHMP/SAWP/230506/2007	15 November 2007	Quality, Non-Clinical, Clinical

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Martina Weise Co-Rapporteur: Joseph Emmerich

The application was received by the EMA on	26 October 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	16 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	31 August 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	6 September 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	20 September 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	16 October 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	5 November 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Macimorelin Aeterna Zentaris on	15 November 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Macimorelin Aeterna Zentaris is a product for the diagnosis of growth hormone deficiency (GHD) in adults.

2.1.1. Epidemiology

In Europe, data on incidence rates are scarce in GH deficiency (GHD).

The estimated average incidence rate for AGHD in Denmark (Stochholm et al., 2006) was 1.90 (95%CI, 1.77–2.04) in males, and 1.42 (95%CI, 1.31–1.54) in females, both per 100,000, and with an average of 1.65 (95%CI, 1.57–1.75) per 100,000 for the whole population.

This is slightly higher than the published incidence rates for France (1.2 per 100,000) (Sassolas et al., 1999), and data published by The Growth Hormone Research Society (1.0 per 100,000) (Carroll et al., 1998).

2.1.2. Aetiology and pathogenesis

The most common causes of AGHD include a history of childhood-onset growth hormone deficiency, hypothalamic/pituitary diseases, tumors (e.g. pituitary adenoma, carniopharyngioma, non-pituitary intracranial tumors), head trauma, pituitary haemorrhage/ infection, surgery or irradiation to the hypothalamic/pituitary areas.

2.1.3. Clinical presentation, diagnosis

GHD in adult life is associated with increased fat mass, particularly distributed in the truncal region, reduced lean mass, osteopenia, an adverse lipid profile, glucose intolerance, insulin resistance, impaired fibrinolysis, altered cardiac structure and function, reduced exercise capacity, and reduced quality of life

Current published guidelines recommend that evaluation of AGHD be based on clinical findings, medical history and using an appropriate GH stimulation test (GHST) for biochemical confirmation (Ho et.al, 2007). The exception is with patients with $\geq$ 3 pituitary hormone deficiencies and low serum IGF-I levels < -2 standard deviation scores (SDS) in the appropriate clinical context or in patients with congenital/genetic GHD, where the diagnosis of AGHD can be made without requiring stimulatory GH testing. Otherwise, 2 independent GHST are recommended before making this rare diagnosis. The presence of a low IGF-I increases the likelihood that the diagnosis is correct. However, normal IGF-I does not exclude GHD.

All GH stimulation tests are based on the concept that a pharmacological agent stimulates pituitary GH secretion, with peak GH levels detectable by timed frequent serum sampling after administration of the stimulus. The insulin tolerance test, the combined arginine-GH-releasing hormone (ARG-GHRH) test, and the glucagon test are validated GHST in the adult.

The insulin tolerance test (ITT) is currently considered the “gold standard” test for evaluation of AGHD, but requires adequate hypoglycaemia (blood glucose <40 mg/dL) for interpretability of the results. In patients in whom an ITT cannot be performed (contraindicated in patients with ischemic heart disease or seizures, and in the elderly), the glucagon stimulation test (GST) is a safe alternative and has been assessed against the ITT in evaluating GH reserve. The ARG-GHRH test is essentially the arginine test

with improved diagnostic accuracy by combining it with a potent priming agent (a GHRH analogue) in one test, but GHRH is not widely available.

All GHST have limitations with regard to performance characteristic (sensitivity, specificity and/or reproducibility) (Molitch et.al, 2011). Dependency of results on aging, BMI and/or gender may also be an issue. Testing for confirmation of AGHD should only be performed if there is a high pre-test probability, and with the intention to treat if the diagnosis is confirmed.

2.1.4. Management

Once the diagnosis of AGHD is established, GH replacement therapy (subcutaneous injection of somatropin/ recombinant human growth hormone) is usually initiated by an experienced endocrinologist, in particular in patients with severe GHD.

About the product

Macimorelin Aeterna Zentaris is a potent, orally active growth hormone secretagogue (GHS) that is intended for AGHD testing, by measuring the stimulated GH level after an oral dose.

The claimed indication for Macimorelin Aeterna Zentaris was for evaluating the pituitary gland secretion of growth hormone (GH) in response to an oral dose of the product in adults.

The indication approved by the CHMP was for the diagnosis of growth hormone deficiency (GHD) in adults.

The recommended single dose of the reconstituted suspension is 500 micrograms macimorelin per kg body weight.

Type of Application and aspects on development

The applicant sought scientific advice from the CHMP in 2015. This was a follow-up to advice that was given to the original sponsor of the product in 2007.

The advice related to quality, non-clinical development and clinical issues including design of the pivotal study, cut-off points for the growth hormone stimulation tests and statistical acceptance criteria.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as granules for oral suspension in sachets containing 60 mg of macimorelin (as acetate) as active substance.

Other ingredients are: lactose monohydrate, colloidal anhydrous silica, crospovidone type A, saccharin sodium dihydrate and sodium stearyl fumarate.

The product is available in LDPE/Alu/LDPE/paper sachets as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of macimorelin acetate is
2-amino-*N*-[(2*R*)-1-[[(1*R*)-1-formamido-2-(1*H*-indol-3-yl)ethyl]amino]-3-(1*H*-indol-3-yl)-1-oxopropan-

2-yl]-2-methylpropanamide-acetate corresponding to the molecular formula $C_{28}H_{34}N_6O_5$. It has a molecular mass of 534.6 g/mol and the following structure:

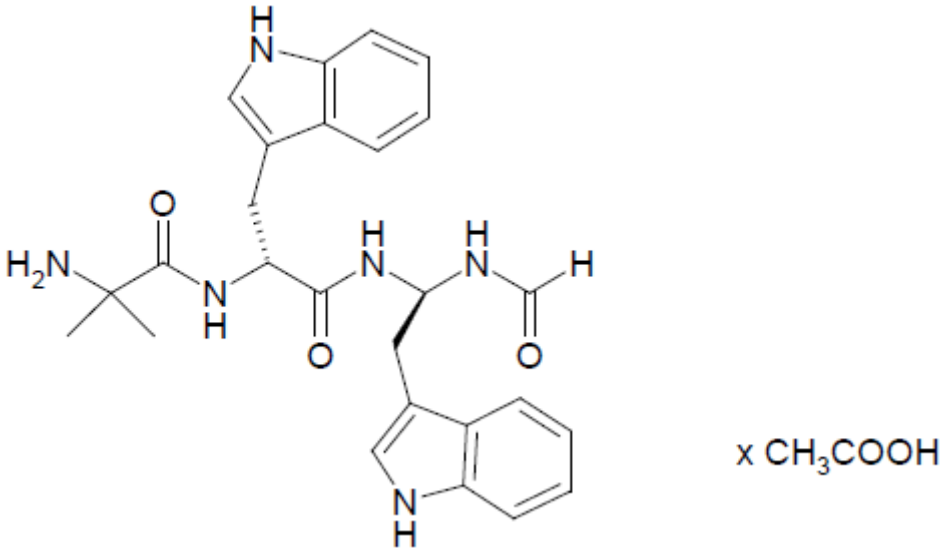


Figure 1: active substance structure. The ratio of the free base to acetate is in the range of 0.8 – 1.1 equivalents.

The chemical structure of macimorelin acetate was elucidated by a combination of ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), mass spectrometry (MS), two dimensional exchange spectroscopy (2D-EXSY), elemental analysis, Fourier transform infrared (FT-IR) spectroscopy, and ultraviolet-visible (UV-Vis) spectroscopy.

The solid state properties of the active substance were measured by X-ray diffraction (XRD), Scanning Electron Microscopy (SEM) and a wet dispersion method for determination of particle size distribution.

The active substance is an off-white to pale yellow, hygroscopic, amorphous powder. Macimorelin acetate is highly soluble in buffered aqueous solutions at different pH values (pH 1 – pH 8).

Macimorelin exhibits stereoisomerism due to the presence of two chiral centres. Enantiomeric purity is controlled routinely by specific optical rotation and capillary electrophoresis. The stereoisomerism of the active substance originates from the starting materials in which the minor enantiomer is controlled by specification.

Polymorphism has not been observed for macimorelin acetate as it is amorphous.

Manufacture, characterisation and process controls

Macimorelin acetate is synthesized in nine main steps which include solution peptide synthesis in six steps, followed by HPLC purification, salt exchange and lyophilisation. Two commercially available well defined starting materials with acceptable specifications are used. Two manufacturers are involved in the manufacture of the active substance. The first is responsible for manufacturing steps 1-5 and the second for steps 6-9.

The nine-step manufacturing process starts from D-tryptophan and 2-aminoisobutyric acid synthesis. During the assessment, additional information was requested regarding the synthesis of D-tryptophan which the applicant had difficulty obtaining due to confidentiality issues. As this information does not impact he positive risk-benefit ratio of the product, it is recommended to provide further details of the synthesis of D-tryptophan (incl. the host microorganism) in order to understand the likely impurities present once it is obtained from the suppliers.

At several stages of the synthesis, reprocessing is optionally performed. Whenever the specified purity levels of the in process controls (IPCs), which mostly involve testing the intermediates by HPLC, are not met, the respective isolation and workup strategy is repeated.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. During the manufacture of macimorelin acetate, two intermediates are isolated and characterized.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance has been changed during development and the minor changes introduced have been presented in sufficient detail and have been justified.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

Specification

The active substance specification includes tests for: description, identity (HPLC, ^{1}H-NMR, specific optical rotation), residual solvents (GC), water content (KF), sulfated ash (Ph. Eur.), heavy metals (USP), related substances (HPLC), chiral purity (capillary electrophoresis), assay, content of acetate (HPLC) and microbial enumeration (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The omission of a routine test for one residual solvent in the active substance has been adequately justified based on the available batch analysis data. A scale-up of the batch size is under development at the time of the MAA with one batch manufactured and 2 additional batches planned for manufacturing. The applicant commits to evaluate the specification limits after the production of three batches with the increased batch size in order to tighten the specification limits where supported by batch data.

The finished product manufacturer, based on the risk assessment considering the risk of water uptake of the active substance during sampling for identity testing, does not test the active substance prior to finished product manufacture. The testing is omitted as the finished product manufacturer is currently unable to close the active substance bottles under argon as provided by the active substance manufacturer. The tests are performed during quality control, where an assay of macimorelin content is performed routinely. This approach was accepted with a recommendation to submit the active substance specification issued by the finished product manufacturer within one year after the approval of this marketing authorisation.

Acceptance limits for content of acetate form part of the active substance specification. Under consideration of batch-to-batch variability and variability of the analytical method, a range has been implemented.

Batch analysis data from 14 pilot to production scale batches of the active substance were provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 2 primary stability and 5 supportive batches of active substance manufactured at commercial scale and approximately a third of the commercial scale, respectively, from the proposed manufacturer stored in the intended commercial package for up to 48 months under long term conditions (2-8 ºC), up to 48 months at 25 ºC / 60% RH, up to 12 months at 30 ºC / 65% RH and up to 6 months at 40 ºC / 75% RH according to the ICH guidelines were provided.

The parameters tested were: appearance, the content of acetate and macimorelin by HPLC, the identification of related substances by HPLC, the water content and examination of the microbial purity (TAMC and TYMC) and the limits are the same as for release. The analytical methods used were the same as for release and were stability indicating

The proposed retest period is regarded as justified for macimorelin acetate.

None of the other samples demonstrated an increase in water content.

Photostability testing following the ICH guideline Q1B was performed on one batch. Exposure to light showed degradation, demonstrating that the active substance is sensitive to light.

Further studies of the degradation pathway have been carried out (storage in the open container at 60 °C / 75% RH for 3 weeks, light exposure equating to double the dose of that requested by ICH Q1B, acidic hydrolysis in 0.1 mol/L HCl for 6 hours, basic hydrolysis in 0.1 mol/L NaOH for 6 hours and oxidation stressed condition in 3% H_2O_2 for 24 hours. The results showed an increase in impurities of up to 8.5 % under all investigated conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months at 2-8 ºC in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as granules for oral suspension in sachets containing 60 mg of macimorelin (as acetate) as active substance. The granules are white to off-white and following dissolution in water prior to administration, the final oral suspension can be described as a “slightly turbid suspension”.

The goal of formulation development was to develop a powder formulation for oral administration containing macimorelin acetate indicated for the diagnosis of growth hormone deficiency in adults. The medicinal product is for diagnostic use only. The dosing is weight-based and the recommended single dose of the reconstituted suspension is 500 micrograms of macimorelin per kg body weight. Macimorelin Aeterna Zentaris granules are to be reconstituted with water and must be used within 30 minutes of preparation.

The acetate salt was chosen as a counter ion for macimorelin during pharmaceutical development in order to enhance the solubility of the active substance while providing good tolerability and safety. The solubility of the active substance was shown not to be a critical parameter in the reconstitution medium (water) or in the gastrointestinal tract.

Macimorelin acetate has a peptide-like structure and is lyophilized after HPLC purification leading to an amorphous compound. The manufacturing process of the active substance results in a narrow range of particle sizes. The influence of particle size distribution of the active substance on the content uniformity of the finished product was not found to be significant.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

Compatibility of macimorelin acetate with each of the excipients was investigated in 1:1 physical mixtures under accelerated conditions (60 °C for 1 week). For crospovidone (type A), colloidal silicon dioxide and sodium stearyl fumarate, no changes in the purity profile compared to the active pharmaceutical ingredient (API) alone were observed. In the presence of saccharin sodium, the amount of unidentified degradation products increases, indicating a chemical reaction under these conditions. However, as the saccharin sodium in the finished product is low, this finding is considered not relevant, which was confirmed by stability data obtained with the finished product under the intended storage conditions. Macimorelin acetate is a hygroscopic compound and the impact of the water content was evaluated. The formation of the impurities was well controlled

An overfill has been justified to compensate for the incomplete emptying of the sachet, as well as the adsorption of the active substance to water-insoluble sodium stearyl fumarate. The amount of macimorelin per sachet and the quantity of added macimorelin acetate in the batch formula is adjusted to compensate for the stoichiometry, i.e. the macimorelin content of the actual macimorelin acetate active substance batch based on the results of assay testing.

The compatibility of macimorelin with reconstitution containers was demonstrated. It was sufficiently justified that a reproducible and accurate dose of the product is delivered under testing conditions which simulate how the product is intended to be used in practice.

In-use stability testing after reconstitution supports the SmPC statement “the suspension must be used within 30 minutes after preparation”.

During clinical development, different formulations and procedures for the preparation of the macimorelin suspension have been used: ‘Formulation 1’, ‘Formulation 2’ and ‘Formulation 3’. The formulation used during Phase III clinical studies (Formulation 3) is the same as that intended for marketing.

Manufacturing process development was initially aimed at finding a formulation which could be filled as a powder mixture into sachets. Early trials established that a homogeneous filling of the powder mixture was not possible due to separation of the components (Formulation 1). To overcome this problem roller compaction and dry granulation steps were introduced in the manufacture of ‘Formulation 2’ and ‘Formulation 3’. Relative bioavailability studies were used to successfully bridge between different clinical formulations.

The primary packaging is LDPE/Alu/LDPE/paper sachets. The materials comply with Ph. Eur. and EC requirements. Due to the hygroscopicity of the API and the potential impact on product stability, a tightly sealed primary package was required. Sachets were evaluated as possible primary package and found to be suitable since they are hermetically sealed. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of five main steps: powder mixing, compaction, dry granulation, mixing of the granules and filling of granules into sachets. The process is considered to be a standard manufacturing process. Critical steps are controlled using an IPC.

A process validation report for 3 consecutive commercial scale batches has been provided. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended

quality in a reproducible manner. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

The omission of a test for water content as an IPC or release test of the finished product was justified by presenting values for the water content of the finished product and with the presented control strategy for avoiding a significant increase of water content in the active substance and in the finished product and was considered acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description of the sachet, content of the sachet and reconstituted suspension (visual), identity (HPLC, UV), average filling quantity (weighing), degradation products (HPLC), assay (HPLC), uniformity of dosage units (Ph. Eur.), concentration after reconstitution (HPLC) and microbiological examination (Ph. Eur.).

The omission of a test for water as release test of the finished product was appropriately justified.

In developing a control strategy for elemental impurities in macimorelin granules for oral solution a risk assessment according to guideline ICH Q3D was performed. For one finished product unit, the predicted level of each investigated elemental impurity relative to the permitted daily exposure (PDE) of the elemental impurity is clearly expected below the 30% control threshold, defined by ICH Q3D. This conclusion is verified by analysing three representative finished product batches. The test results support the omission of elemental impurity testing in the finished product specification.

Experimental results showing that a stirring time of 2 minutes is necessary for sufficient reconstitution of the finished product were provided. The analytical method for determination of total amount of macimorelin in the drinking suspension (undissolved and dissolved) was changed during the procedure from “Average concentration of macimorelin in drinking suspension” to “Average total API amount in drinking suspension” at the request of CHMP. Since it wasn’t possible to fully validate this method during the procedure, the applicant committed to do so post-approval.

The applicant also commits to implement a stirring time of 2 minutes in the new analytical method for determination of the total API amount in drinking suspension. The applicant confirmed that the implementation of this parameter would take place as soon as the corresponding analytical method had been validated.

Based on this justification and the commitment of the applicant, the parameter “reconstitution time” in the release and shelf-life specification of the finished product is omitted.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results were provided for 8 batches manufactured at approximately half the size of the commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from seven batches manufactured at approximately half the size of the commercial scale of the finished product stored for up to 48 months under long term conditions (2-8 ºC), for up to 12 months at 25 ºC / 60% RH, for up to 12 months at 30 ºC / 65% RH and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical or representative (differing in fill weight) to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identity of macimorelin (HPLC and UV), degradation products (HPLC) and content of macimorelin (HPLC). Microbial tests were performed annually and a single batch was tested for content after reconstitution (HPLC) as well. The analytical procedures used are stability indicating.

No significant changes were observed for batches of the product stored at 2-8 °C for a period of 48 months.

Storage at accelerated conditions showed out of specification result at latter time-points.

The observed out of specification results do not pose any concern as the product will be stored under refrigeration.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Compared to the dark control, the light exposed sample demonstrate that the finished product is slightly photosensitive.

Based on available stability data, the proposed shelf-life of 48 months stored in a refrigerator (2 °C - 8 °C in the original package in order to protect from light and moisture as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The instability of the hygroscopic active substance and incompatibility with the excipient lactose in the presence of elevated water content has been addressed during development, resulting in a product which is sufficiently stable. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

Description of post-authorisation measure(s)
1. Quality: A scale-up of the drug substance batch size is under development. It is recommended to evaluate the specification limits after the production of three batches with the increased batch size.
2. Quality: It is recommended to provide information about further details regarding one of the starting materials.
3. Quality: It is recommended to submit within one year after the approval of this marketing authorisation the active substance specification issued by the finished product manufacturer.
4. Quality: It is recommended to implement a new parameter “Average total API amount in drinking suspension” into release and shelf life specification of the drug product, which replaces the parameter “Average concentration of macimorelin in drinking suspension”.
5. Quality: It is recommended to implement a stirring time of 2 minutes into the new analytical method for determination of the total API amount in drinking suspension as soon as the corresponding analytical method had been validated.
6. Quality: It is recommended to perform post-approval validation of the analytical method for determination of the total API amount in drinking suspension.

2.3. Non-clinical aspects

2.3.1. Introduction

Macimorelin acetate (hereafter referred to as macimorelin) is an orally-available ghrelin receptor agonist with growth hormone secretagogue (GHS) activity, which was developed for the diagnosis of adult growth hormone deficiency (AGHD) by evaluating the pituitary gland secretion of growth hormone (GH) in response to a single oral dose of the product.

The pharmacological and physiological properties of ghrelin have been described in the scientific literature (van der Lely et al. 2004). Ghrelin is a 28-amino acid peptide, is mainly produced by the stomach and has GH-releasing activity mediated through binding to the GHS receptor type 1a (GHS-R 1a, a G-protein-coupled receptor. Binding of ghrelin to the GHS-R 1a activates the phospholipase C signaling pathway, leading to increased inositol phosphate turnover and protein kinase C activation, followed by Ca^{2+} release from intracellular stores; GHS-R 1a activation also inhibits K^{+} channels leading to an opening of L-type Ca^{2+} channels.

Ghrelin secretion can be stimulated by fasting, by insulin-induced hypoglycemia, by leptin administration, and it can be inhibited by glucose. Ghrelin has activities including hypothalamic effects that result in stimulation of prolactin (PRL), ACTH, GH and AVP secretion and inhibition of gonadotropin secretion, inhibitory influence on the pituitary gonadal axis, increase of appetite and body weight (orexigenic action, positive energy balance), influence on sleep and behavior (anxiogenic activity), stimulation of gastric motility and acid secretion, inhibition of pancreatic exocrine function, inhibition of insulin secretion from pancreatic ß-cells thereby increasing plasma glucose concentration, a role in adipogenesis, cardio-protective effects (improving myocardial contractility and inducing vasorelaxation), and modulation of proliferation of neoplastic cells as well as of the immune system (anti-proliferative effects).

2.3.2. Pharmacology

Primary pharmacodynamic studies

In-vitro

The binding affinity of macimorelin to the human GHS-receptor, was determined in competition binding assays. Membranes containing the GHS-receptor were prepared from human pituitary gland and hypothalamus and based on their ability to displace ^{125}I-labeled ghrelin from the binding sites, the following IC_{50} values were obtained (in nM): human ghrelin 10.2, hexarelin 12.3, and macimorelin 15.6, (Broglio et al. 2002).

The IC_{50} values for binding of macimorelin were 22.9 nM for the human pituitary GHS receptor and 123 nM for the cloned hGHS-R 1a receptor transiently expressed in LLC PK-1 cells (Guerlavais et al. 2003).

Binding and functional activity for the human, rat and mouse ghrelin receptors, Study 8100_2010_807

This study aimed at confirming the affinity binding of macimorelin to human GHS-R1A and to demonstrate its functional ghrelin agonistic activity in various cell based assay systems (calcium release, induction of CRE-dependent reporter gene expression (CRE/Luc), ß-arrestin recruitment and IP-3 generation).

Data were calculated in % efficacy according to cells treated with saturating concentrations of ghrelin as positive, and non-treated cells as negative control. EC_{50} values are reported in **Table 1**.

Table 1. Macimorelin ghrelin agonistic activity for the human, rat and mouse ghrelin Receptor (Study 8100_2010_807)

Ghrelin Receptor	Human				Rat			Mouse
Assay	Competitive Binding	Calcium Release	CRE/Luc	ß-Arrestin	Calcium Release	CRE/Luc	IP-One	Calcium Release
EC50 [µM]	0.0133	0.0009 ± 0.0003	0.0084 ± 0.0016	0.0022 ± 0.0001	0.0012 ± 0.0001	0.0052	0.0017	0.0016 ± 0.0001

Single EC_{50} or mean EC_{50} values +/- SEM are shown of up to three independent experiments performed in quadruplicate measurements. All assay systems employed make use of recombinant cell lines stably overexpressing the human, rat or mouse ghrelin receptor. Competitive binding and different functional assays have been conducted, i.e. calcium release (calcium release), CRE-dependent luciferase reporter gene expression (CRE/Luc), ß-Arrestin recruitment (ß-Arrestin) and IP-3 generation (IP-One).

In vitro activity studies of macimorelin synthesis by products, impurities, stereosimers and degradation products, Study 8100_2014_997

The potential agonistic ghrelin activity of macimorelin synthesis by products, impurities, stereoisomers and degradation products were investigated in two functional assays, the CRE/Luc induction test and the calcium release assay. All data were calculated in % efficacy according to cells treated with saturating concentrations of ghrelin as positive, and non-treated cells as negative control.

To exclude potential antagonistic activities, the reporter cell line was stimulated with 10 nM Ghrelin for four hours together with the test compounds in the presence of Rolipram, a phosphodiesterase inhibitor. Neither macimorelin, nor any of the assessed byproducts, impurities, stereoisomers and degradation products showed significant antagonistic activity. The EC_{50} values could not be determined, since the maximum effect at the highest test concentration of 31.6 µM was below 50%.

In-vivo

In rats, s.c. administration of 300 µg/kg macimorelin or 300 µg/kg hexarelin increased GH plasma concentrations to a similar extent (Broglio et al. 2002).

In dogs, macimorelin, ibutamoren (MK-677, reference compound) and hexarelin were orally administered each at a dose of 1 mg/kg. Whereas hexarelin was ineffective, both macimorelin and ibutamoren stimulated GH secretion to a comparable extent (Guerlavais et al. 2003).

Secondary pharmacodynamic studies

Potential off-targets of macimorelin were investigated in an *in vitro* study using the commercially available Cerep Eurofins Diversity Profile. Macimorelin was tested at a concentration of 10 µM (representing approx. 500-fold of the clinical total C_{max}) in duplicate.

Among the 96 targets tested, only 4 targets showed a mean inhibition >25%. Follow-up studies to determine the IC_{50} values for these targets are currently ongoing.

Safety pharmacology programme

An overview of the safety pharmacology studies with macimorelin is presented in **Table 2**.

Table 2. Overview of safety pharmacology studies performed with macimorelin

Systems Evaluated / Study No / GLP	Test System / Test conditions	Duration / Doses	Noteworthy Findings
Central nervous system			
Irwin profile test/ AA32756 (GLP)	Rat (Wistar) 6M/group / Evaluation at 0.5, 1, 2, 5 and 24 hours after dosing	Single dose IV 1, 10 and 30 mg/kg	**≥ 10 :** ↓ rectal temperature Dose-dependent impairment of behaviour: subdued attitude with signs of hypoactivity, limp and sleepy posture, decreased arousal, exploratory and grooming activities. All neurobehavioral signs appeared between 0.5 and 1 hour and disappeared from the 2 hour time-point Dose-dependent effects on eating behaviour: frequent eating and drinking. **NOAEL = 1 mg/kg**
Cardiovascular system			
Binding to hERG channel/ 8100_2010_808 (Non-GLP)	Membrane preparation of hERG channel overexpressing SF9 cells *In vitro*	Up to 56.8 µM	No binding to the hERG channel protein
Effect of macimorelin on hERG/ 8100_2012_883	HEK293 cells (n=3 per group) *In vitro*	10 and 300 µM	Macimorelin did not induce any effect on hERG currents. Macimorelin inhibited hERG current by 1.2 ± 0.5 % at 10 µM and 1.9 ± 0.3 % at 300 µM versus 1.4 ± 0.5 %in control. **IC_{50} >300µM**

<table>
<tr><th>Systems Evaluated / Study No / GLP</th><th>Test System / Test conditions</th><th>Duration / Doses</th><th>Noteworthy Findings</th></tr>
<tr><td>(GLP)</td><td></td><td></td><td></td></tr>
<tr><td>Hemo and pulmodynamics evaluation/ AA34941 (GLP)</td><td>Dog beagle
Anaesthetized
6M</td><td>IV
escalating doses on one day with a minimum of 30 min in between each dose
0.3, 1, 10 and 30 mg/kg</td><td>1 :
Transient change in the breathing patterns in one animal (10 min post-treatment)
10 :
<u>Pulmodynamic parameters</u> : severe ↑ respiratory rate and minute volume (marked in the first 5 min),
Moderate ↓ tidial volume, inspiratory time and expiratory time.
Slight ↑ pulmonary resistance (during the first 5 min) although lung compliance was slightly ↓ (for about 10 min post-treatment)
<u>Cardiovascular parameters</u>: slight ↓ arterial BP, moderate ↑ carotid BF, ↓ carotid vascular resistance followed by a slight rebound (during the first 5 minutes post treatment).
This hypotensive episode was associated light and transient baroreflex-mediated tachycardia and, paradoxically, by a sustained ↓ in left ventricular dP/dt max reflecting a negative inotropic effect on myocardial contractility
30 :
Cardiovascular arrest in one animal. Death preceded by severe toxic signs consisting in convulsive spasms and tremors. The other animal also demonstrated early episodes of convulsions and tremors associated with hypersalivation and emesis.

Exposure : 5 males 1 mg/kg
<table>
<tr><td>Animal no</td><td>3051</td><td>3052</td><td>3053</td><td>3054</td><td>3056</td><td>Mean or range</td></tr>
<tr><td>T_{max} (h)</td><td>5</td><td>1</td><td>1</td><td>1</td><td>1</td><td>1 to 5</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>3385</td><td>9976</td><td>5433</td><td>3683</td><td>6136</td><td>5722</td></tr>
</table>
</td></tr>
<tr><td colspan="4">Respiratory system</td></tr>
<tr><td>Respiratory functions
AA32757 / (GLP)</td><td>Rat 8M/group
Plethysmography chambers
<u>Examination</u> :
mortality, clinical signs, respiratory function</td><td>IV
1, 10 and 30 mg/kg</td><td>≥ 10 : dose-dependent effects on respiratory function
↑ respiratory rate (between 30 and 60 minutes post-dosing),
↑ peak expiratory and inspiratory flow (during the first 75 min post-dosing)
↑ tidial volume and minute volume (during the first 90 min after treatment)
30 : ↓
expiratory time (during the first 45 min)</td></tr>
<tr><td colspan="4">Other</td></tr>
<tr><td>Adverse effect</td><td>Standardized</td><td>30 mg/kg</td><td>Moderate ↓ in systolic BP and heart rate in normotensive</td></tr>
</table>

Systems Evaluated / Study No / GLP	Test System / Test conditions	Duration / Doses	Noteworthy Findings
profiling/ AA32756/ (Non-GLP)	adverse event profiling in 3-5 animals (mice, rats, guinea pigs) per test or tissue	oral 30 µM *in vitro*	rats (at 30 min post dose). While the values were normal at 1 h time point, values for systolic BP were moderately ↑ 2h after administration
Histamine release/ 8100_2010_811 (Non-GLP)	Rat RBL-2H3 cells *In vitro*	88.8 and 177.5 µM	No evidence of histamine release.

BP: blood pressure/ BF: blood flow

In order to assess whether macimorelin exerts delayed effects on the cardiac ion channels hERG and Nav1.5, the *in vitro* effect of macimorelin on these channels in HEK293 cells was assessed after 5 minutes and 4 hours treatment (Study 180527.BFA). For this purpose, cells were either loaded directly into wells of the Population Patch ClampTM (PPC) planar electrode and incubated for 5 min with the test items, or preincubated for 4 h on an orbital shaker and the loaded into the wells of the PPC planar electrode.. For hNav1.5 two voltage test pulses TP1 (tonic inhibition) and TP2 (inactivated state inhibition) were applied.

The effects of macimorelin and of the reference compound anamorelin were tested over a concentration range of 0.1 – 300 µM. The positive controls for the hNav1.5 assay were Lidocaine (1 – 3000 µM) and Amiodarone (0.01 – 30 µM) for the 5 min exposure and Lidocaine (150 µM) as well as Amiodarone (0.01 – 10 µM) for the 4 h exposure. For the hERG assay the positive controls were Cisapride (0.001 – 3 µM) and Amiodarone (0.01 - 30 µM) for the 5 min exposure and Cisapride (0.5 µM) as well as Amiodarone (0.01 – 10 µM) for the 4 h exposure.

The IC_{50} values of hERG and Nav1.5 channel inhibition with the test article and the reference compounds / controls are presented in **Table 3**.

Table 3. IC_{50} Values for hERG and Nav1.5 channel inhibition with macimorelin and reference compounds / positive controls in HEK 293 cells (Study 180527.BFA)

Test Item	Short Term (5 min) IC50 [µM]			Long Term (4 h) IC50 [µM]		
		Nav1.5			Nav1.5	
	hERG	TP1	TP2	hERG	TP1	TP2
Macimorelin	>300	>300	>300	>300	>300	>300
Anamorelin	16.35	103.86	81.69	50.25	20.42	19.45
Amiodarone	1.01	>30	>30	1.13	6.38	2.25
Cisapride	0.011	-	-	<0.5	-	-
Lidocaine	-	383.38	14.00	-	>150	<150

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions with macimorelin were submitted.

2.3.3. Pharmacokinetics

Absorption

In vitro permeability across Caco-2 cell monolayers

The bi-directional permeability of macimorelin was investigated in Caco-2 cells over a concentration range of 2.5 – 1000 µM (Study 8100_2013_950). The apparent permeability (Papp) values for macimorelin were similar across the concentration range and the mean values were 1.33 ± 0.19 cm/s $x10^{-6}$ for the a→b direction, and 2.37 ± 0.36 cm/s $x10^{-6}$ for the b→a direction.

Single dose studies

The pharmacokinetic profile of macimorelin after oral or iv administration of a single dose was investigated 3 studies in Han Wistar rats (**Table 4**).

Table 4. Summary of single dose PK parameters (p. os and i.v.) in Han Wistar rats

Study ID/ number/ sex/dose	Dose Level (mg/k	AUC_{0-6h} (ngxh/mL)		C_{max} (ng/mL)		t_{max} (h)	
		M	F	M	F	M	F
AA33729 9/sex/dose/group	0.5 (po)	NC	NC	NC	NC	NC	NC
	5 (po)	0.84*	0.80**	0.58	0.45	0.5	1.0
	50 (po)	9.14	12.4	3.29	8.56	0.5	0.25
	50 (iv)	23800	25500	24400	38700	--	--
2732/003 6/sex/ group	50 (po)	13.4	11.9	5.15	5.17	1.0	0.25
	100 (po)	16.2	15.8	6.48	6.87	0.5	0.5
	250 (po)	40.1	34.3	13.6	13.1	0.5	0.5
	500 (po)	71.6	93.0	74.2	55.7	0.25	0.5
	1000 (po)	118	213	110	369	0.25	0.25
8100-2011-845 9/sex/group	1	65.0	57.2	279	215	0.083	0.083
	3	190	224	747	701	0.083	0.083
	10 (iv)	1490	1330	3670	2780	0.083	0.083
	30 (iv)	7100	6080	14500	12900	0.083	0.083

* AUC_{0-4h} was calculated instead of AUC_{0-6h}
** AUC_{0-2h} was calculated instead of AUC_{0-6h}
NC – not calculated
T_{max} after iv dosing corresponds to the first sampling time point

Macimorelin was also administered to beagle dogs via either the oral (gavage) or i.v. (bolus) route and a summary of these results are presented in **Table 5**.

Table 5. Summary of single dose PK parameters (po and iv) in Beagle dogs

Study	Dose Level (mg/k	AUC0-8 h		Cmax		tmax (h)	
		M	F	M	F	M	F
AA33730 1/sex/dose	0.5 (po)	1.3*	1.3**	0.6	0.9	1.0	1.0
	10 (po)	132	107	69.3	22.0	0.5	1.0
	40 (po)	413	301	132	74.6	2.0	1.0
	0.5 (iv)	134	178	133	179	0.25	0.25
	10 (iv)	5440	6860	5900	7510	0.25	0.25
	40 (iv)	53400	52000	47300	46800	0.25	0.25

* AUC0-4h was calculated instead of AUC0-6h
** AUC0-2h was calculated instead of AUC0-6h
Tmax after i.v. dosing corresponds to the first sampling time point

Repeat dose (oral route)

The pharmacokinetics after repeated dosing was studied in rats and dogs as part of the repeat dose toxicity studies. An overview of TK results from the two pivotal repeat-dose toxicity studies is provided in **Table 6**.

Table 6. Toxicokinetics of macimorelin after repeated oral administration

Study ID	Species number/ sex/dose	Dose	Sampling time	$AUC_{0\text{-last}}$ (ng.h/mL)		C_{max} (ng/mL)		T_{max} (h)		$t_{1/2}$ (h)	
				M	F	M	F	M	F	M	F
1502-002	Rat 10/sex/ dose	250	Day 1	28.8	40.2	24.1	168	0.25	0.17	NC	NC
			Day 27	13.6	152	13.4	939	0.25	0.17	2.16	NC
		500	Day 1	63.7	90.0	71.5	125	0.17	0.17	NC	1.09
			Day 27	45.0	260	31.2	1320	0.25	0.17	NC	1.11
		1000	Day 1	322	280	441	493	0.25	0.17	1.13	NC
			Day 27	163	719	256	2080	0.25	0.25	1.82	1.35
1502-001	Dog 4/sex/dose	25	Day 1	325	433	313	386	0.25	0.50	1.9	1.61
			Day 28	197	201	146	173	0.35	0.70	1.95	1.89
		50	Day 1	388	444	466	535	0.39	0.29	3.39	NC
			Day 28	334	465	354	368	0.35	0.27	3.31	2.37
		100	Day 1	1530	1310	1740	1430	0.35	0.35	NC	2.56
			Day 28	1030	1830	868	1620	0.29	0.64	2.73	2.36

Distribution

Plasma protein binding studies for macimorelin were conducted for rat, dog and human plasma by equilibrium dialysis (Study 100044583). The results of this study are summarized in **Table 7.**

Table 7. Plasma protein binding of macimorelin in rat, dog and human plasma (Study 100044583)

Species	Protein binding [%]*				Mean [%]*
Test concentration [µM]	0.01	0.1	1	10	
Rat	nd	57	55	62	58
Dog	nd	68	66	69	68
Human	nd	78	68	62	nc

*: rounded values
nd: not detectable, the assay did not yield acceptable results due to analytical limitations
nc: not calculated, due to the apparent concentration dependent protein binding, a mean value was not calculated

Metabolism and Excretion

In vitro liver metabolism

The *in vitro* phase I metabolism of macimorelin was investigated using pooled male and pooled female human, rat, mouse and dog liver microsomes (Study 2012-01).

Macimorelin was quickly metabolized by hepatic microsomal CYPs in a NADPH dependent manner with 18.0 % of macimorelin remaining after one hour of incubation at 37 °C in mouse liver microsomes. In microsomes of other species macimorelin was determined to be more stable with 47.2 % (human), 50.7 % (rat) and 61.6 % (dog) remaining, respectively, clearly showing species dependency of Phase I metabolism.

Phase II metabolism was investigated *in vitro* in mixed-gender human S9 fractions in the presence and absence of cofactors required for cytochrome P450 enzymes (NADPH) or transferases (UDPGA, GSH, PAPS) *(Study 2012-01).* No evidence of contribution of Phase II enzymes to the overall metabolism of macimorelin was found.

CYP identification of macimorelin metabolism was performed using two independent methods, chemical inhibition in human liver microsomes and recombinant human CYPs enzymes (Study 2012-01). Both experiments demonstrated that macimorelin is mainly metabolized by CYP3A4.

Excretion

No excretion studies with macimorelin were submitted.

Pharmacokinetic drug interactions

In vitro Cytochrome P450 Induction

The ability of macimorelin to induce increases in the mRNA levels of the P450 isozymes CYP1A2, CYP2B6 and CYP3A4/5 was assessed using primary cultures of cryopreserved human hepatocytes. At concentrations of $\geq$ 10 µM, macimorelin showed concentration-dependent induction of both CYP2B6 and CYP3A4 (up to 4.4 and 3.7

induction values). However, these values were low compared to the prototypical inducers (phenobarbital for CYP2B6, rifampicin for CYP3A4), and no clear induction was observed at a concentration of 3.16 µM macimorelin, which is >100-fold the mean C_{max} values for macimorelin observed at clinically relevant doses in humans. Macimorelin did not induce CYP1A2.

Pgp inhibition *in vitro*

The ability of macimorelin to inhibit the ATPase activity of P-glycoprotein (Pgp) was assessed using Pgp over-expressing SF9 cell membrane preparations in the presence of ATP and the Pgp substrate verapamil. Macimorelin at test concentrations of up to 88.8 µM did not inhibit Pgp ATPase activity.

2.3.4. Toxicology

Single dose toxicity

One single dose toxicity study following intravenous administration of macimorelin was performed in CD rats (Study R14810).

There was no mortality observed in any dose group. The first clinical changes were sedation and shallow breathing observed in animals treated at the high dose (60 mg/kg) immediately after injection, followed by hypoactivity, piloerection, hunched posture and blood in urine. Animals treated at 45 mg/kg showed sedation immediately after dosing and later hypoactivity and piloerection. Recovery was achieved in the animals within one week of treatment. At necropsy, no noteworthy macroscopic changes were observed in any dose group.

Repeat dose toxicity

Study R14828

Macimorelin was administered once per day for two consecutive weeks intravenously (IV) to Spargue Dawley rats (4/sex/group) at doses of 0, 3, 10 and 30 mg/kg.

There was no mortality at any dose group. The main clinical symptoms were sedation/hypoactivity, ear redness and blood in the urine of animals dosed at 10 and 30 mg/kg and tachypnea in the 30 mg/kg group only. At necropsy, a slight increase in mean pituitary weight was observed at doses of 10 and 30 mg/kg without histopathological findings. The NOAEL was 3 mg/kg.

Study 2732/008

Macimorelin was given by oral gavage at doses of 50, 250 and 1000 mg/kg to Han Wistar rats (3/sex/group). Macimorelin was well tolerated and produced no signs of systemic toxicity. Toxicokinetic evaluation demonstrated dose-dependent exposure.

Study AA32387

Macimorelin was given by oral gavage at doses of 10, 50 and 150 mg/kg to Wistar rats (5/sex/group) for 14 consecutive days. 6M and 6F per dose group served as satellite animals for toxicokinetics. No mortality occurred during the study. No clinical signs of toxicity were observed. Toxicokinetic evaluation confirmed rapid absorption with dose-dependent exposure.

Study 1502-002

Macimorelin was given by oral gavage at doses of 0, 250, 500 and 1000 mg/kg to CD rats (10/sex/group) for at least 27 consecutive days. During week 1, one animal at 500 mg.kg/day died following dose

administration. However, the incident was considered not to be associated with the test article. All other animals survived until the scheduled termination interval. The toxicology evaluation did not identify any test article-related findings. Therefore, the NOAEL was determined to be greater than or equal to 1000 mg/kg/day.

Toxikokinetic results from this study are presented in **Table 8**.

Study AA32386

The maximum tolerated dose (MTD) by iv, was investigated in beagles dogs in this study in two phases. In phase 1, single ascending doses were administered up to 60 mg/kg. In phase 2, animals were treated for 7 days at the dose level of 40 mg/kg. The observed clinical signs were mainly hypersalivation, redness of mucosa, vomiting and head shaking during and/or after injection. At the higher doses, unsteady gait or poor motor coordination, tremors, stiffness of hindlimbs, abdominal breathing, subdued behaviour and vomiting were observed in a dose-related manner.

Macimorelin was also given by oral gavage at escalating doses of 5, 20, 50, 100 and 200 mg/kg to 1 male beagle dog. Each dose was administered on 2 consecutive days for a total of 10 days of treatment. Macimorelin was well tolerated and produced no signs of systemic toxicity. Toxicokinetic evaluation demonstrated dose-related exposure.

Study 2732/007

Macimorelin was given for a total of 5 days by oral gavage at daily escalating doses of 50, 100, 250, 500 and 1000 mg/kg to 2 male and 2 female beagle dogs/dose level.

Administration up to 1000 mg/kg/day was well tolerated except for vomiting which was observed immediately or 0.25 up to 1 hour post-dose.

Systemic exposure generally increased with the dose.

Study 2732/009

One beagle dog per sex and group received 0, 50, 250 or 1000 mg/kg macimorelin for five days.

Systemic exposure of macimorelin was dose related, being generally sub-proportional upon initial dosing and becoming supra-proportional upon repeated dosing. Macimorelin administration resulted in a treatment related increase in growth hormone levels in the dog, although the response seen at 1000 mg/kg/day was less than that seen at 50 mg/kg/day. Maximal growth hormone response occurred within 1 hour of dosing, and levels were similar to the control group by 8 hours post-dose in most animals receiving macimorelin.

Sporadic incidences of emesis (mostly immediately post-dose on Day 1) were seen in animals given 250 or 1000 mg/kg/day and soft/liquid or pale faeces were seen in animals given 50, 250 or 1000 mg/kg/day.

Study 1502-001

Macimorelin was given by oral gavage for 28 consecutive days at doses of 25, 50 and 100 mg/kg to 4 male and 4 female beagle dogs/ dose level.

All animals survived until the schedule termination interval. The toxicology evaluation did not identify any test article-related findings. All doses were well tolerated, and the NOAEL was determined to be greater than or equal to 100 mg/kg/day.

Toxikokinetic results from this study are presented in **Table xx**.

- **Toxicokinetics**

Table 8 summarises the exposures and safety margins in the two pivotal toxicology studies in rats and dogs.

Table 8. Calculation of exposure margins for pivotal toxicity studies in relation to the exposure in humans at the anticipated dose of 0.5 mg/kg body weight

Study	Mean AUC [ngxh/ml]	Exposure margin	Mean Cmax [ng/ml]	Exposure margin
4-week toxicity in rats[1,2]	371	16x	816	73x
4-week toxicity in dogs[3]	944	41x	925	82x
Clinical study AEZS-130-047[4]	23.21		11.24	

[1] *Mean of AUC_{0-6h} and C_{max} values on days 1 and 27 (males and females) of high dose group (1000 mg/kg)*

[2] *It is of note, that in female rats variability between individual animals occasionally was extremely high. This variability was mainly observed on day 27. However, verification of bioanalytical raw data did not indicate any evidence for analytical errors. All suspect values were confirmed by re-analysis, and therefore not excluded.*

[3] *Mean of AUC_{0-8h} and C_{max} values on days 1 and 28 (males and females) of high dose group (100 mg/kg)*

[4] *Mean of AUC_{0-6h} and C_{max} values (males and females, 48 subjects) at 0.5 mg/kg dose*

Plasma protein binding studies for macimorelin by equilibrium dialysis were also performed. The results of this study are summarized in **Table 9**.

Table 9. Plasma protein binding of macimorelin in rat, dog and human plasma

Species	Protein binding [%]*				Mean [%]*
Test concentration [µM]	0.01	0.1	1	10	
Rat	nd	57	55	62	58
Dog	nd	68	66	69	68
Human	nd	78	68	62	nc

*: rounded values
nd: not detectable, the assay did not yield acceptable results due to analytical limitations
nc: not calculated, due to the apparent concentration dependent protein binding, a mean value was not calculated

The effective free plasma concentration ($C_{max,u}$) in humans (C_{max} = 11.2 ng/ml in clinical study AEZS-130-047) can be calculated as follows: $C_{max,u}$ = Clinical C_{max} x (fraction unbound) = 11.2 ng/ml x 0.22 = 2.5 ng/ml.

If the effective unbound plasma concentration of macimorelin in humans is compared to the unbound plasma concentrations obtained at the highest tested doses in the pivotal toxicity studies performed with macimorelin in rats and dogs the calculated exposure margins for the unbound C_{max} values increased to 137x for rats and 118x for dogs. Similarly, exposure margins for unbound AUC increased to 15x and 29x in rats and dogs respectively.

Genotoxicity

A summary of the studies conducted to evaluate the genotoxicity of macimorelin is presented in **Table 10**.

Table 10. Overview of *in vitro* genotoxicity studies performed with macimorelin

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria/ R14830/ GLP	Salmonella strains TA98, TA100, TA1535, TA1537 and TA102	5, 15, 50, 150, 500, 5000 µg/plate +/- S9	negative
Gene mutations in mammalian cells/ VV0344/ GLP	Mouse Lymphoma TK +/- cells	+S9: up to 1800 µg/ml - S9: up to 1700 µg/ml	negative
Micronucleus assay *in vitro*/ 8100_2010_810/ Non-GLP	CHO-K1 cells using the commercial MicroFlow© assay kit	Up to 53.3 µM	negative

Carcinogenicity

No carcinogenicity studies were submitted.

Reproduction Toxicity

No reproductive and developmental toxicity studies were submitted.

2.3.5. Ecotoxicity / environmental risk assessment

Table 11. Summary of main study results

Substance (INN / Invented Name): Macimorelin acetate			
CAS-number (if available): 945212-59-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 117 OECD 107	0.72 (pH = 2.0) 0.73 (pH = 4.0) 1.05 (pH = 7.4) 0.66(pH unknown)	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.000685	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

2.3.6. Discussion on non-clinical aspects

The binding affinity of macimorelin towards the human pituitary GHS receptor (IC_{50}: 13.3 - 22.9 nM) and the cloned hGHS-R1a receptor transiently expressed in LLC PK-1 cells (IC_{50}: 123 nM) was similar to that of the natural ligand ghrelin. Lower EC_{50} values for macimorelin (0.9 – 8.4 nM) were obtained in 3

functional assays (calcium release, induction of CRE-dependent reporter gene expression and ß-arrestin recruitment) in GHS-R 1a-expressing cell lines. These differences in the EC_{50} values are similar to those that have been observed in a study for ghrelin and several ghrelin agonists in different assays for the ghrelin receptor (Holst *et al.*, 2005). In that study, the ghrelin receptor agonists binding affinity did not correlate to potency in functional assays, nor was there a trend that the EC_{50} values in functional assays were lower than the K_d for the binding assay. Therefore there is no evidence that the GSHR1a has a receptor reserve.

Ghrelin has lower efficacy to activate the ghrelin receptor than the synthetic ligands (like macimorelin) and, therefore, ghrelin is a partial agonist (Bennett et al. 2009). The binding sites of the endogenous agonist ghrelin overlap with those of the growth hormone secretagogues and growth hormone-releasing peptides. The ghrelin receptor functions as a homo-dimer, where ghrelin binding occurs only in 1 subunit. Both growth hormone-releasing peptides and small-molecule growth hormone secretagogues act as agonists at the ghrelin receptor and are “ago-allosteric” ligands at the ghrelin receptor because, in addition to producing direct activation of the receptor, when co-administered with ghrelin such ligands increase the maximum efficacy of ghrelin (Holst et al. 2005).

In comparison to macimorelin, synthesis by-products, impurities, stereoisomers and degradation products show reduced or no agonistic activity in mouse LTK-cells overexpressing the human ghrelin receptor.

In secondary pharmacodynamic studies, macimorelin showed only limited inhibitory activity for 4 out of the 96 targets investigated at a concentration much higher (approx. 500-fold) than the clinical C_{max} and therefore these observed effects are unlikely to be relevant for the proposed indication

In safety pharmacology studies performed *in vitro*, macimorelin did not inhibit hERG or Nav1.5 currents at micro-molar concentrations. In anaesthetized dogs after i.v. administration of macimorelin ECG parameters (especially QT intervals) were not markedly affected by macimorelin. This is in contrast with findings in humans (see clinical section). At an IV dose of 30 mg/kg macimorelin, cardiovascular and respiratory effects were observed. The exposure of the animals after IV administration is very high compared to the oral route (due to the low oral bioavailability) so these findings are most likely not relevant for human use of macimorelin.

Since QT prolongation was observed in patients with a temporal delay compared to Cmax, the Applicant submitted another *in-vitro* study to evaluate longer-term effects of macimorelin on human cardiac ion channels. In this study, both short term (5 min) and long term (4 hour) treatments with macimorelin had no significant effect on hERG and Nav1.5 channel currents. Positive controls produced concentration dependent inhibition of hERG and Nav1.5 channel currents with more than 50% inhibition at the highest test concentrations.

In the *in vitro* permeability assays the efflux ratio of Papp values (efflux/influx) of 1.8 ± 0.3 indicates only moderate efflux.

In study AA33729 pharmacokinetics and absolute bioavailability of macimorelin was assessed in rats (n=9 per sex) following single oral administration at doses of 0.5, 5 and 50 mg/kg or intravenous (bolus) administration at a dose of 50 mg/kg. In parallel, stimulation of GH release was assessed following oral and intravenous administration in comparison to basal levels at day -1.

Macimorelin is quickly absorbed after oral administration but the oral bioavailability is low, below 1% in rats and around 0.5 to 2.5% in dogs.

In rats and dogs, protein binding did not change significantly with the concentration. The mean plasma protein binding over the tested concentration range was 58% in rats and 68% in dogs, corresponding to an unbound fraction of 42% and 32%, respectively.

Although sufficient exposure in the toxicology studies was demonstrated by toxicokinetic data, no pharmacodynamic effects were observed in the rat studies. Macimorelin is a ghrelin agonist, and in humans ghrelin affects appetite and body composition and leads to growth hormone (GH) release. Increasing plasma GH levels were not observed in rats and macimorelin did not affect body weight and food consumption. It is possible that the handling of the animals as well as the blood sampling procedure under anesthesia on day -1 and day 0 most likely induced suppression of growth hormone release and /or induction of erratic release of GH at individual time points. Anesthetics as well as stress are known to influence GH secretion in rats (and in other species) (Grealy and O'Donnell, 1991; Takahashi *et al.*, 1971; Terry *et al.*, 1976). Further, it should be noted that the animals were not fasted. Since food intake has a direct effect on GH levels, it is conceivable that this also had an impact on the pharmacodynamic assessment.

At very high exposure, achieved with IV administration, transient central nervous system effects became obvious. Similar effects were also observed in the IV PK/PD studies and consisted among others of sedation/hypoactivity, subdued behaviour and tachypnoea/hyperventilation in both species (rats and dogs). In a rat PK/PD study unscheduled deaths occurred at high exposure after IV administration of macimorelin. The applicant explained that these most likely were related to procedures or anaesthesia but most likely not to macimorelin.

The lack of metabolism and excretion studies was considered acceptable, as macimorelin is a tri-peptide and therefore its metabolic pathways are generally understood.

Macimorelin is mainly metabolized by CYP3A4 as determined by both chemical inhibition and recombinant CYP studies. Therefore, strong CYP3A4 inhibitors might have the potential to inhibit the metabolism of macimorelin thereby increasing its plasma concentration. Macimorelin is not a clinically significant inhibitor of Pgp nor an inducer or inhibitor of CYP1A2, CYP2B6 and CYP3A4 and, therefore, the risk for drug-drug-interactions via these CYP isozymes is negligible.

In the repeat dose toxicity studies, a high exposure margin compared to the diagnostic human exposure becomes obvious in respect to AUC and Cmax.

No carcinogenicity studies were submitted and this was considered acceptable as macimorelin is intended for single-use only.

Macimorelin was negative in an *in vitro* genotoxic test battery and no pharmacokinetic effects are expected *in vivo* which could impact the genotoxic potential of macimorelin. In addition, macimorelin will only be applied as a single dose resulting in low human exposure. Therefore, the lack of *in vivo* genotoxicity testing was considered acceptable.

Reproductive toxicity testing, as well as placental transfer and excretion into milk of macimorelin were not performed. However, in the repeat-dose toxicity studies up to 4 wk in rats no effects on reproductive organs by assessment of organ weight, macroscopic and microscopic evaluation were observed.

As there are no data for the use of macimorelin in pregnant women and studies in animals are insufficient with respect to reproductive toxicity the potential risk for humans is unknown. Macimorelin is therefore not recommended during pregnancy and women of childbearing potential must use adequate contraceptive methods at the time when macimorelin will be administered. Furthermore, as it is unknown whether macimorelin or its metabolites are excreted in human milk a risk to the suckling child cannot be excluded and the decision on whether to discontinue breast feeding or to abstain from macimorelin,

should take into account the benefit of breast feeding for the child and the benefit of the test for the woman.

Based on the environmental risk assessment macimorelin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

Considering that macimorelin is intended for single-use, the submitted non-clinical pharmacology, pharmaco- kinetic and toxicology studies are considered sufficient.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Objective	Design	Module	Route	Dose [mg/kg]	N (M/F)	Type of subjects	Location of study report	Study status, Report type
Broglio 2002	Safety, PD	Open, randomized, cross-over, SD (+2nd dose)	**2.7.2**	IV	0.001	2 (2/0)	Healthy volunteers	5.4	Completed, Publication only
				PO	0.06				
				PO	0.125				
				PO	0.25				
				PO	0.5				
AEZS-130-IIT-1	Safety, PK/PD	Open, randomized, PC, PG, SD	2.7.1 **2.7.2**	PO	Placebo	9 (9/0)	Healthy volunteers	5.3.4.1.1	Completed, Full
				PO	0.005	27 (27/0) in total			
				PO	0.05				
				PO	0.125				
				PO	0.25				
				PO	0.5				
				ID	0.2				
				ID	0.35				
				ID	0.5				
ARD-0705-003	Food effect	Open randomized, cross-over SD	**2.7.1** 2.7.2	PO fasted	0.5	16 (8/8) in total	Healthy volunteers	5.3.1.1.1	Completed, Full
				PO fed	0.5				
AEZS-130-047	Efficacy, Safety	Open, SD	2.7.2 **2.7.3**	PO	0.5	52 (31/22)	AGHD patients, Healthy controls	5.3.5.1.1	Completed, Full
					0.5	48 (30/18)			
AEZS-130-052	Efficacy, Safety	Open, randomized,	2.7.2 **2.7.3**	PO	0.5	154 (90/64)	AGHD likelihood	5.3.5.1.2	Completed, Full
					ITT	157 (93/64)			

		cross-over, SD			(insulin)		patients, healthy matched controls		
AEZS-130-054	Safety, PK/PD	Open, randomized, PC, PG, SD	**2.7.1 2.7.2**	PO	Placebo	7 (4/3)	Healthy volunteers	5.3.4.1.4	Completed, Full
					0.5	6 (2/4)			
					1.0	6 (3/3)			
					2.0	9 (4/5)			
AEZS-130-055	Thorough QT PK/ECG	DB, randomized, PC+AC, 3-cross-over, SD	2.7.1 **2.7.2**	PO	Placebo	57 (34/23)	Healthy volunteers	5.3.4.1.5	Completed, Full
					2.0	57 (33/24)			
					Moxi	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. DB: double-blind
Module refers to CTD Modules. The module in which the study is primarily described is shown in bold+underlined.

2.4.2. Pharmacokinetics

Seven clinical trials contributed clinical pharmacology data to the clinical development of macimorelin (also referred to as AEZS-130), including the two phase 3 trials AEZS-130- 047 and -052. In most cases, PK and PD were addressed in the same study. PD was measured as increase in serum growth hormone (GH) level.

Data were not systematically pooled for PK evaluations because of different formulations and sampling schedules used in different studies. Although no relevant differences in the systemic uptake between the different formulations were noted, it is important to mention the most recent studies AEZS-130-052, -054, and -055, that provide the pivotal safety and efficacy data for the use of the product in the target indication, used the formulation intended for marketing.

Absorption

No PK study for determining bioavailability was performed. The applicant presented a report from published literature (Broglio et al., 2002) in which the PD effect of macimorelin, i.e. serum GH increase was determined after oral vs. intravenous administration. An IV dose of 1 µg/kg elicited a similar serum GH increase as did 0.25 mg/kg orally, indication that roughly 1/250 (i.e. 0.4%) of the oral dose reached the circulation. See also the Pharmacodynamic section of this report.

- **Influence of food**

The influence of food on PK and PD of oral macimorelin were studied in the food effect trial ARD-0705-003.

A total of 16 healthy subjects (8 males and 8 females) were included in a cross-over design, receiving 0.5 mg/kg macimorelin with food on Day 1 and without food on Day 4 or vice versa. All 16 subjects completed the study.

Oral administration of macimorelin took place on study Day 1 either in fasting condition or with a concomitant standard liquid meal. Time zero was defined as the time of oral administration of the study drug. On study Day 4 subjects who received macimorelin in fasting condition on Day 1 now received macimorelin with a concomitant meal while subjects who received macimorelin with a concomitant meal on Day 1 now received macimorelin in fasting condition.

The time course of the plasma macimorelin concentration after oral administration with or without food is shown in **Figure 2** and the calculated descriptive PK parameters in **Table 12**.

Figure 2. Macimorelin concentration over time: Food effect. Study ARD-0705-003. Means, N = 16 for both curves

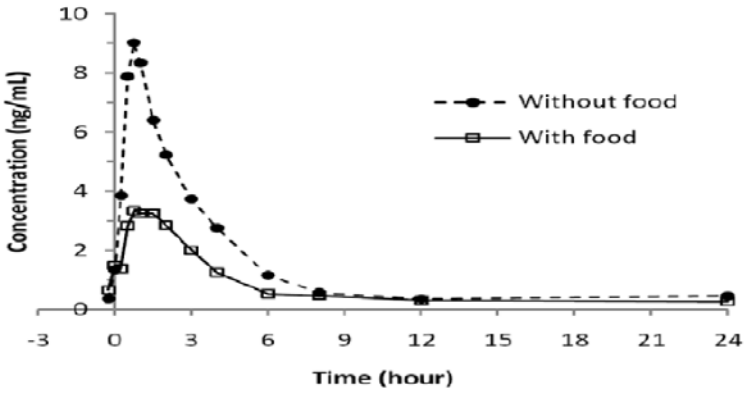


Table 12. Effect of food on the pharmacokinetics of macimorelin, Study ARD-0705-003

Parameter	Without food N=16	With food N=16
AUC0-t [µg x h/L]	29.5 (17.2)a	14.1 (5.5)
AUC0-∞ [µg x h/L]	32.0 (18.0)	15.9 (6.4)
Cmax [µg/L]	10.6 (6.2)	4.4 (1.9)
tmax [h]	0.75 (0.25-2.0)	0.88 (0.25-2.0)
$t_{1/2}$ [h]	3.9 (2.0)	3.8 (2.1)

Given are mean (SD), except for tmax: Median (range)
Macimorelin calculated as free base.

Distribution

The results from plasma protein binding studies for macimorelin in humans are summarised together with the results in rats and dogs in the non-clinical section of this assessment report (2.3.3).

Elimination

Excretion

Excretion studies with macimorelin were not submitted.

- **Metabolism**

In-vitro data (see non-clinical section of this Report) indicate that macimorelin is metabolised by CYP3A4. The nature of the resulting metabolites was not determined.

Dose proportionality and time dependencies

The objective of study AEZS-130-IIT-1 was to evaluate the pharmacological profile and the growth hormone releasing activity of increasing single oral doses of macimorelin acetate in healthy volunteers.

The study was conducted as a randomized, placebo-and positive-controlled, dose escalating study. Two treatments were given in 36 healthy male subjects; one treatment consisted of one oral dose of either macimorelin or placebo while the second treatment consisted of a GHRH stimulation test. The following doses of macimorelin were tested: 0.005, 0.05, and 0.5 mg/kg. A subgroup of subjects received in a randomized fashion two additional oral doses of macimorelin (0.125 and 0.25 mg/kg). The time course of macimorelin plasma levels is shown in **Figure 3**, and the calculated PK parameters are presented in **Table 13**.

Figure 3. Study AEZS-130-IIT-1

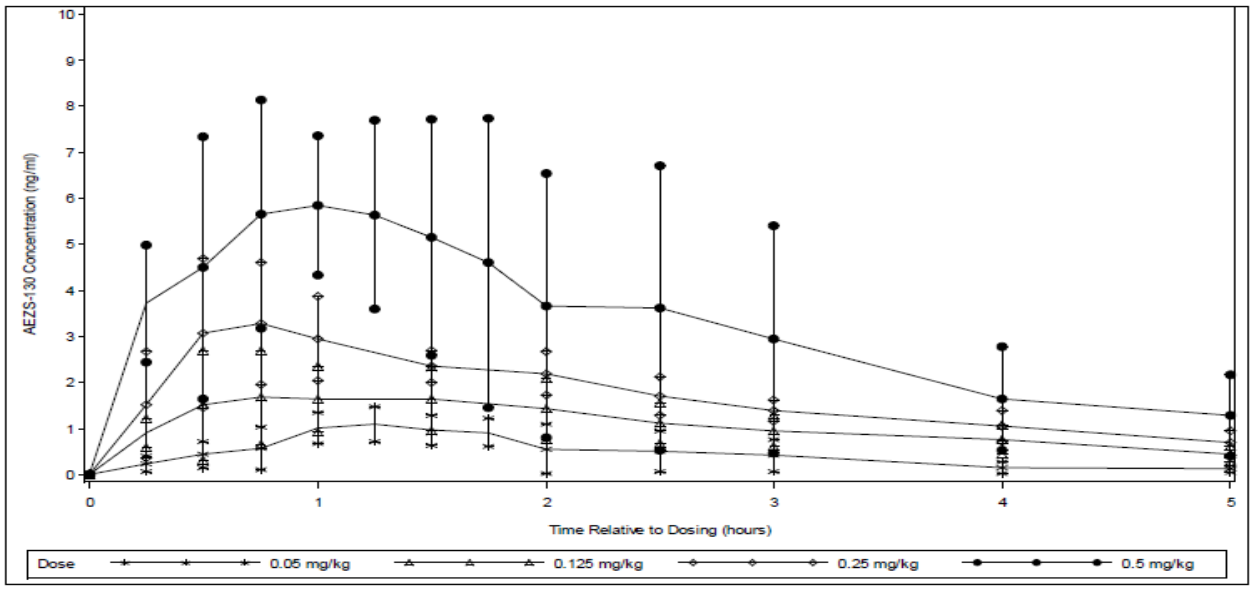


Table 13. Main PK parameters after oral doses of macimorelin, Study AEZS-130-IIT-1

Oral dose of macimorelin [mg/kg]	N	AUC(0-inf)[ng x h/mL]	AUC(0-5h)[ng x h/mL]	Cmax[ng/mL]
0.05	9	2.25 ± 1.61	1.92 ± 1.56	0.86 ± 0.72
0.125	6	6.63 ± 2.29	5.31 ± 1.97	2.33 ± 0.96
0.25	6	10.6 ± 2.14	8.59 ± 1.51	3.85 ± 1.36
0.5	9	19.7 ± 9.76	15.95 ± 7.39	7.59 ± 2.49
P-value[a]		<0.0001[d]	<0.0001[d]	<0.0003 [e]
P-value[b]		<0.0001	<0.0001	<0.0001
R[c]		0.986	0.990	0.977

a: Treatments compared using ANOVA, stratified by subject
b: Dose proportionality tested using linear regression, slope significant
c: Correlation coefficient from linear regression
d: All treatments significantly different from each other (all pairwise p < 0.001)
e: All treatments significantly different from each other (all pairwise p < 0.05)

Phase 3 study AEZS-130-052

The administered dose of macimorelin was 0.5 mg/kg as oral solution. The mean maximal observed macimorelin plasma concentration (Cmax) of 10.63 ng/mL was reached at mean tmax = 48.5 minutes (n=138); median Cmax was 9.38 ng/mL and median tmax was 45.0 minutes. Highest values for mean/median macimorelin plasma concentrations per scheduled time point were determined at 45 and 60 minutes post dose with 8.8 ng/mL/7.4 ng/mL and 8.5 ng/mL/7.1 ng/mL. These were the same time points when highest total GH concentrations were measured (see Clinical Efficacy section of this report).

No significant differences in the mean Cmax for macimorelin per AGHD likelihood group was observed. AUC was not calculated.

Phase 3 study AEZS-130-047

Pharmacokinetic evaluations were only performed on a small subset of subjects enrolled in this trial when it was resumed by the current applicant as the previously obtained samples were out of stability. The mean maximal observed concentration (Cmax) was 10.25 ng/mL in AGHD patients (n = 10) and 11.50 ng/mL in matched controls (n = 38). The mean time to reach maximal observed concentration (tmax) was 1.2 hours after oral administration in AGHD patients and 0.82 hours in normal controls. The terminal half-life was 3.56 hours in AGHD patients and 2.77 hours in normal controls.

AEZS-130-054

This was a single-dose, randomized, placebo-controlled, double-blind study to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of three ascending oral doses of macimorelin in healthy male and female subjects. Overall, 28 subjects were planned to be included: 6 subjects each in the first two dosing groups (0.5 and 1.0 mg/kg macimorelin) and 9 subjects in the highest dose group (2.0 mg/kg macimorelin).

The calculated PK parameters are given in **Table 14**.

Table 14. Main PK parameters in Study AEZS-130-054

Parameter	0.5 mg/kg, n=6	1.0 mg/kg, n=6	2.0 mg/kg, n=9
AUC0-t [µg x h/L]	38.8 (15.8)	40.2 (26.5)	87.4 (35.5)
AUC0-∞[µg x h/L]	40.7 (17.0)	42.4 (27.9)	90.6 (38.7)[a]
Cmax [µg/L]	9.85 (3.92)	14.9 (9.50)	23.7 (12.30)
tmax [h]	0.533 (0.25-0.75)	0.534 (0.25-1.0)	0.75 (0.52-1.5)
$t_{1/2}$ [h]	4.1 (2.6)	4.9 (4.6)	8.4 (1.4)

Given are arithmetic means and SD (in brackets), except for tmax: Median (range)
[a] N=8, due no reliable λZ in 1 subject, Macimorelin calculated as free base.

- **Time dependency**

Repeated administration was not tested in humans so no information on time-dependency of PK in humans is available. Accumulation of macimorelin was observed after repeated administration in animals (female rats, see non-clinical section of this Report).

Special populations

No data are available in patients with renal or hepatic impairment, elderly or paediatric patients.

Pharmacokinetics in target population

PK in patients with (suspected) GH deficiency was (partly) determined in the phase 3 trials 047 and 052. No relevant differences in GH deficiency patients as compared to healthy control subjects were observed.

Pharmacokinetic interaction studies

No pharmacokinetic studies in humans were submitted. Macimorelin is metabolised by CYP3A4 according to *in vitro* data (see non-clinical section of this Report).

2.4.3. Pharmacodynamics

Mechanism of action

Macimorelin (macimorelin acetate) is a small molecule peptidomimetic ghrelin agonist that stimulates the release of growth hormone and is intended to be used for stimulating GH release in a diagnostic test in GH deficiency.

GH concentrations in blood can be determined by different types of assays (e.g., immunoassays with fluorescence, chemiluminescence or radio detection) using different calibration standards. During the conduct of the clinical studies with macimorelin, different GH assays were used.

In study **AEZS-130-047**, an immunochemiluminometric assay was employed. As this assay was no longer available when multi-centre study 052 started, as an alternative, the IDS-iSYS Human Growth Hormone assay (Immunodiagnostic Systems Ltd., UK) was used. This assay, used in phase 3 study **AEZS-130-052**, is standardized to the recombinant growth hormone calibration standard WHO 98/574, and complies with recommendations on assay standardization as outlined by Clemmons 2011.

In Study **AEZS-130-IIT-1**, which was conducted at a university hospital, GH and other hormones were determined in the central laboratory of the hospital by radio-immuno assay (RIA).

For Study **AEZS-130-054**, the Cobas 601hGH assay was chosen. This assay is a validated two-step immunoassay using the ElectroChemiLuminescence (ECL) technology.

The design of studies AEZS-130-047, AEZS-130-IIT-1 and AEZS-130-054 are described in the pharmacokinetics section of this report above. Results from the phase 3 studies, AEZS-130-047 and AEZS-130-052 are presented in the clinical efficacy section of this report.

Primary and Secondary pharmacology

The first administration of macimorelin in man occurred in the study by Broglio et al., 2002 and involved 2 young healthy male subjects.

Both subjects received IV ghrelin (1 µg/kg), IV macimorelin (1 µg/kg), IV placebo and incremental doses of oral macimorelin (0.06, 0.125, 0.25 and 0.5 mg/kg). The IV and oral administration was at least 10 days apart. The highest oral macimorelin dose (0.5 mg/kg) was repeated on two consecutive days. No details on the assay used for determining GH in serum were provided.

A marked and prompt increase in GH levels was observed after IV macimorelin administered at a low dose of 1.0 µg/kg as illustrated in the figure below. Cmax of GH was around 100 µg/L (ng/mL) for one subject and around 40 µg/L for the other volunteer (mean around 70 ng/mL).

Oral macimorelin dose-dependently induced a marked increase in serum GH levels lasting for approximately 180 minutes. The Cmax of GH following 0.25 mg/kg macimorelin PO was around 70 ng/mL, i.e. in the same order of magnitude as with 1 µg/kg macimorelin IV.

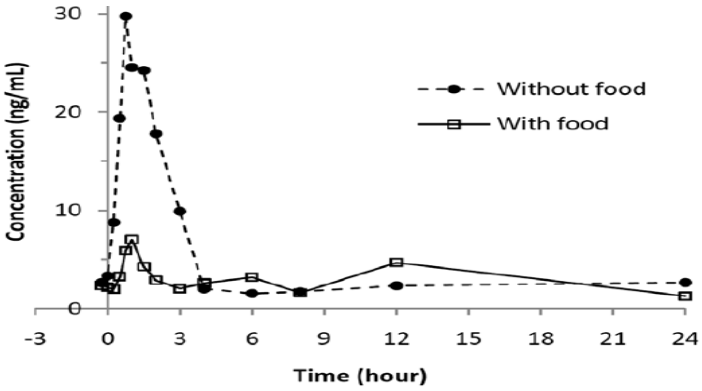
ARD-0705-003

Pre-dose values of GH were similar before the with food administration (mean ± SD = 2.4 ± 5.6 ng/mL) and the without food administration (mean ± SD = 2.6 ± 3.5 ng/mL).

The highest concentration of GH (mean ± SD = 29.8 ± 23.6 ng/mL) was observed at 45 minutes after dosing in the without food group. The highest concentration of GH with food administration (mean ± SD = 7.0 ± 15.3 ng/mL) was achieved at 60 minutes. Thus, the food effect on GH Cmax was larger than on

macimorelin Cmax; GH AUC was not calculated. The time course of plasma GH level is shown in **Figure 4**.

Figure 4. GH concentration over time following oral macimorelin – Food effect, Study ARD-0705-003



AEZS-130-IIT-1

The design of this study is described in the pharmacokinetic section of this report above.

The PD results of this study. i.e. the increase in serum GH levels are summarised in **Figure 5** and **Table 15**. Orally administered macimorelin stimulated GH release in a dose-dependent manner (see figure and table below).

Figure 5. GH concentration following different doses of oral macimorelin, Study AEZS-130-IIT-1

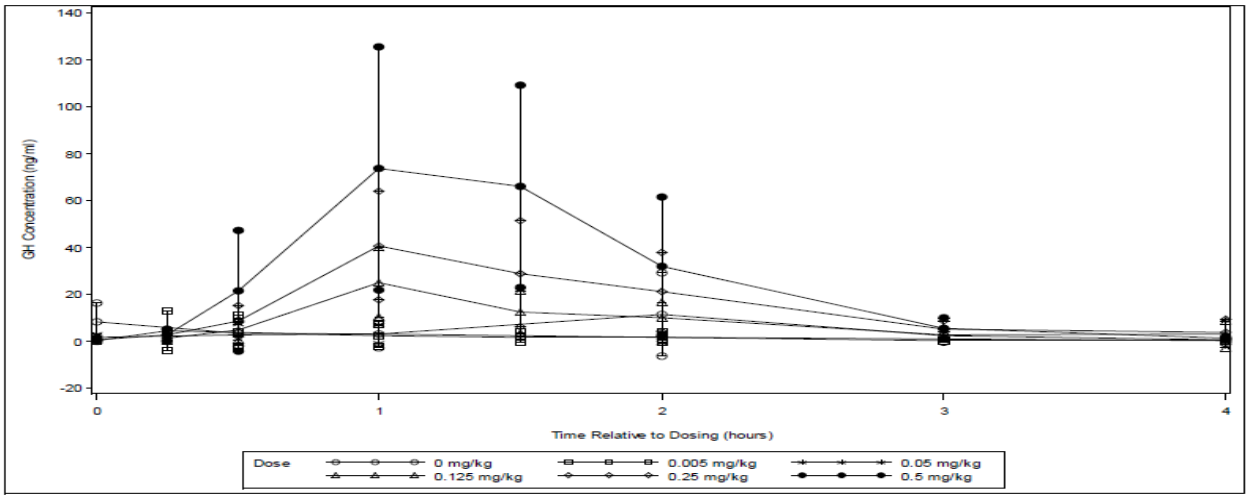


Table 15. Effect of Increasing Oral Doses of Macimorelin, Placebo, and IV GHRH on GH Secretion, Study AEZS-130-IIT-1

	N	AUC(0-4h) (ng*h/mL)	Cmax (ng/mL)	Tmax (h)
Placebo	9	18.35 ± 23.81	15.57 ± 14.53	1.11 ± 1.17
IV GHRH 1 µg/kg	36	60.92 ± 60.78	47.23 ± 43.84	0.58 ± 0.22
Oral macimorelin 0.005 mg/kg	9	5.98 ± 7.80	5.73 ± 7.87	1.00 ± 0.96
0.05 mg/kg	9	6.13 ± 6.15	4.64 ± 4.95	0.56 ± 0.46
0.125 mg/kg	6	30.88 ± 6.91	28.63 ± 8.98	1.17 ± 0.41
0.25 mg/kg	6	58.74 ± 31.21	45.60 ± 17.91	1.17 ± 0.41

0.5 mg/kg	9	100.46 ± 61.69	82.17 ± 50.26	1.22 ± 0.36
P-value [a]		0.0006	0.0009	0.0308

a: All treatment groups compared using ANOVA, stratified by subject

AEZS-130-054

The time course of serum GH increase after macimorelin administration is depicted in **Figure 6** and the calculated PD parameters (GH Cmax and GH Tmax) are listed in **Table 16**.

Figure 6. Mean serum concentrations of GH, Study AEZS-130-054

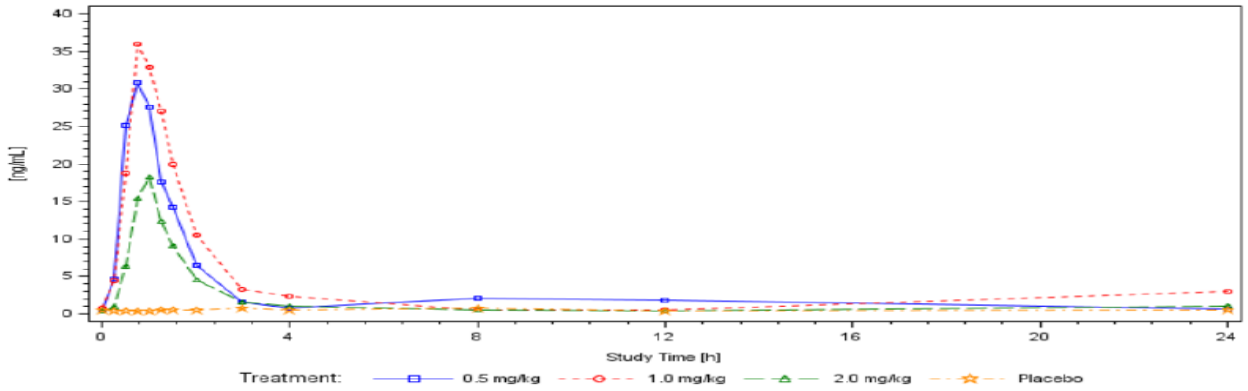


Table 16. Pharmacodynamics of macimorelin after single dose administrations: effects on GH secretion, Study AEZS-130-054

		GH		
Dose [mg/kg] (PO)	Subjects (No.(M/F))	AUC(0-t) (ng·h/mL)	Cmax (ng/mL)	tmax
Placebo	7 (4/3)	-	2.0	4.2
0.5	6 (2/4)	-	31.9	0.9
1.0	6 (3/3)	-	37.8	0.9
2.0	9 (4/5)	-	18.4	1.0

2.4.4. Discussion on clinical pharmacology

The applicant determined the PK profile (exposure, Cmax, Tmax, t1/2) of macimorelin after a single dose. The increase in exposure was approximately linear with dose in the dose range tested. More extensive PK data, covering bioavailability, metabolites, excretion routes, interactions and PK in special populations were not provided. Considering that the intended use of macimorelin is for a single dose only, the provided data are considered sufficient to characterise the pharmacokinetic profile of the product.

Macimorelin was absorbed rapidly and the maximum plasma macimorelin concentrations (Cmax) were observed approximately 30 minutes to 1 hour and 10 minutes after oral administration of 0.5 mg/kg macimorelin after fasting for at least 8 hours. A liquid meal decreased the macimorelin Cmax and AUC by 0.42 and 0.5 fold, respectively. Hence, the macimorelin test should be conducted in the fasting state as recommended in the SmPC.

In line with findings in animals, the oral availability appeared to be low (Broglio et.al, 2012). However, the reliability and robustness of this finding is limited sine only two subjects were tested, the macimorelin formulation used is not known and the assay used for serum GH determination was not described.

Macimorelin is moderately bound to plasma proteins. Plasma protein binding decreases with increasing concentrations from 78% at 0.1 µM to 62% at 10 µM. At the clinically relevant concentration of 0.1 µM (clinical Cmax = 11.2 ng/ml = approx. 0.02 µM), the unbound fraction of macimorelin in human plasma is 22%.

According to *in vitro* data macimorelin is mainly metabolised by CYP3A4. First-pass metabolism by this enzyme could lead to PK interactions with CYP3A4 inhibitors and inducers. However, it is not known to which extent macimorelin plasma level increase in the presence of CYP3A4 inhibitors. Whilst it is acknowledged that patients treated with (weak) CYP inhibitors in the pivotal study 052 (see Clinical efficacy section of this report) did not show a significantly different GH response, the number of those subjects was low and thus firm conclusions cannot be reached. Therefore, and in the absence of confirmative data, concomitant use of CYP3A4 inhibitors should be discouraged when performing the test. This is reflected in the product information which states, that co-administration of a CYP3A4 inhibitor may increase the macimorelin plasma concentration, and this, in turn, could yield higher plasma GH levels. Increased GH levels due to CYP inhibition may decrease sensitivity of the assay (leading to increased number of false negatives, by raising the GH level above the cut-off). Based on current understanding, this is unlikely to decrease specificity of the test.

The lack of studies to evaluate the pharmacokinetics of macimorelin in paediatric patients is acceptable as the product is intended for use in adult patients only and the product information states that the safety and diagnostic efficacy of macimorelin in children and adolescents below 18 years has not yet been established.

There are no data available on the extent of macimorelin excretion via liver or kidney. In clinical studies, patients were excluded from macimorelin intake in case of elevation of laboratory parameters indicating hepatic or renal dysfunction or damage (ASAT, ALAT, GGT > 2.5 x Upper Limit of Normal (ULN); creatinine or bilirubin > 1.5 x ULN). Therefore, no dose adjustment recommendations in case of renal and/or hepatic impairment can be given.

Only limited pharmacokinetic data are available in the elderly. As growth hormone secretion normally decreases with age the efficacy of macimorelin in patients aged over 65 years has not yet been established.

PD studies were conducted to address the effect relevant for the intended diagnostic use, increase of plasma GH level. All other physiological effects of ghrelin agonists were not studied. This is acceptable since most of these effects, such as regulation of appetite and body composition, are not expected to be affected after a single dose of macimorelin administration.

Exposure (AUC) and Cmax increased proportionally with dose in the dose range tested (0 to 0.5 mg/kg PO) in Study AEZS-130-IIT-1. Plasma drug concentrations after oral administration peaked (Cmax) between 50 and 75 minutes with the shortest time observed after the highest dose of macimorelin. Dose proportionality was shown by linear regression analysis: a significant linear correlation was seen, both for AUC ($P < 0.001$, $R = 0.986$) and for Cmax ($P < 0.05$; $R = 0.977$). t½ ranged from 1.8 to 2.1 hours with no statistically significance difference between dose groups ($p = 0.5430$). Maximal GH release has been observed at macimorelin plasma concentrations of $\geq$ 7 ng/ml.

Other studies with PK data yielded similar results. The only exception was the AUC at 0.5 mg/kg of macimorelin in Study AEZS-130-054, which was quite high and similar to the AUC at 1 mg/kg; on the other hand, the AUC at 2 mg/kg was about twice the AUC at 1 mg/kg as expected.

No studies were performed to address potential PD interactions although several compounds are known to affect GH secretion or GH levels. Concomitant use of macimorelin therefore should be avoided with

medicinal products that directly affect the pituitary secretion of growth hormone, or transiently elevate growth hormone concentrations or that may blunt the growth hormone response to macimorelin. Sufficient washout time (five elimination half-lives) of these medicinal products prior to administration of macimorelin is recommended. Growth hormone medicinal products should be discontinued at least 1 month before administering macimorelin.

2.4.5. Conclusions on clinical pharmacology

Macimorelin has been adequately characterised from a clinical pharmacology perspective despite the lack of information on bioavailability, metabolites, excretion routes, interactions and PK properties in special populations, as the intended use of the product is limited to single administration for diagnostic purposes.

2.5. Clinical efficacy

2.5.1. Dose response study

No formal dose response studies were submitted.

2.5.2. Main study

Study No. AEZS-130-052: 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)

Methods

The performance of the macimorelin GHST ('MAC') and the ITT was compared in this open-label, randomized, single dose, 2-way crossover study.

Study subjects were assigned to groups of descending likelihood of having AGHD (Group A: high likelihood of GHD, Group D: healthy controls).

The sequential order of the GHSTs for the suspected AGHD subjects was determined by stratified randomization; healthy control subjects (Group D) were tested in the same sequence as the matched Group A subjects. The two GHSTs were performed 7 days to 1 month apart. An additional MAC (Test 3) was performed in a subset of Group A, B, and C patients within 8 to 28 days following the second GHST of the core study to provide information on the repeatability of the macimorelin testy.

Study Participants

Study subjects were assigned to three groups (A, B, C) of descending likelihood of having AGHD and to a control group of healthy subjects matching Group A subjects (D).

With regard to likelihood of AGHD, the following definitions were used:

Group A: High likelihood of GHD (approx. 25% of the study population)

- Structural hypothalamic or pituitary lesions and low 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.

Group B: Intermediate likelihood of GHD:

- Eligible subjects not qualifying for either high or low likelihood (Group A/C)

Group C: **Low likelihood of GHD (**approx. 25% of the study population)

- 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.

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

Healthy controls were included after the successful completion of both GHSTs (adjudication by the DRC) in a subject that had been registered with 'high likelihood AGHD' criteria, irrespective of the actual ITT outcome in that subject. Matching criteria were as follows: Sex, age +/- 5 years, BMI +/- 2 kg/m^2

Inclusion criteria

Groups A, B and C

- Male or female, aged between 18 and 65 years.
- Suspected growth hormone deficiency (GHD), based on either of the following (Group A-C):
  - structural hypothalamic or pituitary disease, or
  - surgery or irradiation in these areas, or
  - head trauma as an adult, or
  - evidence of other pituitary hormone deficiencies, or
  - idiopathic childhood onset GHD (without known hypothalamic or pituitary lesion or injury).

OR (recruitment at a dedicated Phase I Unit only)

Group D: Healthy control

Subject matching a Group A subject by:

- Sex, age (± 5 years), BMI (± 2 kg/m2), and oestrogen status** (women only);

* 'Healthy' comprising:

- History of normal growth and development,
- Serum prolactin concentration within normal range limits,
- History of regular, age-appropriate menses in females
- Serum testosterone concentration within normal range limits for males.

** Matching for 'oestrogen status':

- Group A subjects below 50 years and on oral oestrogen therapy will be matched to control subjects who are also taking oestrogen (as an oral contraceptive or for replacement); the route of oestrogen administration (e.g. oral versus transdermal) must also be matched.
- Group A subjects 50 years or older and with untreated oestrogen deficiency will be matched to female control subjects who are not receiving oestrogen

Main exclusion criteria

1. GH therapy within 1 month prior to anticipated first GHST within this study (within 3 months in case of long-acting GH formulation).

2. GHST within 7 days prior to the anticipated first test day within the study.

3. Subjects that are not euthyroid, or subjects who had a change in thyroid therapy within 8 weeks prior to anticipated first test day within the study.

4. Untreated hypogonadism or not on a stable substitution treatment within 30 days prior to anticipated first test day within the study.

5. Treatment with drugs directly affecting the pituitary secretion of somatotropin (e.g., somatostatin analogues, clonidine, levodopa, and dopamine agonists) or provoking the release of somatostatin; antimuscarinic agents (atropine).

6. Concomitant use of a cytochrome (CYP) 3A4 inducer (e.g., carbamazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's Wort).

7. Medical history of ongoing clinically symptomatic psychiatric disorders.

8. Parkinson's disease.

9. Cushing disease or patients on supraphysiologic glucocorticoid therapy within 30 days prior to the anticipated first test day within the study.

10. Type 1 diabetes or untreated or poorly controlled Type 2 diabetes, as defined by HbA1c > 8%.

11. Body mass index (BMI) ≥ 40.0 kg/m2.

12. Participation in a study with any investigational drug within 30 days prior to study entry.

13. Vigorous physical exercise within 24 hours prior to each GHST within this study.

Prior and concomitant therapy

As macimorelin is metabolized mainly by CYP3A4, concomitant treatment with strong CYP3A4 inducers was prohibited during the study.

Patients were also excluded in case of concomitant treatment with any drugs that might prolong QT/QTc.

Treatments

Macimorelin oral solution was prepared by study personnel and dosed according to the following general instruction:

• Weigh the patient and determine the number of pouches/sachets needed. (one pouch was required for a patient equal or less than (≤) 120 kg, a second pouch was required if the patient weighted more than (>) 120 kg).

• Dissolve the entire contents of each pouch in 120 mL of water in a suitable transparent container and stir gently for about 2 to 3 minutes. (a small amount of un-dissolved particles will remain).

• Based on the dose of 0.5 mg/kg (included per CSP 2.0), determine the required volume of the solution, which corresponds to the patient body weight, i.e., 1 mL/kg. (for example, a 70 kg patient will require 70 mL of the prepared solution).

• Measure the required volume for the subject by using a graduated 50 mL syringe and transfer it to a drinking glass.

• The solution must be used within 30 minutes after preparation.

Regular human insulin was administered intravenously (i.v.) as one or two injections on the day of the ITT. The recommended standard dose was 0.10 U/kg for the first injection (0.15 U/kg in subjects with a BMI > 30 kg/m2). The second injection as an additional insulin bolus of 0.05 U/kg was administered if glucose did not show a value of less than 2.2 mmol/L (40 mg/dL) AND symptomatic hypoglycaemia (e.g., diaphoresis, confusion, sensation of warmth, weakness, or fatigue) had not been achieved within 45 minutes after the initial insulin dose. At the investigator's discretion, individual adaptions with lower and higher doses were allowed as clinically indicated.

Objectives

The primary objective of this study was:

- to validate the use of single dose oral macimorelin for the diagnosis of AGHD, using the insulin tolerance test (ITT) as comparator (non-reference standard) GHST.

The secondary objective of this study was:

- to characterize the safety profile of single dose oral macimorelin in suspected AGHD subjects.

Outcomes/endpoints

There were two **co-primary** efficacy variables in this study:

• Percent of Negative Agreement;
• Percent of Positive Agreement.

The following cut-off values for stimulated GH levels were used:

•Macimorelin-GHST: GH: 2.8 ng/mL
•ITT: GH: 5.1 ng/mL

A peak GH value below the cut-off value (i.e., < 2.8 or < 5.1, respectively) was considered '**test positive'**, a value above the cut-off '**test negative'.**

The key secondary variables were:

- Percent of overall agreement
- Estimated sensitivity and specificity, of both GHSTs (macimorelin and ITT) when using predefined cut-off points of both GHSTs, and derived based on the subjects with high likelihood of having the disease and their matching healthy subjects.
- Receiver Operator Characteristics ROC based on item 2 above.

The **secondary** diagnostic accuracy measure was 'percent overall agreement'. The accuracy measures are defined as follows:

		Insulin Tolerance Test		Total	
		+	-		
MAC	+	a	b	a+b	Positive Agreement (%)=100% x a/(a+c)
	-	c	d	c+d	Negative Agreement (%)=100% x d/(b+d)
Total		a+c	b+d	a+b+c+d	Overall Agreement (%)=100% x

				(a+d)/(a+b+c+d)

Safety endpoints:

Safety endpoints include the following:

- Incidence of TEAEs
- Clinical laboratory test results
- Vital sign measurements
- Physical examination findings

Sample size

At least 55 'ITT-positive' and 55 'ITT-negative' subjects were to complete the crossover. Since it was unlikely that the number of ITT-positive and the number of ITT-negative would be equal among the first 110 subjects with valid tests outcomes, the actual number of subjects needed to complete the study was likely to be greater than 110. Among these, about 25% subjects with high likelihood to have the disease were to be included as well as matching healthy subjects.

Randomisation

The study followed a cross-over design. Subjects were assigned to their respective group bases on risk factors for AGHD as described above. Within this procedure, the sequence for the performance of the first MAC and the ITT in Group A/B/C subjects was assigned by stratified randomisation.

Blinding (masking)

This was an open-label study.

Statistical methods

There were two primary efficacy variables in this study: 'Percent Negative Agreement' and 'Percent Positive Agreement', using the ITT as the comparator (non-reference standard). The estimated percentages of the agreements and the exact two-sided 95% confidence interval (or one-sided 97.5% confidence interval) of the percent agreement based on Clopper-Pearson were presented.

With the planned sample size of 55, the lower bound of the two-sided 95% Clopper-Pearson exact confidence interval (or the lower bound of the one-sided 97.5% confidence interval) based on an observed agreement of 82% would be approximately 70% (69.3%). Based on the above consideration, the performance of the GHST with Macimorelin was considered to be acceptable if the lower bound of the two-sided 95% confidence interval (or lower bound of the one-sided 97.5% confidence interval) for the primary efficacy variables was 75% or higher for 'percent negative agreement', and 70% or higher for the 'percent positive agreement'.

Estimated sensitivity and specificity, derived based on the subjects with high likelihood of having the disease and their matching healthy subjects. The sensitivity and specificity were estimated treating the subjects with high likelihood of having AGHD as "true" diseased subjects and the matching healthy subjects as "true" non-diseased subjects. Sensitivity, specificity, and two-sided 95% confidence intervals of sensitivity and specificity were presented.

Based on the mITT population the primary efficacy and the key secondary efficacy measures (percent negative and percent positive agreement) were analyzed by a hierarchical testing procedure with regard to the sampling time for the macimorelin test:

1. Peak GH among all post baseline samples;

2. Highest GH among 60 and 45 minutes post dose;

3. GH at 60 minutes post dose;

4. GH at 45 minutes post dose.

To control for overall Type I error rate, sufficient agreements for a method can be claimed only when sufficient agreements can be claimed for all prior methods, if any.

The repeatability analysis was based on the mITT population as determined in the core study part, but restricted to only those patients/subjects with both macimorelin tests performed.

The primary efficacy variable for repeatability analysis (difference of the peak GH level following the two macimorelin treatments (peak value from the assay repetition [Test 3] – peak value from the first assay [Test 1 /Test 2] in the randomized core study part) was summarized by macimorelin test positive and negative outcome groups in the core study part and overall. The two-sided 95% confidence intervals of the difference were presented.

Post-hoc analyses

In January 2017, the results of the planned analyses of the study showed that one of the two co-primary endpoints, i.e., positive agreement between the macimorelin GHST (MAC) and the comparator (insulin tolerance test; ITT), was not met. After careful review of the study data, the sponsor concluded that supplementary analyses of the data could demonstrate that the MAC is a feasible, robust, safe, and highly reproducible test to diagnose AGHD, with the potential of being a better means for evaluating a patient with suspected AGHD than the ITT.

Exploratory analyses would also include the hierarchical testing to assess the performance of the assay at the recommended GH cut-off point for the different sparse sampling scheme options. The rationale and general concept for the different exploratory analyses of the original study data is outlined below.

The following criteria need to be considered when defining an optimal GH cut-off point for the MAC based on the available data:

- Percent negative agreement of MAC with ITT should have a lower CI limit above 75%.
- Percent positive agreement of MAC with ITT should have a lower CI limit above 70%
- Repeatability of the MAC outcome in the core study and in the repeatability study should be high.
- Sensitivity and specificity of the MAC, as derived from GHST outcome in Group A and Group D subjects in the core study should be high.
- Due to the exploratory nature of the post-hoc analyses and the overall limited size of the data pool, sensitivity analyses should be performed that exclude data from subjects in the mITT population whose data – based on additional information – are very likely invalid and that might bias conclusions if not excluded. (Data from only one subject (RS01-06) with apparent non-compliance or dosing error in the MAC of the core study were excluded from such analyses)

- As the performance characteristics of the MAC assay will depend on the recommended number and timing of blood samples for measuring GH serum concentrations, all above criteria should also be subjected to the planned hierarchical testing evaluating the different 'sparse sampling' scheme options.

Orientating analyses: In a first part, the performance characteristics of the MAC were calculated for GH cut-off points that corresponded to an observed peak GH in a MAC of the core study. For practical reasons, the lower end of the GH cut-off points was selected at 2.21 ng/mL (the highest value below the pre-defined value of 2.8 ng/mL), and the upper end was selected at 8.31 (an arbitrary value reflecting the higher peak GH in the MAC than in the ITT).

Exploratory analyses: In a second part, the same set of analyses was performed for selected GH cut-off points including the pre-defined value of 2.8 ng/mL and evenly spaced values in a 'range of potential interest' ranging from 4.6 to 8.1 ng/mL, i.e., 2.80, 4.60, 5.10, 5.60, 6.10, 6.60, 7.10, 7.60, and 8.10 ng/mL, that includes 5.10 ng/mL as the pre-defined cut-off point for the ITT and 7.10 ng/mL as a value reflecting the 1.4-fold higher mean peak GH levels in MACs compared with ITTs.

Results

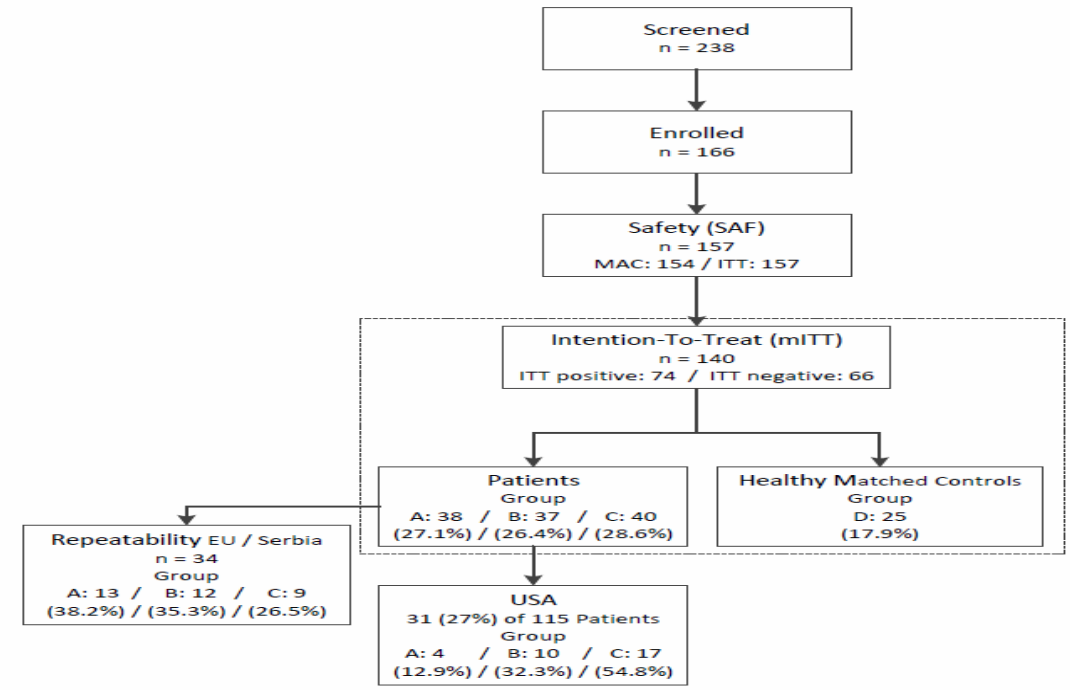
Participant flow

Out of a total of 238 subjects screened, altogether 166 subjects were enrolled in a total of 25 study centres in nine countries (20 centres in Europe and 5 centres in the USA). The safety population (SAF) consisted of 157 subjects, who had received at least 1 dose of study drug. Out of these 157 subjects, 17 subjects did not fulfill the criterion for being included in the modified intention-to-treat (mITT) population, i.e., not both GHSTs of the cross-over were evaluable or performed. Thus, 140 subjects formed the mITT: 38 (27.1%) in Group A, 37 (26.4%) in Group B, 40 (28.6%) in Group C, and 25 (17.9%) in Group D (see Figure 1). 34 patients from the mITT were included in the repeatability extension (Amendment no. 1) and underwent a repeated MAC (‘Test 3’).

14 (8.9%) subjects of the SAF prematurely terminated the study, i.e., 2 subjects had withdrawn their consent and 12 for other reasons, either because the first ITT was non-evaluable and no test repetition was performed or the subjects were not available for the EOS visit.

Participant flow is presented in **Figure 7.**

Figure 7. Participant flow in Study AEZS-130-052



Recruitment

Study Start Date: 01-Oct-2015 (Screening of first subject)
Study Completion Date: 29-Nov-2016 (Last patient last visit)

Conduct of the study

The following major protocol deviations were reported in more than on subject:

- Informed consent procedures (8 subjects);

- Failure to take IGF – sample (1 subject), Samples not shipped to the Lab and other Lab protocol violations (4 subjects);

- Deviations from controlled samples storage conditions at -20° (6 subjects) ;

- Patient was asked to withdraw HGH therapy in order to be included in the study (2 subjects);

- ECG not performed at screening, not reporting a broken arm as a SAE, blood draw taken by personal that was not trained and listed (2 subjects);

-Other issues (6 subjects)

Amendments to the study protocol:

Two versions of the clinical study protocol and two general Amendments to the clinical study protocol (Amendment no. 1 (repeatability extension), Amendment no. 2) were implemented. During the study approval process, two local Amendments were prepared to comply with requests from the Regulatory Authority in France and in Italy, respectively. Amendment no. 2 and country-specific Amendments were mainly related to administrative changes or clarification of protocol texts and did not require any modification of the analyses or the exclusion of data obtained prior to implementation of an Amendment.

Amendment no 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.

Additional exploratory subgroup analyses were performed to determine if there is a need for different cut-off points when considering the following subgroups:

- Obesity class I: BMI (30.0 - 34.9)
- Obesity class II: BMI (35.0 – 39.9)
- Age group 18 to 25 years
- Gender (male, female).

Baseline data

Demographic and other baseline characteristics of the trial population are presented in **Tables 17** and **18**.

Table 17. Sex and race for all groups at screening in Study AEZS-130-052 (SAF)

Parameter		AGHD likelihood group								Total	
		A		B		C		D			
		N	%	N	%	N	%	N	%	N	%
Sex	Male	25	59.52	18	42.86	35	79.55	15	51.72	93	59.24
	Female	17	40.48	24	57.14	9	20.45	14	48.28	64	40.76
	Total	42	100.00	42	100.00	44	100.00	29	100.00	157	100.00
Race	Asian	2	4.76	1	2.38	2	4.55	0	0.00	5	3.18
	White	36	85.71	36	85.71	34	77.27	29	100.00	135	85.99
	Black / African American	0	0.00	1	2.38	2	4.55	0	0.00	3	1.91
	Pacific Islands	0	0.00	0	0.00	1	2.27	0	0.00	1	0.64
	Other	4	9.52	4	9.52	5	11.36	0	0.00	13	8.28
	Total	42	100.00	42	100.00	44	100.00	29	100.00	157	100.00

Table 18. Age, height, weight, BMI, for all AGHD likelihood Groups at screening in Study AEZS-130-052 (SAF)

Parameter / Group		N	Mean	Standard deviation	Min	Median	Q3	Max
Age (years)	A	42	42.33	15.04	20	43.50	56.00	66
	B	42	45.79	11.79	20	48.50	53.00	65
	C	44	34.86	10.501	18	35.00	43.50	57
	D	29	40.03	12.45	18	39.00	48.00	62
	Total	157	40.74	13.10	18	41.00	51.00	66
Height (cm)	A	42	169.25	11.79	149.3	169.50	178.00	195
	B	42	169.22	10.24	142.5	169.75	175.30	191
	C	44	173.01	10.19	139.8	173.25	181.00	191
	D	29	171.66	9.44	158	171.00	180.00	188
	Total	157	170.74	10.56	139.8	170.20	178.00	195
Weight (kg)	A	42	79.26	16.97	50	77.60	91.05	120.7
	B	42	85.71	17.73	50.8	82.05	100.00	121
	C	44	84.07	21.06	44	87.50	101.62	123.3
	D	29	77.45	15.09	59	75.00	87.00	114
	Total	157	82.00	18.23	44	82.00	94.00	123.3
Body Mass Index (kg/m^2)	A	42	27.56	4.59	19.16	27.11	30.99	36.59
	B	42	29.75	4.49	20.44	28.79	32.81	39.38
	C	44	27.86	5.68	16.16	28.43	31.73	39.71
	D	29	26.09	3.23	20.76	25.65	27.97	33.58
	Total	157	27.96	4.81	16.16	27.50	31.27	39.71

BMI = body mass index, Max = maximum; Min = minimum; N = number; Q3 = third quartile;

Numbers analysed

A total of 140 subjects formed the mITT population and thus were included in the efficacy analysis: 38 (27.1%) in Group A, 37 (26.4%) in Group B, 40 (28.6%) in Group C, and 25 (17.9%) in Group D. 34 patients from the mITT were included in the repeatability extension (Amendment no. 1) and experienced a repeated MAC ('Test 3'), i.e., 13 (%) in Group A, 12 (%) in Group B, 9 in Group C (**Table 19**).

Table 19. Analysis populations in study AEZS-130-052

Parameter	N Planned	N SAF	N mITT
All	at least 110	157	140
ITT-positive	at least 55	n.a.	74
ITT-negative	at least 55	n.a.	66
Group A (High likelihood of AGHD)	25% (26-28)	42	38
Group B (Intermediate likelihood of AGHD)		42	37
Group C (Low likelihood of AGHD)	25% (26-28)	44	40
Group D (Healthy controls)	20-25	29	25

Outcomes and estimation

Performance of the tests

Performance of the ITT: In 27 of 157 (17%) subjects, the first performance of the ITT did not provide an evaluable result, commonly due to the lack of a confirmed hypoglycemia in venous blood. In 17 of these 27 (63%) subjects, the ITT was actually repeated, and the outcome of the repeated test was evaluable in 13 subjects, but was non-evaluable for a second time in 4 of the 17 (24%). Thus, 14 of 27 (52%) of the subjects with a non-evaluable first ITT could finally not be included in the mITT due to test performance issues with the ITT. In summary, 143 subjects had an evaluable ITT, of whom 3 withdrew before having their MAC performed, so that eventually 140 subjects could be included in the mITT.

Performance of the MAC: Only one of 154 (0.65%) MACs in the core study was non-evaluable and had to be repeated. In this case, the site had only collected blood samples for PK but not for GH measurements at the initial GHST.

In the repeatability extension, all 34 MACs were evaluable upon first performance.

Primary endpoint

Evaluation of 'Step 1 - Peak GH level among all post baseline samples' was the first analysis performed according to the hierarchical testing procedure **(Table 20**). Results are based on samples obtained 30 minutes after the test was performed.

Table 20. Peak GH levels in Study AEZS-130-052 (mITT)

Macimorelin stimulation test outcome: Step 1 - Peak GH level among all post baseline samples	**Insulin tolerance test outcome**				**Total**	
	Positive		Negative			
	N	%	N	%	N	%
Positive	55	39.29	4	2.86	59	42.14
Negative	19	13.57	62	44.29	81	57.86
Total	74	52.86	66	47.14	140	100.00

Based on the assessments (positive/negative) for MAC and ITT, the negative agreement was 93.94% and the positive agreement was 74.32%, and corresponding 95% Confidence intervals are presented in **Table 21**.

Table 21. 95% confidence intervals for negative and positive agreement in Study AEZS-130-052 (mITT)

95 % confidence interval (Pearson Clopper) for negative agreement		
Negative agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
93.94	85.20	98.32
95 % confidence interval (Pearson Clopper) for positive agreement		
Positive agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
74.32	**62.84**	83.78

One of the two co-primary endpoints did not show sufficient agreement and the target endpoint of this study based on the pre-defined cut-off point for macimorelin was not achieved. Consecutively, no 95% confidence limits are presented for the other steps of the hierarchical testing procedure.

Results were almost identical if for the MAC the highest GH level among 45 and 60 min values was evaluated (data not shown) which was step 2 in hierarchical testing.

Overall, mean/median peak GH levels correlated well with the likelihood of having AGHD as the highest GH values were determined in healthy subjects and patients of Group C, and the lowest GH levels were analysed in Group A (**Figure 8**).

Figure 8. GH serum concentration profiles for Group A and Group D subjects after MAC in Study AEZS-130-052 (mITT)

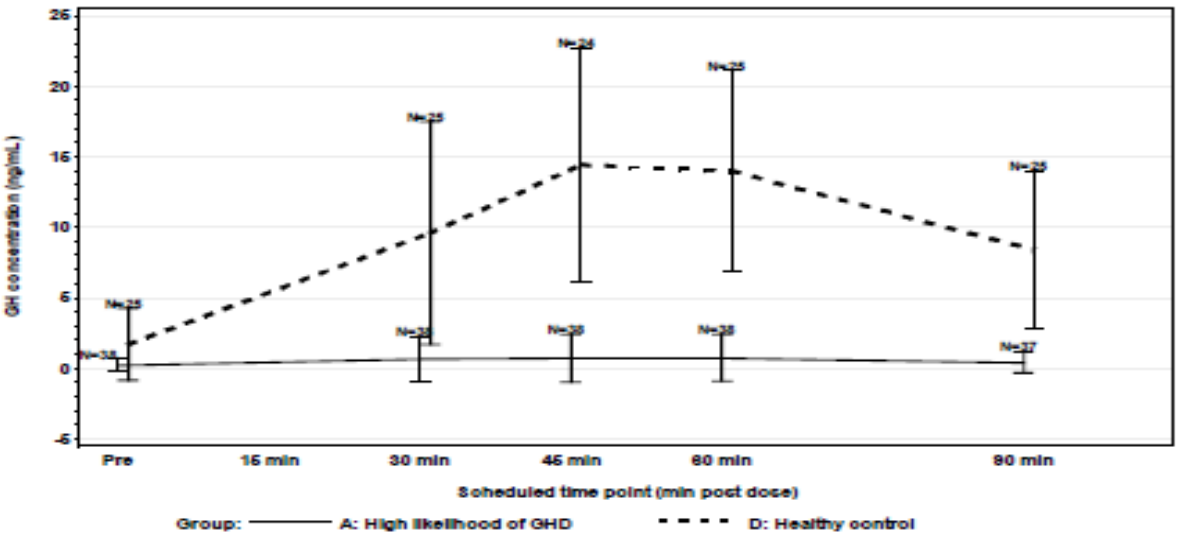


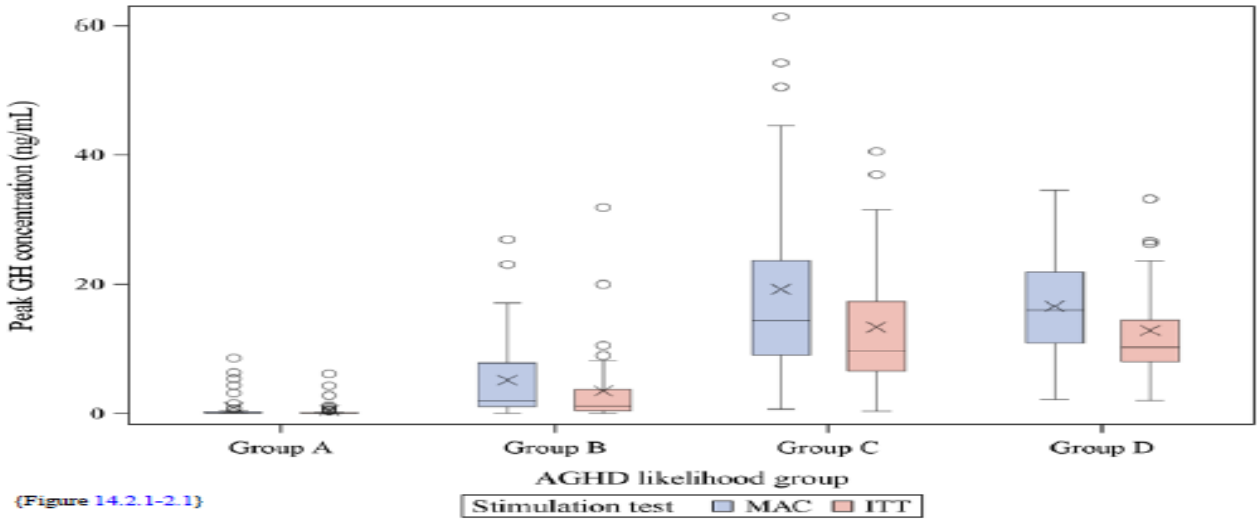
Table 22 summarizes for all subjects of the mITT population the peak GH concentrations in the MAC and the ITT.

Table 22. Statistics on peak GH concentrations stratified by AGHD likelihood Group in Study AEZS-130-052 (mITT)

Stimulation test	Peak GH concentration (ng/mL)							
- AGHD likelihood Group	N	Mean	Std	Min	Q1	Median	Q3	Max
MAC - mITT	**140**	**10.1**	**12.3**	**0.1**	**0.6**	**6.0**	**15.7**	**61.2**
MAC - Group A	38	0.9	2.0	<0.05	<0.05	0.1	0.4	8.6
MAC - Group B	37	5.2	6.5	0.1	1.0	2.0	7.9	27.0
MAC - Group C	40	19.2	15.5	0.7	9.0	14.5	24.2	61.2
MAC - Group D	25	16.6	7.4	2.2	10.8	16.1	22.2	34.6
ITT - mITT	**140**	**7.2**	**8.9**	**0.1**	**0.3**	**4.4**	**10.3**	**40.5**
ITT - Group A	38	0.5	1.3	<0.05	<0.05	0.1	0.2	6.2
ITT - Group B	37	3.5	6.2	0.1	0.5	1.2	4.0	31.9
ITT - Group C	40	13.4	9.7	0.4	6.6	9.7	17.6	40.5
ITT - Group D	25	12.9	7.5	2.1	7.8	10.3	15.4	33.2

GH levels in the macimorelin GHST, as compared to the ITT, are shown in **Figure 9**.

Figure 9. Peak GH concentrations in MAC and ITT by GHD likelihood category in Study AEZS-130-052 (mITT)



{Figure 14.2.1-2.1}

Secondary endpoints

The percent of overall agreement between MAC and ITT based on the pre-defined macimorelin cut-off point is presented below. Since one of the primary endpoints failed to meet the predefined range, these calculated confidence intervals are provided for information only.

Step 1 - Peak GH level among all post baseline samples

95 % Confidence interval (Pearson Clopper) for overall agreement

Overall agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
83.57	76.38	89.29

Step 2 - Highest GH-level among 60 and 45 minutes post dose

95 % Confidence interval (Pearson Clopper) for overall agreement

Overall agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
84.29	77.18	89.88

Step 3 - GH-level at 60 minutes post dose

95 % Confidence interval (Pearson Clopper) for overall agreement

Overall agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
87.14	80.44	92.20

Step 4 - GH-level at 45 minutes post dose

95 % Confidence interval (Pearson Clopper) for overall agreement

Overall agreement (%)	Lower confidence limit (%)	Upper confidence limit (%)
81.43	73.98	87.50

Sensitivity and specificity

Sensitivity and specificity for both GHSTs were estimated, assuming all high likelihood AGHD subjects of Group A as 'true' AGHD subjects and all healthy matching subjects of Group D as 'true' AGHD negative subjects and using the pre-defined cut-off points of 2.8 ng/mL for the MAC and 5.1 ng/mL for the ITT (**Table 23).**

Table 23. Sensitivity and specificity for MAC and ITT in Group A (n=38) and Group D (n=25) with 95% CI in in Study AEZS-130-052 (mITT)

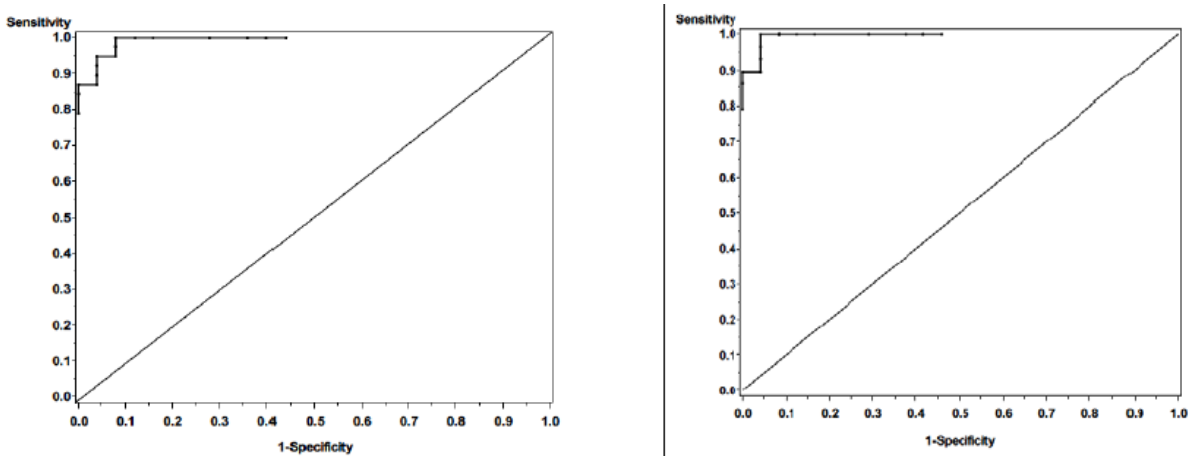
Parameter	Value	Lower confidence limit	Upper confidence limit
MAC			
Sensitivity	0.87	0.72	0.96
Specificity	0.96	0.80	1.00
MAC, excluding Group A subjects without a matching healthy control subject in Group D			
Sensitivity	0.90	0.73	0.98
Specificity	0.96	0.79	1.00
ITT			
Sensitivity	0.97	0.86	1.00
Specificity	0.96	0.80	1.00
ITT, excluding Group A subjects without a matching healthy control subject in Group D			
Sensitivity	1.00	0.88	1.00
Specificity	0.96	0.79	1.00
Definitions: Sensitivity: Probability that the test result is positive given the subject has the disease. **Specificity:** Probability that the test result is negative given the subject does not have the disease.			

Results were similar when subjects were excluded from not matched Group A subjects. When using the pre-defined cut-off points of 2.8 ng/mL for the MAC and 5.1 ng/mL for the ITT, point estimates for sensitivity ranged from 0.87 to 0.90 for the MAC and from 0.97 to 1.0 for the ITT, depending on the inclusion or exclusion of data from not matched Group A subjects, respectively. For both GHSTs, the

estimated specificity was 0.96, irrespective of the in/exclusion data from not matched Group A subjects. All lower 95% confidence limits were in the range of 0.72 to 0.80 for the MAC and in the range of 0.79 to 0.88 for the ITT.

Based on the assumptions regarding the "true" disease status, receiver operator characteristics (ROC) curves were established to illustrate the dependence of the sensitivity and specificity of both assays as the cut-off points of the assays are changed. ROC curves were prepared for the MAC (**Figure 10**) and the ITT and show the results for growth hormone for all subjects of Group A and Group D and for all subjects of Group A and matching Group D subjects.

Figure 10. ROC curve: MAC in group A and Subjects (left panel) and matching D (right panel)



The effect of varying the GH cut-off point for the MAC on the point estimates and lower 95% confidence intervals of the estimated sensitivity and specificity is illustrated in **Figures 11** and **12** respectively.

Figure 11. MAC: Sensitivity for varying GH cut-off points of group A and D subjects

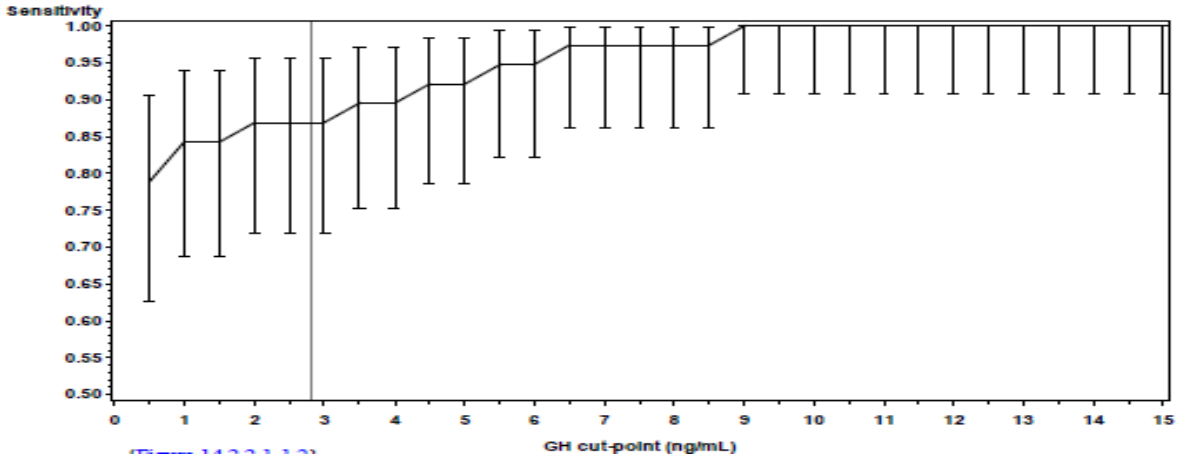
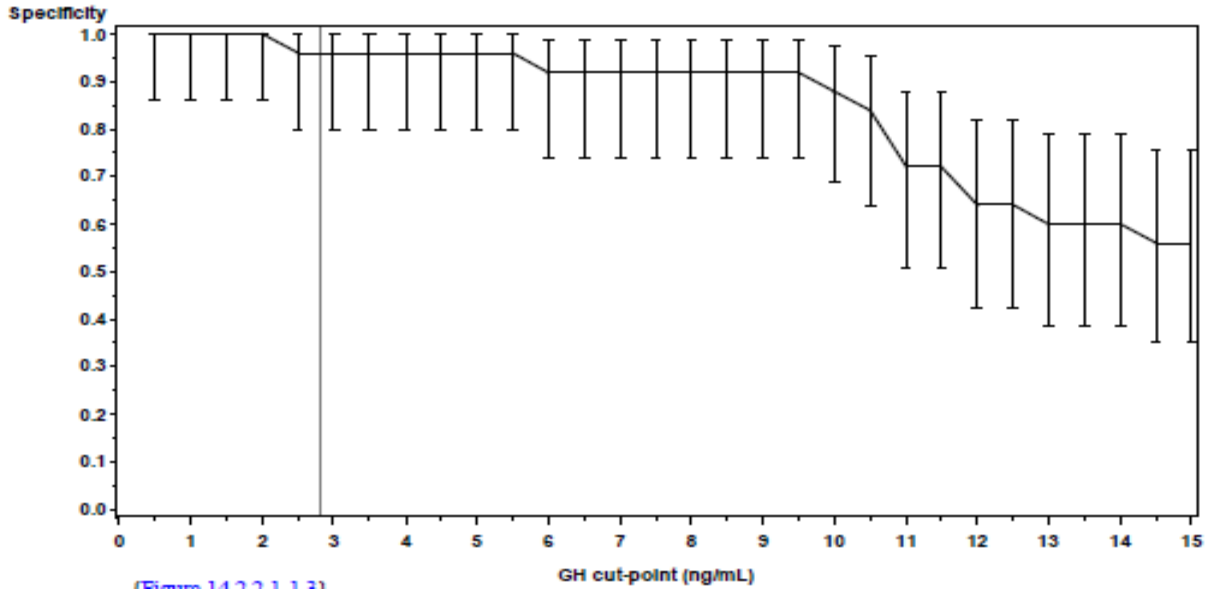


Figure 12. MAC: Specificity for varying GH cut-off points of group A and D subjects



Macimorelin repeatability assessment

Repeatability assessment (MAC Test 3) was performed in a subgroup of 34 subjects of the mITT as described above. The results are summarized in **Table 24**.

Table 24. Growth hormone concentrations after both MACs

Time point	Growth hormone concentrations ng/mL							
	N*	Mean	Std	Min	Q1	Median	Q3	Maximum
MAC (core study)								
Pre-dose	34	1.076	2.5970	0.05	0.050	0.135	0.620	10.87
30 minutes post dose	34	4.948	8.5064	0.05	0.110	0.585	6.160	34.52
45 minutes post dose	34	8.242	13.3036	0.05	0.110	1.000	10.930	54.27
60 minutes post dose	34	8.577	14.8284	0.05	0.170	1.235	9.600	53.64
90 minutes post dose	34	5.069	9.1058	0.05	0.120	1.610	4.460	37.32
Peak GH concentrations	34	9.427	14.9952	0.05	0.210	1.635	12.250	54.27
MAC Test 3								
Pre-dose	34	0.399	0.5187	0.05	0.050	0.150	0.700	1.96
30 minutes post dose	34	4.109	8.1642	0.05	0.150	0.985	4.190	39.38
45 minutes post dose	34	7.228	13.0953	0.05	0.190	1.330	7.900	59.84
60 minutes post dose	34	7.515	13.1178	0.05	0.160	1.985	8.480	54.82
90 minutes post dose	34	5.112	8.4660	0.05	0.120	1.245	4.190	32.02
Peak GH concentrations	34	8.671	14.2671	0.05	0.190	3.275	8.730	59.84

*mITT population, N=140, only subjects with repeated tests, N=34
Concentrations below limit of quantification (<0.05 ng/mL) were set to this limit for presentation
In case of results from retest, these are used in the calculation
Min = minimum, N = number, Q1 = first quartile, Q3 = third quartile, Std = standard deviation.

The difference in peak GH concentrations between the core study and repeated study differentiating between test positive and test negative subjects is shown in **Table 25**.

Table 25. MAC: Difference in peak GH concentration (core – repeated)

Outcome in core study	MAC-GHST: Difference in peak GH concentration (core study - repeated)						
	N*	Mean	Std	Median	Lower 95% confidence limit	Upper 95% confidence limit	P-value for test of zero mean
Positive	18	-0.493	1.7359	-0.02	-1.356	0.370	0.2449
Negative	16	2.163	7.6341	1.08	-1.905	6.230	0.2750
Total	34	0.757	5.4638	0.00	-1.150	2.663	0.4251

Subgroup-analysis

Results were provided for results for Groups A and D in patients with BMI-class 30.0 to 34.9 kg/m² and BMI class 35-39.9 kg/m²(**Table 26** and **27** respectively) .

Table 26. Macimorelin stimulation test results in high probability AGHD subjects (group A) and healthy subjects (group D) all subjects of group A and group D in BMI class 30-34.9 kg/m² (upper panel) and Sensitivity and specificity for Macimorelin stimulation test with 95% confidence intervals (Pearson Clopper) (lower panel)

Macimorelin stimulation test outcome	AGHD group				Total	
	A: High likelihood of GHD		D: Healthy control			
	N	%	N	%	N	%
Positive	6	85.71	0	0	6	66.67
Negative	1	14.29	2	100.00	3	33.33
Total	7	100.00	2	100.00	9	100.00

Parameter	Value	Lower confidence limit	Upper confidence limit
Sensitivity	1.00	0.40	1.00

Table 27. Macimorelin stimulation test results in high probability AGHD subjects (group A) and healthy subjects (group D) all subjects of group A and group D in BMI class 35-39.9 kg/m² (upper panel) and Sensitivity and specificity for Macimorelin stimulation test with 95% confidence intervals (Pearson Clopper) (lower panel)

Macimorelin stimulation test outcome	AGHD group		Total	
	A: High likelihood of GHD			
	N	%	N	%
Positive	4	100.00	4	100.00
Total	4	100.00	4	100.00

Parameter	Value	Lower confidence limit	Upper confidence limit
Sensitivity	1.00	0.40	1.00

No subjects of group D are available for this BMI-class

The comparison of MAC performance in the sub-population with a BMI > 35 kg/m2 (N=15), the sub-population with a BMI > 30 kg/m2 (N=41) and the mITT (N=139) is presented in **Table 28**.

Table 28. Agreement, repeatability, sensitivity and specificity for ITT GH cut-off point 3.0 ng/mL and MAC GH cut-off points of 2.8 mg/mL and preselected based on exploratory analyses of peak GH values in MAC for sub-populations with various BMI

MAC GH cut-off point	Core study analysis Agreement between MAC and INTT INTT cut-off point 3.0 ng/mL w.o. RS01-06[a]						MAC Repeatability (M-core vs. M-rep.; *w.o. RS01-06;)*		ROC analysis for MAC (Groups A+D)		
	Negative agreement		Positive agreement		Overall agreement		Overall agreement		Sensi-tivity	Speci-ficity	YInd
	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	(%)	J
	mITT; N=139						N=33		N=38+25		
2.8	94.74	87.07	85.71	74.61	90.65	84.54	96.97	84.24	87	96	83
	mITT; BMI > 30kg/m²; N=41						N=10		N=11+2		
1.6	100	81.47	78.26	56.3	87.8	73.8	100	69.15	91	100	91
2.2	100	81.47	86.96	66.41	92.68	80.08	90	55.5	91	100	91
2.8	100	81.47	86.96	66.41	92.68	80.08	100	69.15	91	100	91
	mITT; BMI 30-35kg/m²; N=26						N=8		N=7+2		
1.6	100	73.54	78.57	49.2	88.46	69.85	100	63.06	86	100	86
2.2	100	73.54	85.71	57.19	92.31	74.87	87.5	47.35	86	100	86
2.8	100	73.54	85.71	57.19	92.31	74.87	100	63.06	86	100	86
	mITT; BMI > 35kg/m²; N=15						N=2		N=4+0		
1.6	100	54.07	77.78	39.99	86.67	59.54	100	15.81	100	NA	NA
2.2	100	54.07	88.89	51.75	93.33	68.05	100	15.81	100	NA	NA
2.8	100	54.07	88.89	51.75	93.33	68.05	100	15.81	100	NA	NA

** One subject was excluded due to a compliance error*

Ancillary analyses

Exploratory analyses based on post hoc changes in the definition of the cut-off point

The performance characteristics of the MAC calculated for GH cut-off points that corresponded to an observed peak GH in a MAC of the core study are summarised in **Table 29**.

For practical reasons, the lower end of the GH cut-off points was selected at 2.21 ng/mL (the highest value below the pre-defined value of 2.8 ng/mL), and the upper end was selected at 8.31 (an arbitrary value reflecting the higher peak GH in the MAC than in the ITT).

These results are based on the complete modified intention-to-treat (mITT) data set, but exclude data from one subject in whom no macimorelin levels were found after dosing. Since formally being a valid data set, this subject was included in the mITT analysis of Study 052 (N=140), but was excluded as a blatant compliance error in the present exploratory analysis (N=139).

Table 29. Agreement, repeatability, and sensitivity and specificity explored for GH cut-off points selected on peak GH values in MAC

GH cut-off point (peak GH for a MAC in core study)	Core study analysis Agreement between MAC and ITT w.o. RS01-06 (mITT=139)						MAC Repeatability (M-core vs M-repeat. w.o. RS01-06 (N=33)		ROC analysis for MAC (Groups A+D (N=38+25)	
	Negative agreement		Positive agreement		Overall agreement		Overall agreement		Sensi-tivity	Speci-ficity
	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	(%)
2.21	96.92	**89.32**	74.32	62.84	84.89	77.84	**93.94**	**79.77**	87	**100**
3.16	95.38	**87.10**	74.32	62.84	84.17	77.02	**96.97**	**84.24**	87	**96**
3.21	95.38	**87.10**	75.68	64.31	84.89	77.84	**96.97**	**84.24**	89	**96**
3.66	95.38	**87.10**	77.03	65.79	85.61	78.66	**93.94**	**79.77**	89	**96**
4.41	95.38	**87.10**	78.38	67.28	86.33	79.48	**90.91**	**75.67**	89	**96**
4.46	95.38	**87.10**	79.73	68.78	87.05	80.31	**90.91**	**75.67**	**92**	**96**
4.74	95.38	**87.10**	81.08	**70.30**	87.77	**81.14**	**93.94**	**79.77**	**92**	**96**
4.88	95.38	**87.10**	82.43	**71.83**	88.49	**81.98**	**93.94**	**79.77**	**92**	**96**
5.20	93.85	**84.99**	82.43	**71.83**	87.77	**81.14**	**93.94**	**79.77**	**92**	**96**
5.43	93.85	**84.99**	83.78	**73.39**	88.49	**81.98**	**90.91**	**75.67**	**92**	**96**
5.79	93.85	**84.99**	85.14	**74.96**	89.21	**82.83**	**90.91**	**75.67**	**95**	**96**
5.90	92.31	**82.95**	85.14	**74.96**	88.49	**81.98**	**90.91**	**75.67**	**95**	**92**
6.16	92.31	**82.95**	86.49	**76.55**	89.21	**82.83**	87.88	71.80	**95**	**92**
6.18	92.31	**82.95**	87.84	**78.16**	89.93	**83.68**	87.88	71.80	**95**	**92**
6.41	90.77	**80.98**	87.84	**78.16**	89.21	**82.83**	**90.91**	**75.67**	**95**	**92**
7.00	89.23	79.06	87.84	**78.16**	88.49	**81.98**	**90.91**	**75.67**	**97**	**92**
7.85	89.23	79.06	89.19	**79.80**	89.21	**82.83**	**90.91**	**75.67**	**97**	**92**
7.86	89.23	79.06	90.54	**81.48**	89.93	**83.68**	**90.91**	**75.67**	**97**	**92**
8.04	87.69	77.18	90.54	**81.48**	89.21	**82.83**	**90.91**	**75.67**	**97**	**92**
8.31	87.69	77.18	91.89	**83.18**	89.93	**83.68**	**90.91**	**75.67**	**97**	**92**

The bolded frame in the table indicates the range of GH cut-off points in which multiple performance characteristics match the favorable criteria for the exploratory analyses as defined above (methods, post hoc amendments).

Another exploratory analysis on the performance of the MAC cut-off point of 2.8 ng/mL (as pre-defined in Study 052) based on an INTT cut-off point of 3.0 ng/mL as recommended by The European consensus guidelines for the diagnosis and treatment of adults with GH deficiency II (Ho et al, 2007) is presented in **Table 30.**

Table 30. Agreement, repeatability, and sensitivity and specificity explored for INTT GH cut-off points "3.0 ng/mL" based on peak GH values in MAC

MAC GH cut-off point	Core study analysis Agreement between MAC and INTT (mITT *w.o. RS01-06; N=139*)						MAC Repeatability (M-core vs. M-rep.; *w.o. RS01-06; N=33)*		ROC analysis for MAC (Groups A+D; N=38+25)		
	Negative agreement		Positive agreement		Overall agreement		Overall agreement		Sensi-tivity	Speci-ficity	YInd
	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	Lower CI limit (%)	(%)	(%)	J
	INTT cut-off point 3.0 ng/mL										
2.8	94.74	87.07	85.71	74.61	90.65	84.54	96.97	84.24	87	96	83
	INTT cut-off point 5.1 ng/mL										
2.8	95.38	87.1	74.32	62.84	84.17	77.02	96.97	84.24	87	96	83
5.6	93.85	84.99	85.14	74.96	89.21	82.83	93.94	79.77	95	96	91

The results for agreement between MAC and ITT in the group of patients with intermediate likelihood of having disease for the two different cut-off points is shown in **Table 31**.

A patient based analysis for discrepant results was also provided by the applicant. In 3 cases with discrepant test outcome, the disagreement between both GHSTs can be attributed with high likelihood to a failure of either test. When taking the subjects' medical background into account, an ITT failure appeared as a reasonable alternative among other potential reasons for the disagreement in 4 additional cases.

In 6 cases, the increase in the cut-off point from 2.8 to 5.1 ng/mL leads to 'positive agreement', i.e., to the agreement of the MAC in an ITT-positive subject, and the new agreement would be (more) consistent with the clinical background. In one ITT-negative subject, the revised cut-off point would convert the previously negative agreement into negative disagreement. Considering the clinical background in this subject with an a priori low likelihood of having AGHD, it is unlikely that a MAC positive classification at a GH peak of 4.88 ng/mL would be considered as a strong argument to start or continue GH replacement treatment solely based on this test result.

It should be noted that in 10 ITT-positive subjects with test-negative macimorelin GHST, the peak GH in the ITT ranged between 3 ng/mL and 5.1 ng/mL, i.e. the peak GH release was above the previously used GH cut-off point for the ITT of 3 ng/mL (e.g., Ho 2007). In other words, these subjects had a residual release of GH that would often be referred to as GH Insufficiency (GHI).

Table 31. Estimated sensitivity (= positive agreement with ITT) and estimated specificity (= negative agreement with ITT) of MAC in AGHD likelihood Groups B and C for GH cut-off points of 2.8 ng/mL and 5.1 ng/mL

Group B		ITT		
		Positive	Negative	Total
MAC	Positive	**20**	1	21
(2.8 ng/mL)	Negative	**10**	6	16
	Total	30	7	
Sensitivity = 20 / (20 + 10) = 67%; Specificity = 10 / (10 + 1) =91%				
MAC	Positive	**23**	1	24
(5.1 ng/mL)	Negative	**7**	6	13
	Total	30	7	
Sensitivity = 23 / (23 + 7) = 76%; Specificity = 7 / (7 + 1) = = 88%				
Group C		ITT		
		Positive	Negative	Total
MAC	Positive	**2**	**2**	4
(2.8 ng/mL)	Negative	**4**	**32**	36
	Total	6	34	
Sensitivity = 2/ (2 + 4) = 33%; Specificity = 32 / (32 + 2) = 94%				
MAC	Positive	**3**	**3**	6
(5.1 ng/mL)	Negative	**3**	**31**	34
	Total	6	34	
Sensitivity = 3 / (3 + 3) = 50%; Specificity = 31 / (31 + 3) = 91%				

Among the subjects in whom the 'superior' stimulation in the MAC resulted in higher peak GH levels, one subject experienced , up to 10-fold higher peak GH values in the MAC which could be explained by the subject's medical history: idiopathic forms of childhood onset GHD are suspected often to be caused by a hypothalamic dysfunction, so that the GH response to MAC seems to indicate the 'normal' pituitary function.

Discordant results between INTT and GHRH induced growth hormone secretion have been observed in the literature in about 50% of cases among hyperprolactinemic patients (Beentjes 1996).

From the mITT population of Study 052, altogether nine patients showed a hyperprolactinemia in their medical history, and for six of those the disease was reported as ongoing. When reviewing the INTT and MAC outcomes, only one case was found with a positive INTT outcome versus a negative MAC outcome. Three other patients were identified with positive agreement between INTT and MAC, and four further patients were observed with negative agreement between INTT and MAC.

Furthermore, six patients were identified in the Study 052 mITT population with elevated prolactin levels at study baseline. Using an INTT cut-off point of 3.0 ng/mL and a MAC cut-off point of 2.8 ng/mL, five patients were found with positive agreement between INTT and MAC.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 32. Summary of Efficacy for trial AEZS-130-052

Title: 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)		
Study identifier	**Clinical Study No. AEZS-130-052, EudraCT No. 2015-002337-22**	
Design	It was an open-label, randomized, single dose, 2-way crossover study comparing the diagnostic performance of Macimorelin 0.5 mg/kg p.o. (MAC) with an insulin tolerance test (ITT) with a prespecified repeated test vor Macomrelin in a subgroup (repeatability extension).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Single dose not applicable not applicable
Hypothesis	Non-inferiority Macimorelin test vs. ITT	
Treatments groups	Group A, B, and C Adult patients with high (A), intermediate (B) and low (C) likelihood of AGHD Group D: Matched healthy subjects	Cross over randomized ITT vs. Macimorelin 0.5 mg/kg p.o.

Endpoints and definitions	Co-Primary endpoints		There were two **co-primary** efficacy variables in this study: • Percent of Negative Agreement; • Percent of Positive Agreement. The following cut-off values for stimulated GH levels were used: •Macimorelin-GHST: GH: 2.8 ng/mL •ITT: GH: 5.1 ng/mL The primary efficacy measures (negative and positive agreement, respectively) were analyzed by a hierarchical testing procedure with regard to the sampling time for the macimorelin test: 1. Peak GH among all post baseline samples 2. Highest GH among 60 and 45 minutes post dose 3. GH at 60 minutes post dose 4. GH at 45 minutes post dose Per Amendment no. 1, the primary efficacy variable for the repeatability extension was the comparison of peak GH levels following repeated treatments with macimorelin
	Secondary, other		The **secondary** diagnostic accuracy measure was 'percent overall agreement'. **GHST acceptance** using a study specific questionaire
	Post-hoc analyses		Post-hoc analyses were performed for the Co-primary efficacy endpoints applying the same hierarchical testing procedure as outlined above
	Start: 01-Oct-2015 screening of the first subject. Completed: 29-Nov-2016 Last-Patient-Last-Visit.		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Screened n=238, Enrolled n=166, Safety n=157, mITT n=140, Repeatability: subgroup out of mITT n= 34 primary analysis: mITT n=140, Repeatability: mITT n=34			
Effect estimate per comparison		ITT Positive	ITT negative	Total
		n/%	n/%	n/%
	MAC positive	55/39.29	4/2.86	59/42.14
	MAC negative	19/13.57	62/44.29	81/47.86
	total	74/52.86	66/47.14	140/100.00
	Negative agreement/lower /upper 95% confidence limit (Pearson Clopper)	93.94	85.20	98.32
	Positive agreement/lower /upper 95% confidence limit (Pearson Clopper)	74.32	62.84	83.78
Notes	Results were almost identical if for the MAC the highes GH level among 45 and 60 min values was evaluated (step 2 in hierarchical testing). Due to the failure to achieve the predefined non-inferiority margin for positive agreement, step 2 – 4 of the hierarchical testing procedure regarding time points of assessment for MAC was not performed.			
Analysis description	**Secondary and exploratory analyses**			

Secondary analyses:

percent of overall agreement between MAC and ITT

Overall agreement (%; Lower;upper 95% confidence limit)
- Peek level among all post baseline samples: 83.57 (76.38; 89.29)
- Highest GH level among 60/45 minutes post dose: 84.29 (77.10; 89.88)
- GH-level at 60 minutes post dose: 87.14 (80.44; 92.20)
- GH level at 45 minutes post dose: 81.43 (73.98; 87.50)

Exploratory post hoc analyses

Exploratory post-hoc analyses indicated a higher positive agreement with a minor decrease in negative agreement and a higher overall agreement with a post-hoc defined GH cut-off point for MAC between 4.74 and 5.20.

Sensitivity and Specificity:

(Definitions: Sensitivity: Probability that the test result is positive given the subject has the disease. Specificity: Probability that the test result is negative given the subject does not have the disease.)

Macimorelin stimulation test results in high probability subjects (group A) and healthy subjects (group D)

MAC	AGDH group A (High likelihood)		Group D (Healthy control)		Total	
	N	%	N	%	N	%
Positive	33	86.84	1	4.00	34	53.97
Negative	5	13.16	24	96.00	29	46.03
Total	38	100.00	25	100.00	63	100.00

Sensitivity and specificity for Macimorelin stimulation test with 95% confidence intervals (Pearson Clopper)

Parameter	Value	Lower confidence limit	Upper confidence limit
Sensitivity	0.87	0.72	0.96
Specificity	0.96	0.80	1.00

Repeatability assessment for MAC GHST

Mean results were overall about 0.5. – 1.0 ng/mL lower in the second test, whereas median levels tended to be slightly higher. No significant differences were found between peak GH and GH concentrations measured in the core study and in the repeatability extension. There was 100% negative agreement (79.41; 100.00), positive agreement was lower: 88.89 (65.29; 98.62).

Questionaire on GHST acceptance

In all six questions, subjects voted in favor of the MAC compared to the ITT.

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No specific trials were presented in special populations e.g. with renal failure, hepatic failure or the elderly. In Study AEZS-130-047 (see Supportive study below), 19% of the subjects were aged >65 years and 6% were aged >75 years. In the pivotal Study AEZS-130-052, 2% were aged between 65 and 70 years.

Supportive study

Study AEZS-130-047: A multi-centre study investigating a new, oral growth hormone secretagogue (GHS) (Macimorelin acetate) as a growth hormone (GH) stimulation test in terms of safety and efficacy.

The study was originally designed as an open label, multicentre, randomized, two-way, crossover study (≥ 1 week washout) in subjects with:

- Confirmed AGHD, diagnosed by GHRH-ARG (peak GH < 4.1 µg/L) in adulthood

OR

- Multiple pituitary hormone deficiencies in ≥ 3 hormones (from thyroid stimulating hormone [TSH], adrenocorticotropic hormone [ACTH], gonadotrophin releasing hormone [GnRH], or arginine vasopressin [AVP]) and low IGF-1 concentration (below limit of normal, using age and sex-adjusted normal ranges)
- Normal controls, matched for age, gender, body mass index (BMI) and estrogen status for females

Each subject was to receive the following, in random order while fasting, at least 1 week apart:

- GHRH (Geref Diagnostic, Serono) intravenous (IV) bolus of 1 µg/kg + L-ARG (Ar-Gine®, Pfizer) IV infusion of 30 g over 30 minutes
- Macimorelin 0.5 mg/kg, given in oral solution of 0.5 mg/mL

The original protocol called for exposure to both GHRH-ARG and macimorelin for 40 AGHD patients and 40 matched (age, gender, BMI, oestrogen status) normal controls. At the time of the study termination by the initial sponsor, 42 AGHD patients and 10 matched controls had completed the crossover treatments.

When the study was resumed, it was a Phase III, multi-center, open-label study of approximately 100 subjects. Geref (GHRH) was withdrawn from the US market in 2008 and therefore, no comparative agent was available.

Thirty (30) normal control subjects matching the AGHD patients who completed the original protocol were to be enrolled under the amended protocol as well as 20 additional subjects (10 AGHD patients and 10 matched, normal control subjects). Newly enrolled AGHD patients had GH deficiency confirmed using one of the following stimulation tests and with the following cut-points:

- L-ARG + GHRH (cut-point 4.1 µg/L)
- ITT (cut-point 5.0 µg/L)
- Glucagon (cut-point 3.0 µg/L)
- Arginine (cut-point 0.4 µg/L) OR
- Multiple pituitary hormone deficiencies (MPHD) with deficiencies in ≥ 3 hormones (including TSH, ACTH, GnRH, and/or AVP).

Patients who qualified for the study based on MPHD criteria must also have had low IGF-1 (defined as below the lower limit of normal for age and sex-adjusted normal range for IGF-1).

Fasting patients and matched control subjects were treated with a single dose of macimorelin 0.5 mg/kg, given in an oral solution of 0.35 mg/mL in the morning. Subjects enrolled under Amendment No. 3 and thereafter received only macimorelin because L-ARG+GHRH was no longer available; therefore, the crossover aspect of the design and randomization were not applicable.

The primary efficacy analysis was based on the mITT analysis set. The mITT analysis set consisted of all intent-to-treat subjects that received macimorelin and had at least one GH measurement between 45 and 75 minutes posttreatment.

The per protocol set (PPS) included all patients from the mITT without major protocol violations.

The safety population (safety analysis set) included all subjects who received at least one dose of study medication and for whom any safety information was available.

- The primary efficacy variable was the peak GH concentration for each subject following treatment with macimorelin. The GH concentrations were determined by ICMA assay.

The diagnostic accuracy of macimorelin was established if the ROC AUC was greater than 0.85. This was tested with $\alpha=0.01$ using the one sided hypotheses:

$H0: AUC \leq 0.85$ vs, $HA: AUC > 0.85$

The null hypothesis was rejected in favour of the alternative if the lower bound of the one-sided 99 % confidence interval (CI) on the AUC was greater than 0.85.

The basis for truth for the ROC analysis was the patient or control status of the subject. By definition, the patients were proven AGHD subjects by meeting entry criteria. Patients without confirmed AGHD were identified as having a major protocol deviation and excluded from the PPS. The ROC curve was created by plotting the true positive fraction (TPF or sensitivity) versus the false positive fraction (FPF or 1-specificity) determined by moving the cut-point value along the peak GH concentration range.

Overall, 53 AGHD patients and 48 matched control subjects were enrolled and all subjects, with the exception of 1 AGHD patient, received macimorelin and completed the study. The AGHD patient who discontinued did so due to collapsed veins. This patient received L-ARG + GHRH before discontinuing.

Among the 52 AGHD patients, 46 (88.5 %) had matched control subjects based on all three criteria (age, BMI, sex/estrogen status). Additionally, 2 patient-matched control pairs were matched on two of the three criteria (age and sex/estrogen status). Thus, overall, there were 48 complete AGHD/control matched pairs. Four AGHD patients (7.7 %) had no matched control subject. Two AGHD subjects who were major protocol deviations, i.e. did not meet entry criteria for confirmed AGHD, were not matched. The other two AGHD patients who were not matched had high BMI (34.8 and 55.7 kg/m2), were of a young age, and on estrogen therapy (one oral, one transdermal).

A summary of the demographic and baseline characteristics for all subjects is presented in **Table 33**.

Table 33. Demographics and baseline characteristics of subjects in Study AEZS-130-047 (all enrolled subjects)

	AGHD Patient N = 53	Matched Control N = 48
Sex (N, %)		
Male	31 (58.5)	30 (62.5)
Female	22 (41.5)	18 (37.5)
Race (N, %)		
White	49 (92.5)	29 (60.4)
Black or African American	2 (3.8)	18 (37.5)
Asian	2 (3.8)	0 (0.0)
Other	0 (0.0)	1 (2.1)
Ethnicity (N, %)		
Hispanic or Latino	11 (20.8)	9 (18.8)
Not Hispanic or Latino	42 (79.2)	39 (81.3)
Age (N, %)		
< 50 years	27 (50.9)	19 (39.6)
≥ 50 years	26 (49.1)	29 (60.4)
Mean (SD)	52.2 (13.39)	53.5 (12.89)
Median	49.0	53.5
Min-Max	25-80	24-77
Estrogen Status (N, %)		
None	12 (22.6)	12 (25.0)
Oral	9 (17.0)	6 (12.5)
Patch	1 (1.9)	0 (0.0)
BMI (kg/m^2)		
Lean (<25)	7 (13.2)	7 (14.6)
Overweight (≥ 25 and < 30)	15 (28.3)	13 (27.1)
Obese (≥ 30)	31 (58.5)	28 (58.3)
Mean	32.1 (7.42)	31.8 (7.15)
Median	31.3	31.7
Min-Max	19.1-55.7	19.5-52.4

AGHD = adult growth hormone deficient; BMI = body mass index

Primary Efficacy Analysis: ROC Analysis on Peak GH Concentrations

Scatter plots of peak growth hormone levels in response to macimorelin are shown in **Figure 13**, and corresponding mean values in **Table 34**.

Figure 13. Peak growth hormone concentration in response to macimorelin in study AEZS-130-047

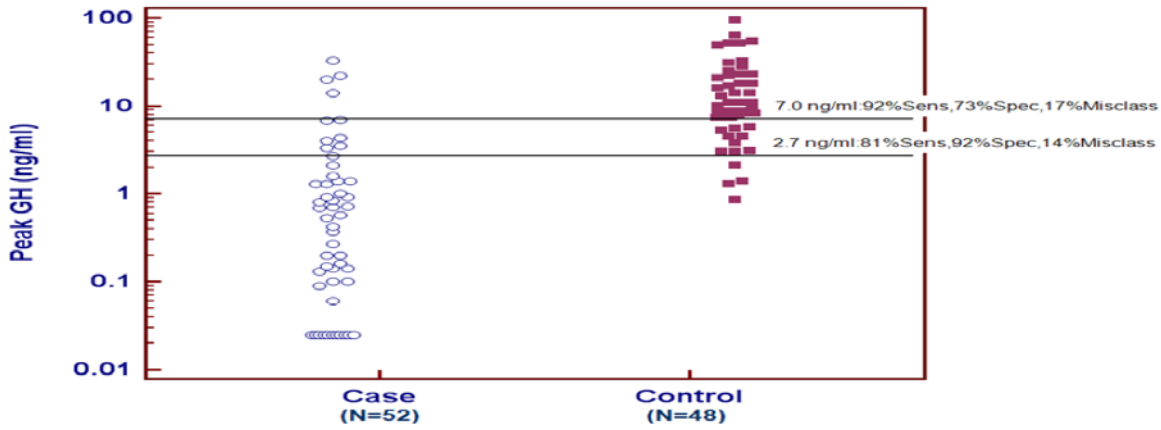


Table 34. Mean peak growth hormone concentration (ng/mL) following macimorelin administration in in study AEZS-130-047

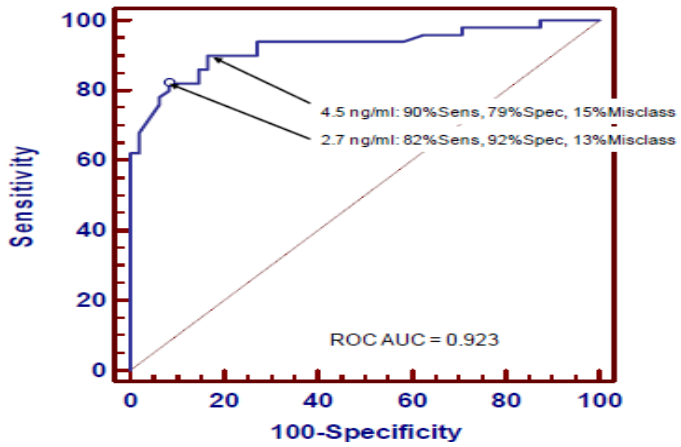
Analysis Population	AGHD Patients				Matched Controls			
	N	Mean (SD)	Median	Min-Max	N	Mean (SD)	Median	Min-Max
mITT	52	2.70 (6.22)	0.55	0.025-33.00	48	17.71 (19.11)	10.5	0.85-94.00
PPS	50	2.36 (5.69)	0.55	0.025-33.00	48	17.71 (19.11)	10.5	0.85-94.00

AGHD = adult growth hormone deficiency; mITT = modified intent to treat; PPS = per protocol analysis set; SD = standard deviation; min = minimum; max = maximum

The diagnostic accuracy of macimorelin was considered to be established if the lower bound of the 1-sided 99 % CI for the ROC AUC, as found by bootstrapping the data with 10,000 samples, was greater than 0.85. This criterion was met in the per protocol analysis set since the lower bound of the 1-sided 99 % CI was 0.8502. The lower bound of the 1-sided 99 % CI was 0.835 in the mITT analysis set and did not meet the pre-established ROC AUC criterion.

Figure 14 show the ROC curve of peak growth hormone in response to macimorelin for the PPS.

Figure 14. ROC curve for analysis of peak growth hormone in response to macimorelin (PPS, Study AEZS-130-047)



The ROC plot analysis showed that the best cut-point was 2.7 ng/mL for both analysis sets. Sensitivity was 81% in the mITT and 82 % in the PPS and specificity 92 % in both analysis sets.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Results from two studies were submitted to support the application.

Study 047 was a multicentre (U.S. only) open label study that was originally designed (by the initial sponsor) as a cross-over trial of oral macimorelin (0.5 mg/kg) vs. GHRH (Geref Diagnostic, Serono) IV bolus (1 µg/kg) + arginine (Ar-Gine, Pfizer) IV infusion (30 g) over 30 minutes in AGHD patients and in matched controls. After 43 AGHD patients and 10 matched controls had been enrolled (of which 42 AGHD patients and 10 matched controls had received macimorelin), Geref Diagnostic was withdrawn worldwide

in 2008. Subsequently, Aeterna Zentaris as the new sponsor had to revise the design of the study. The study was completed by testing 10 more AGHD patients and 38 matched controls with macimorelin alone.

The primary analysis as defined when the study design had to be changed was the receiver operating characteristic curve (ROC) analysis that is based on a reliable knowledge regarding the disease state of the subjects. However, some subjects were included despite not meeting the inclusion criteria, or had been misclassified. Furthermore, the disease status could not be verified in all of the subjects since source data were not available and patients were categorized as having disease based on one test. For patients at an intermediate baseline probability of having AGHD this is not in line with current practice, where two tests are recommended as part of the clinical assessment. Taken these issues together, there is considerable doubt that the ROC analyses could yield reliable results.

Study 052 is considered the pivotal Phase III study. It was an open-label, randomized, multicentre, multinational, 2-way crossover study. The primary objective was to validate the use of single dose oral macimorelin (0.5 mg/kg) as growth hormone stimulation test (GHST) for the diagnosis of AGHD, using the insulin tolerance test (ITT) as comparator GHST.

166 subjects were enrolled in a total of 25 study centres in nine countries in order to include at least 55 'ITT-positive' and 55 'ITT-negative' test outcomes. In addition to subjects with different likelihood of having AGHD (Group A: high; Group B: intermediate, and Group C: low), 20-25 healthy subjects matching a Group A subject were to be included (Group D). Following an amendment to the study protocol, which was implemented as an extension to the core study in selected European sites only, the repeatability of the MAC in a sub-set of about 30 suspected AGHD subjects was also investigated.

The safety population (SAF) consisted of 157 subjects, who had received at least 1 dose of study drug. Of these 143 had an evaluable ITT, but as 3 subjects withdrew before having their MAC performed, the mITT was comprised of 140 subjects: 38 (27.1%) in Group A, 37 (26.4%) in Group B, 40 (28.6%) in Group C, and 25 (17.9%) in Group D. 34 patients from the mITT were included in the repeatability extension

For the evaluation of the GHST, blood samples were collected pre-dose, 30, 45, 60, and 90 minutes post-dose. Cut-off values for the macimorelin stimulation test (MAC) were derived from the results of study 047. The ITT a cut-off point of 5.1 ng/mL was also predefined and had been accepted by the CMHP during a scientific advice procedure, even though it is higher than the cut-off point proposed by a consensus guideline (3.0 ng/mL Ho et al., 2007).

Overall, the size, design and cut-off values for the MAC were considered appropriate to evaluate the use of single dose oral macimorelin as a GHST for the diagnosis of AGHD.

Efficacy data and additional analyses

Study 047

The primary efficacy analysis was based on the mITT. The diagnostic accuracy of macimorelin was considered to be established if the lower bound of the 1-sided 99% CI for the ROC AUC was greater than 0.85. The lower bound of the 1-sided 99% CI was 0.835 in the mITT analysis set and did not meet the predefined ROC AUC criterion. Therefore, the study failed its primary goal. The criterion however was met in the per protocol analysis (99% CI 0.8502). Moreover due to classification issues for some of the patients, the data from this study cannot be considered robust. However, as data for GH stimulation were compared to disease status of the patients, the CHMP considered that the results of the study could be used as a hypothesis generating database for further investigations.

Based on this study, the applicant defined a cut-off value of 2.8 ng/mL for the MAC for the pivotal trial 052. Based on information on the comparability of the assays used for determination of GH plasma concentration in both studies, use of this cut-off value in the pivotal study was considered acceptable.

Study 052

The lower limit of the 95% CIs for the negative agreement was 85.20% and thus conformed to the pre-set criterion of 75% for this parameter. Positive agreement of MAC with ITT was 74.32%, with a lower limit of 62.84% for the 95% CIs, which did not match the predefined criterion of ≥ 70 % for this parameter.

Results were almost identical if for the MAC the highest GH level among 45 and 60 min values was evaluated (step 2 in the hierarchical testing).

Since one of the co-primary endpoints failed to achieve the pre-defined margins, the study formally is a failed study. Not achieving the goal for positive agreement indicates that the MAC, using the pre-defined cut-point of 2.8 ng/mL, is more conservative in diagnosing disease and highly specific and thus avoids unnecessary treatment of patients with a wrong positive test result. As stated by the CHMP during the scientific advice procedure for this product, this is the key attribute that is expected from a GHST. Therefore, failing in the positive agreement with the ITT is a direct consequence of a test designed to confirm AGHD.

Negative and positive agreement between MAC and the ITT in subjects with intermediate or low risk (Groups B and C) were 93% and 61% with lower 95% confidence interval bounds 80% and 43%, respectively. These results were based on peak GH values (maximum GH concentrations across all measurement time-points). Peak GH levels were inversely related to the likelihood of having AGHD, i.e., the subjects assigned to the intermediate likelihood (Group B) had lower GH levels than subjects assigned to the low likelihood (Group C). This observation is consistent with published data showing that peak GH levels are inversely related to the number of pituitary deficiencies (Lisset 1999, Hartman 2002).

Overall agreement was 83.57 % (76.38: 89.29, 95% CI) when the peak GH level was used with similar results for Step 2 and 3 (Highest GH-level among 60 and 45 minutes/ 60 minutes post dose respectively) and slightly lower overall agreement was observed for step 4 (GH-level at 45 minutes post dose).

Sensitivity and specificity were defined as follows: Sensitivity: Probability that the test result is positive given the subject has the disease. Specificity: Probability that the test result is negative given the subject does not have the disease.

Sensitivity and specificity for both GHSTs were estimated, assuming all high likelihood AGHD subjects of Group A as 'true' AGHD subjects and all healthy matching subjects of Group D as 'true' AGHD negative subjects:

For MAC the result for sensitivity was 0.87 (0.72; 0.96) and for specificity 0.96 (0.80; 1.00), both of which are considered acceptable for a diagnostic tool, especially in the absence of a real standard of truth.

Repeatability assessment (MAC Test 3) was performed in a subgroup of 34 subjects of the mITT. Only in 2 of the 34 subjects discrepant results were observed using the predefined cut-off point of 2.8 ng/mL.

Although there was no statistically significant difference, the mean results were at almost all time points about 0.5. – 1.0 ng/mL lower in the MAC Test 3 whereas median levels tended to be slightly higher. The results support the conclusion that the test using the predefined cut-offs is quite robust and intra-individual variability is not an issue of concern.

The CHMP recommended that the proposed indication by the applicnat for the evlaution of the pituitary gland secretion of growth hormone should be modified to: diagnosis of growth hormone deficiency (GHD) in adults to better reflect the ability of the test to confirm AGHD.

At higher cut-off levels (4.74 – 5.20 and 4.74 – 5.90 for peak GH values with/without one subject with a compliance issue) there was a mild decrease in negative agreement, an improvement in positive agreement, a mild improvement in overall agreement and a mild decrease in overall agreement in the repeatability assessment, when comparing MAC and ITT. Based on these analyses the applicant proposed to use a post-hoc defined cut-off of 5.1 ng/m. This was not considered to be appropriate. It is unclear, whether such post-hoc defined cut-offs remain valid in a prospective trial. Furthermore, data indicate that in the MAC repeatability study the overall agreement tends to be slightly better with the predefined cut-off value than with the post-hoc proposed range. With higher cut-off values more patients will receive treatment. In particular in group B and C with intermediate and low risk for disease respectively, it was not obvious that a change in the classification based on post hoc cut-offs was in fact a change to the better, when analysing the data on an individual basis. Furthermore, it is conceivable that when using a lower cut-off for the ITT possibly positive agreement might have been higher. This was confirmed in an exploratory analysis using a cut-point of 3 ng/mL (as recommended by the European Society of Endocrinology), which yielded results for the two primary efficacy endpoints that met the predefined margins for positive and negative agreement. The estimates for negative and positive agreement were 95% and 86% with lower 95% confidence interval bounds 87% and 75%, respectively. Repeatability was 97%. Point estimates for sensitivity and specificity were 87% and 96% from not matched Group A subjects, respectively.

Instead of changing the cut-off value for MAC based on post hoc analyses, the CHMP considered that the predefined value should be maintained in order to avoid overtreatment as results from this study have established that a maximally stimulated serum GH level of less than 2.8 ng/mL (at the 45, 60 and 90 minutes timepoints) following macimorelin administration confirms a diagnosis of adult growth hormone deficiency. As with all GH stimulation tests, also the macimorelin test results should always be interpreted in the context if the outcome of all examinations within the diagnostic work-up for a patient.

Published literature and pathophysiological considerations suggest that discordant results between the two GHST in patients with hyperprolactinemia may arise due to their different mode/site of actions. However, this was not confirmed in study 052. Only one out of 9 patients with a history of hyperprolactinemia and one out of 6 patients with elevated prolactin levels at study baseline in study 052 had discordant results with the two tests. However, since the information from study 052 on this issue is limited and cannot definitely rule out the possibility of discrepant results in some patients with hyperprolactinemia, the applicant should continue to gather information from publications or other reports and be prepared to revise the section on discrepant results in case new evidence accumulates suggesting that hyperprolactinemia may differentially affect MAC and ITT.

Analyses of patients included in study 052 with a BMI between 35 and 40 kg/m2 showed consistently negative test results for ITT and MAC in patients with a low pre-Test probability for disease, consistently positive results for patients with very high pre-test probability and a discrepant result in only one of the patients with intermediate pre Test probability for disease. Whereas these data suggest that the test performance of MAC and ITT in these patients is largely similar this does not entirely exclude a higher risk for false positive test results in obese subjects since stimulated GH release is generally lower in patients with higher BMI. No patients with a BMI >40 kg/m2 had been included in the pivotal trial and therefore a statement has been included in the SmPC that the safety and diagnostic performance of macimorelin have not been established for patients with BMI > 40 kg/m2

Based on the exclusion criteria in study 052 and recommendations in European Guidelines on the diagnosis and treatment of AGHD, patients on replacement therapy with growth hormone (GH, somatotropin) or on medicinal products directly affecting the pituitary secretion of somatotropin (e.g. somatostatin analogues, clonidine, levopoda and dopamine agonists) should be advised to discontinue such treatment at least 1 month before receiving a test dose of macimorelin. Exogenous GH or medicinal products directly affecting the pituitary gland could influence the somatotropic function of the pituitary gland and lead to unreliable GH stimulation results.

In addition, patients with a deficiency affecting hormones other than GH (e.g. adrenal, thyroidal and/or gonadal insufficiency, diabetes insipidus) should be adequately replaced with the other deficient hormones before any testing for a deficiency of GH stimulation is performed, to exclude a stimulation failure.

Finally, as hypercortisolism has a significant impact on the hypothalamic-pituitary-adrenal axis, the diagnostic performance of the test may by affected in patients with Cushing's disease or on supra-physiologic glucocorticoid therapy (e.g. systemic administration of doses of hydrocortisone (or its equivalent) in excess of 15 mg/m^2/day) and lead to false positive test results.

2.5.4. Conclusions on the clinical efficacy

The totality of data indicates that MAC at the proposed dose is a valuable diagnostic tool for adult patients suspected to have AGHD, even if one of the pre-defined criteria of acceptability for the performance of the GHST with macimorelin was not met in the pivotal trial. When using a GH cut-off of 2.8 ng/mL, as derived from study 047 the macimorelin test can reliably confirm a diagnosis of AGHD. The choice of this cut-off point was further supported by a post-hoc analysis that used a cut-point for the ITT of 3.0 ng/mL. Avoiding unnecessary therapy with GH is a key goal of a diagnostic method in AGHD, which is information that can be derived from the MAC.

The CHMP recommended that since there is at least a theoretical concern of a differential influence of hyperprolactinemia on the ITT compared to the MAC which cannot be entirely excluded by the available data the applicant should continue to monitor this issue (e.g. based on publications or spontaneous reports) and update the product information if needed in the future.

2.6. Clinical safety

Patient exposure

During the clinical development, a total of 377 subjects have been exposed to macimorelin summarised in **Table 35**.

Table 35. Exposure to macimorelin in clinical trials

Study	Safety pop.	Placebo [B]	Oral macimorelin doses [mg/kg]			
			Total # of mac. dosed subjects	0.5 (+rep) [C]	>0.5	<0.5
Broglio 2002 [A]	2	2	2	2 (+2)	0	6
AEZS-130-IIT [A]	36	9	27	9	0	30
ARD-0705-003	16	0	16	16 (+16)	0	0
AEZS-130-047	100	0	100	100	0	0
AEZS-130-052	157	0	154	154 (+34)	0	0
AEZS-130-054	28	7	21	6	15	0
AEZS-130-055	60	57 [D]	57 [D]	0	57	0
Sum	399	75	377	287 (+52)	72	36

A: See the text below for subjects receiving macimorelin being "crossed-over" in Studies Broglio 2002 and AEZS-130-IIT.
B: 58 subjects (2 in Study Broglio 2002 and 56 in Study AEZS-130-055) receiving placebo also received macimorelin.
C: See the text below for subjects receiving repeated oral macimorelin doses of 0.5 mg/kg.
D: A single subject from Study AEZS 130-055 received only placebo, and another subject received only macimorelin.

Of the 399 subjects included into the safety analysis, 22 did not receive macimorelin, (9 from AEZS-130-IIT, 7 from Study AEZS-130-054 and 1 from Study AEZS-130-055 received only placebo, 3 from Study AEZS-130-052 withdrew after the insulin tolerance test without receiving macimorelin, and 2 subjects from Study AEZS-130-055 received only moxifloxacin).

The safety of macimorelin in the proposed indication is based on two clinical efficacy studies (AEZS-130-047 and AEZS-130-052), comprising a total of 254 subjects exposed to an oral dose of 0.5 mg/kg. Among the subjects in the diagnostic studies, 70% were enrolled as (suspected) AGHD patients, 30% as healthy control subjects; 60% of the population were male and the 82% were Caucasians ("white"); mean age was 45.5 years and mean BMI 29.4 kg/m2.

Adverse events

In the Phase 3 studies (047 and 052), 126 AEs occurred in 27% of subjects following the Macimorelin GH stimulation test compared with 761 AEs in 96.2% of subjects following insulin tolerance test (ITT).

For the Macimorelin GH stimulation test, dysgeusia was the most frequent adverse event with a total incidence of 7%. This high rate of dysgeusia was mainly due to a high reporting rate during the first part of Study 047. After changing to a taste masking formulation a lower incidence of dysgeusia was observed during the second part of Study 047 and in Study 052. All other adverse events for macimorelin, including dizziness, headache, fatigue, hunger, diarrhea and nausea, were reported at incidences of 3% or lower.

Table 36 summarizes the reported adverse events of the Macimorelin GH Stimulation Test vs. ITT based on the reporter's classification of the causal relationship as possible, likely/ probable or certain.

Table 36. Drug-related Adverse Events (Macimorelin GH Stimulation Test vs. ITT), Phase III safety poulation

	ITT N=157			Macimorelin 047 N=100			Macimorelin 052 core N=154			Macimorelin 052 rep N=34			Macimorelin Total N=254		
SOC / PT	F[A]	(%)[B]	N[C]	F	(%)	N	F	(%)	N	F	(%)	N	F	(%)	N
Any drug-related adverse event	149	(95)	710	16	(16)	21	21	(14)	32	4	(12)	5	38	(15)	58
General disorders and administration site conditions	108	(69)	212	0	(0)	0	6	(4)	7	3	(9)	3	9	(4)	10
Hunger	45	(29)	50	0	(0)	0	1	(1)	1	0	(0)	0	1	(0)	1
Feeling hot	43	(27)	49	0	(0)	0	1	(1)	1	1	(3)	1	2	(1)	2
Fatigue	42	(27)	45	0	(0)	0	4	(3)	4	1	(3)	1	5	(2)	5
Asthenia	30	(19)	32	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Thirst	11	(7)	12	0	(0)	0	0	(0)	0	1	(3)	1	1	(0)	1
Chills	9	(6)	11	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Feeling cold	6	(4)	6	0	(0)	0	1	(1)	1	0	(0)	0	1	(0)	1
Malaise	4	(3)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Nervous system disorders	110	(70)	209	12	(12)	12	13	(8)	16	1	(3)	1	25	(10)	29
Somnolence	56	(36)	60	0	(0)	0	1	(1)	1	0	(0)	0	1	(0)	1
Dizziness	43	(27)	47	0	(0)	0	3	(2)	3	1	(3)	1	3	(1)	4
Tremor	25	(16)	28	0	(0)	0	1	(1)	1	0	(0)	0	1	(0)	1
Headache	13	(8)	14	0	(0)	0	4	(3)	4	0	(0)	0	4	(2)	4
Disturbance in attention	9	(6)	9	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Paraesthesia	8	(5)	8	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Dysgeusia	5	(3)	7	12	(12)	12	7	(5)	7	0	(0)	0	19	(7)	19
Hypoaesthesia	5	(3)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Dysarthria	5	(3)	5	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Lethargy	4	(3)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Slow response to stimuli	4	(3)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Head discomfort	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Slow speech	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Skin and subcutaneous tissue disorders	106	(68)	124	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Hyperhidrosis	104	(66)	118	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Cold sweat	6	(4)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Gastrointestinal disorders	31	(20)	40	5	(5)	5	6	(4)	6	1	(3)	1	12	(5)	12
Nausea	18	(11)	19	1	(1)	1	4	(3)	4	0	(0)	0	5	(2)	5
Dry mouth	13	(8)	14	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Cardiac disorders	30	(19)	33	0	(0)	0	2	(1)	2	0	(0)	0	2	(1)	2
Palpitations	17	(11)	18	0	(0)	0	1	(1)	1	0	(0)	0	1	(0)	1
Tachycardia	14	(9)	14	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Psychiatric disorders	28	(18)	28	1	(1)	1	0	(0)	0	0	(0)	0	1	(0)	1
Confusional state	6	(4)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Nervousness	6	(4)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Psychomotor retardation	6	(4)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Agitation	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Vascular disorders	15	(10)	19	1	(1)	1	0	(0)	0	0	(0)	0	1	(0)	1
Pallor	5	(3)	7	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Hot flush	6	(4)	6	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Peripheral coldness	5	(3)	5	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Eye disorders	14	(9)	15	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Vision blurred	9	(6)	9	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Visual impairment	4	(3)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Investigations	11	(7)	14	1	(1)	2	0	(0)	0	0	(0)	0	1	(0)	2
Electrocardiogram T wave inversion	5	(3)	5	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Heart rate increased	3	(2)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Electrocardiogram T wave amplitude decreased	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Musculoskeletal and connective tissue disorders	4	(3)	4	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Injury, poisoning and procedural complications	2	(1)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Metabolism and nutrition disorders	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0
Respiratory, thoracic and mediastinal disorders	3	(2)	3	0	(0)	0	0	(0)	0	0	(0)	0	0	(0)	0

Serious adverse event / deaths / other significant events

Deaths

No deaths were reported during clinical studies with macimorelin.

Serious adverse events

One patient from Study AEZS-130-047 experienced two AEs that were classified as serious., ECG T wave abnormalities and ECG QT interval prolongation observed simultaneously in a 38-year-old male and were judged as likely related to macimorelin.

In Study AEZS-130-052 one subject was hospitalized due to a broken arm (PT: Upper limb fracture). This SAE was regarded to not be caused by the study medication or any concomitant medication.

Other significant adverse events

ECG related parameters

ECG related adverse events occurred in 7 of 254 subjects (2.76%) exposed to an oral macimorelin dose of 0.5 mg/kg during the clinical studies 047 and 052 (including the patient who experienced the serious ECG abnormalities see **Table 37**).

Table 37. Complete list of ECG related Adverse Events following macimorelin administration in clinical trials.

Study	Subject	PT	AE severity	AE related
AEZS-130-047	0930	ECG QT prolonged	severe	likely
AEZS-130-047	0930	ECG T wave abnormal	severe	likely
AEZS-130-047	1719	ECG change	mild	unlikely
AEZS-130-052	US03-06	ECG QRS complex abnormal	mild	unrelated
AEZS-130-052	US03-11	Bundle branch block right	mild	unrelated
AEZS-130-052	DE04-03	Palpitations	mild	possible
AEZS-130-052	RS01-08	Sinus bradycardia	mild	possible
AEZS-130-052	PL05-05	Sinus bradycardia	mild	unlikely

The effects of oral macimorelin on cardiac safety was also evaluated in a study AEZS-130-055.

AEZS-130-055

AEZS-130-055 was a thorough QT study to evaluate the effects of oral macimorelin on cardiac safety parameters in healthy male and female subjects. It was a randomized, placebo-controlled, double-blind, three-period crossover study with moxifloxacin as positive control.

60 healthy non-smoking, volunteers were included (36 males, 24 females); ECGs were evaluated from 57 subjects (33 males, 24 females). Subjects were hospitalized from Day -1 until after completion of the 24-hour assessments (morning of Day 2) if there were no safety issues. From 1 hour prior to dosing until 24 hours after dosing a continuous Holter ECG was recorded from which the 12 lead standard ECGs were extracted.

Each subject received a single oral dose of 2 mg/kg macimorelin as an oral solution, a 400 mg tablet moxifloxacin and placebo solution in randomized order.

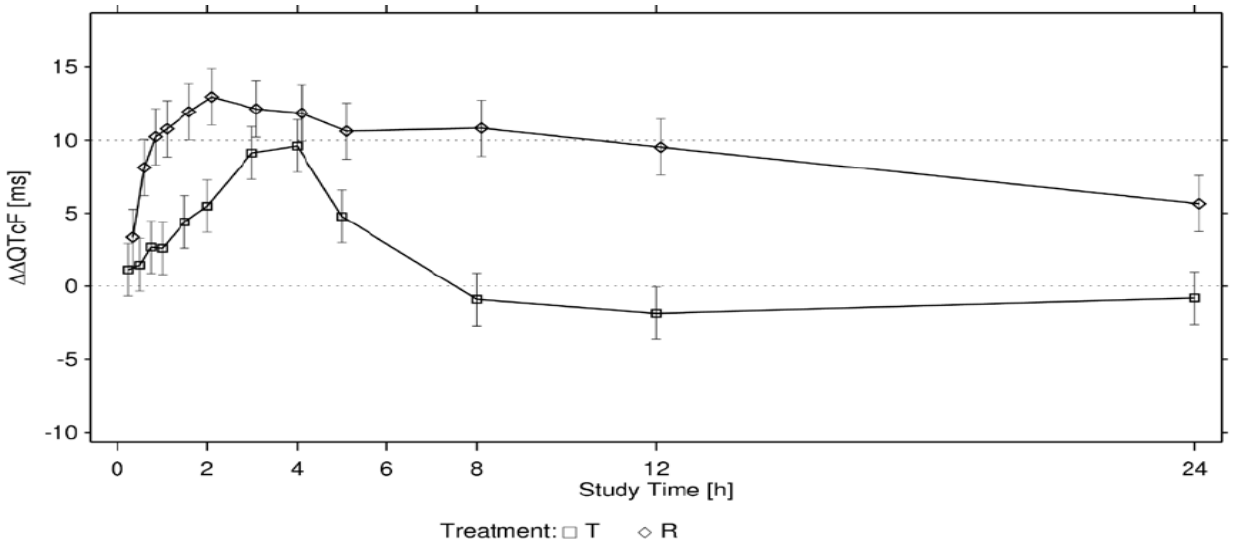
Primary parameter was QTcF (heart rate corrected QT interval using Fridericia's formula) which was measured from standard 10 second 12 lead digital electrocardiograms extracted in triplicates from continuous Holter ECG recordings. The time points for the 10 second 12-lead ECG extractions matched

those of the blood sampling for determination of PK parameters. Other parameters included the intervals PR, QRS, RR as well as HR and ECG morphological variables. PK parameters were also assessed.

ECG results:

The time course of the QTcF interval after dosing with macimorelin or controls is shown in **Figure 15**.

Figure 15. Mean placebo corrected changes in QTcF for macimorelin and moxifloxacin; T = test (macimorelin), R = reference (moxifloxacin), Study AEZS-130-055



The mean baseline- and placebo-corrected QTc intervals and the corresponding 90% CIs are summarised in **Table 38.** The largest placebo-corrected QTc elongations, at 3 h and 4 h, are highlighted.

Table 38. Mean ΔQTcF and ΔΔQTcF for macimorelin and placebo, Study AEZS-130-055

Scheduled study time	Treatment		
	Macimorelin [90% CI] N=57	Placebo [90% CI] N=57	Macimorelin–Placebo [90% CI] N=57
0.25 h	-2.11 [-3.58; -0.64]	-3.24 [-4.72; -1.77]	1.13 [-0.67; 2.93]
0.5 h	0.02 [-1.45; 1.49]	-1.44 [-2.91; 0.04]	1.46 [-0.34; 3.26]
0.75 h	3.32 [1.85; 4.79]	0.64 [-0.83; 2.11]	2.68 [0.88; 4.48]
1 h	3.94 [2.47; 5.41]	1.34 [-0.13; 2.81]	2.60 [0.80; 4.40]
1.5 h	5.06 [3.59; 6.53]	0.65 [-0.82; 2.12]	4.41 [2.61; 6.20]
2 h	5.78 [4.31; 7.25]	0.29 [-1.18; 1.76]	5.49 [3.70; 7.29]
3 h	10.48 [9.01; 11.96]	1.35 [-0.12; 2.82]	**9.14 [7.34; 10.94]**
4 h	10.61 [9.14; 12.08]	1.00 [-0.48; 2.47]	**9.61 [7.81; 11.41]**
5 h	6.58 [5.11; 8.05]	1.79 [0.32; 3.26]	4.79 [2.99; 6.58]
8 h	-8.01 [-9.48; -6.54]	-7.12 [-8.59; -5.64]	-0.90 [-2.70; 0.90]
12 h	-5.29 [-6.76; -3.82]	-3.44 [-4.91; -1.97]	-1.85 [-3.64; -0.05]
24 h	-6.52 [-7.99; -5.05]	-5.72 [-7.19; -4.25]	-0.80 [-2.60; 0.99]

A further ER analysis with adjustment for a delayed effect estimated the mean ddQTcF at 11.1 ms with a mean upper 95% CI of 14.1 ms. The predicted mean ΔΔQTcF value for the macimorelin intended GH test

dose (0.5 mg/kg), at its maximum plasma exposure (9.24 ng/mL), is only 3.7 ms (mean upper 95% CI: 5.5 ms).

An analysis, investigating changes in the T wave segments JTpc and TpTe, showed a borderline effect on the baseline and placebo corrected JTpc at 3 hours post-dose (mean effect 8.35 ms, upper 95% CI 10.43 ms).

None of the ECGs in this study exhibited Type 1 or Type 2 Brugada patterns. A Brugada Type 3 ECG pattern was reported in one subject, in all ECGs including pre-dose ECG, and is therefore unlikely to be macimorelin related.

Results of cardiologist evaluation

A cardiologist interpreted one randomly selected ECG at each time point. The ECGs were presented one-by-one blinded to treatment. The ECGs additionally were presented in random order to the cardiologist and with no comparison to baseline. Findings from this evaluation are presented in **Table 39**.

Table 39. Cardiologist findings post baseline in comparison to pre-dose, Study AEZS-130-055

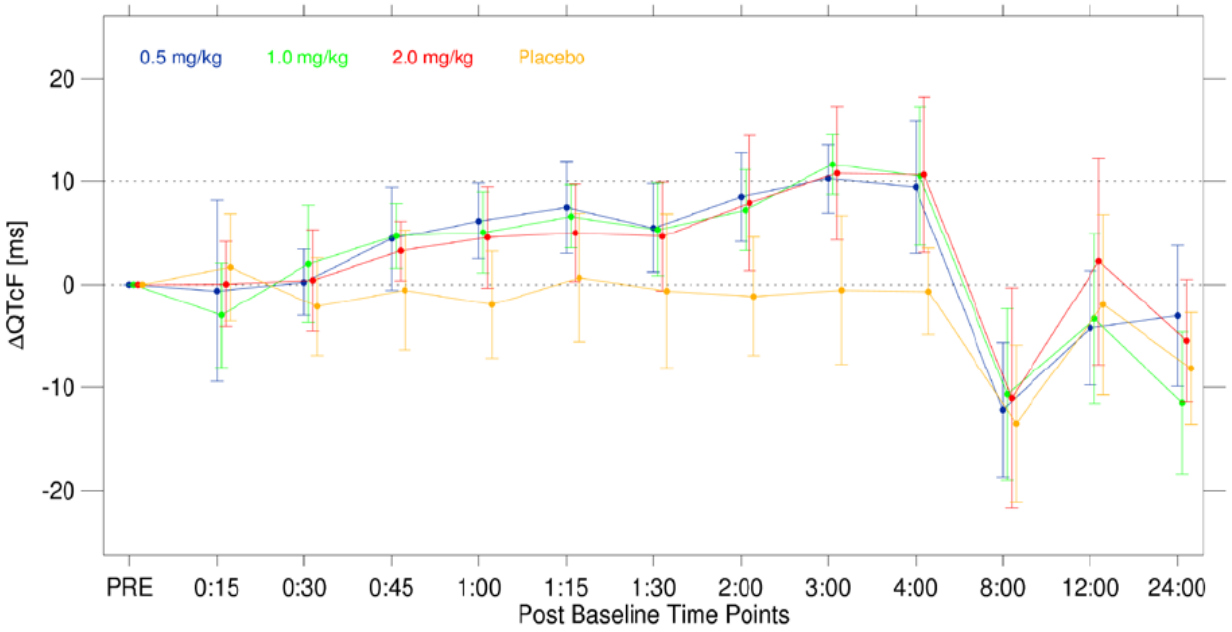
Finding	Treatment					
	Macimorelin		Moxifloxacin		Placebo	
	Σ	max[2] (%), time points	Σ	max (%), time points	Σ	max (%), time points
Sinus bradycardia	47	8 (14.0),1.5 h	33	6 (10.5),0.25 h	58	8 (14.0),0.75 h;1.5 h
1st degree AV block	12	3 (5.3),0.5 h	2	1 (1.8),0.25 h; 0.75 h	16	3 (5.3),0.5 h; 0.75 h;1.5 h
T wave inversion	3	1 (1.8),3 h; 4 h; 8 h	0	0 (0.0)	25	3 (5.3),0.25 h
T waves biphasic	6	3 (5.3),4 h	0	0 (0.0)	7	1 (1.8),0.25 h; 0.5 h;0.75 h; 1 h;1.5 h; 2 h; 3 h
Premature ventricular complex	2	1 (1.8),2 h; 3 h	0	0 (0.0)	1	1 (1.8),1 h
Undetermined supraventricular rhythm	0	0 (0.0)	0	0 (0.0)	1	1 (1.8),1 h
total findings[1]	60		35		108	

[1] multiple findings in one ECG may be present
[2] "max" means the maximal number of patients who had the finding at a given time point; this time point is also indicated

ECG results from study AEZS-130-054

The length of the QT interval corrected for heart rate by the Fridericia formula (**QTcF**) showed an association with macimorelin administration (see **Figure 16**, other correction methods gave similar results). The peak QTcF elongation after 3 to 4 hours occurred somewhat later than Tmax of macimorelin (between half and one hour in this study).

Figure 16. Time Courses for Change from Baseline of QTcF Interval, Study AEZS-130-054; note that the x-axis is not linear



9 subjects were reported to present Brugada Type 3 ECG pattern at multiple study time points, 4 of which were already present at baseline. The observed rates of Brugada Type 3 ECG pattern were similar between the macimorelin, moxifloxacin and placebo groups (4, 7 and 7, respectively).

Laboratory findings

Laboratory changes observed in hematology, clinical chemistry and urinalysis parameters during clinical studies were not considered clinically meaningful or related to macimorelin.

The effects of macimorelin on various hormones during the clinical studies were as follow:

- ARD-0705-003: The highest mean concentrations of IGF-1 were observed at the latest measured time point (24 hours post-dose) and followed the same pattern as GH, i.e., higher concentrations of IGF-1 were observed after administration of macimorelin without food than when administered with food.
- AEZS-130-IIT-1: The AUC, Cmax and tmax were compared for the effect of placebo, IV GHRH or 0.5 mg/kg oral macimorelin on plasma levels of the following hormones: ACTH, cortisol, ghrelin, glucose, insulin and prolactin. Macimorelin marginally increased circulating levels of ACTH, cortisol and prolactin but this increase was not statistically significant. No effects on blood levels of ghrelin, glucose and insulin were observed.
- AEZS-130-047: There was a slight, but not clinically meaningful, decrease in mean IGF-1 in both AGHD patients and matched controls following macimorelin oral administration.
- AEZS-130-052: The effects of macimorelin on other hormones than GH were not assessed.
- AEZS-130-054: No systematic changes in TSH, ACTH, cortisol or prolactin have been observed following dosing with macimorelin.
- AEZS-130-055: The effects of macimorelin on hormones were not assessed.

Safety in special populations

In clinical studies, macimorelin has not been administered to children or subjects with renal or hepatic impairment.

In Study AEZS-130-047, 19% of the subjects were aged >65 years and 6% were aged >75 years.
In Study AEZS-130-052, 2% were aged between 65 and 70 years (see Table 16).

No overall differences in safety were observed between these subjects and younger subjects when administered oral macimorelin at a dose of 0.5 mg/kg.

Safety related to drug-drug interactions and other interactions

No clinical data are available as drug-drug interaction studies with macimorelin have not been conducted.

Discontinuation due to adverse events

No adverse events suspected to be related to macimorelin were reported leading to study (or study drug) discontinuation or dose reduction.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety of macimorelin in the proposed indication is mostly based on two phase 3 studies in which dysgeusia was reported as the most frequent adverse event with a total incidence of 7% followed by headache (3%), diarrhea (3%) and hunger, fatigue, dizziness and nausea (each 2%). Most of these AEs were of mild or moderate intensity.

ECG related adverse events occurred in 7 of 254 subjects (2.76%) exposed to an oral macimorelin dose of 0.5 mg/kg during the clinical studies AEZS-130-047 and AEZS-130-052.

There were two serious adverse events (SAEs) in study AEZS-130-047 judged as likely related to macimorelin, reported simultaneously in one subject. They consisted of ECG related parameters, namely T wave abnormalities and QT prolongation.

A thorough QT (TQT) study was conducted with a 4-fold supra-diagnostic dose of macimorelin. Furthermore, ECG was recorded after dosing in a PK/PD study. Results from these studies were consistent. In the TQT study, a QTC interval prolongation was observed peaking between 3 and 4 hours after dosing and steadily declining thereafter. The peak QTc prolongation was around 10 ms on average with 2.0 mg/kg macimorelin; the same effect was observed in Study 054 at the intended diagnostic dose of 0.5 mg/kg. The peak of QTc prolongation ((≈3.5 h) did not coincide with Tmax of macimorelin (≈1 h). This suggests that macimorelin may need time to penetrate into the heart and/or that macimorelin's effect on QTc prolongation depends on accumulation of the drug in cardiac tissue, reaching higher concentrations with time than in plasma.

No relationship was demonstrated between macimorelin administration and Brugada ECG patterns. None of the ECGs in Study 054 and Study 055 exhibited Type 1 or Type 2 Brugada patterns. The observed rates of Brugada Type 3 ECG patterns were similar in the macimorelin group compared with the active (moxifloxacin) and placebo control groups in the TQT study. Only Type 1 Brugada ECG pattern has been associated with malignant cardiac arrhythmia and risk of sudden cardiac death (Benito 2009). Type 2 and

3 ECG patterns are not considered to be diagnostic of the Brugada syndrome (Antzelevitch 2005) and Type 3 pattern can easily be confused with other normal variants (e.g., early repolarisation and incomplete right bundle brunch block).

In vitro studies were also performed to address potential inhibition of cardiac hERG and Nav1.5 channels both after short and prolonged administration of macimorelin (see Non-clinical section of this report). Macimorelin did not inhibit these channels at micro-molar concentrations and therefore it is unlikely to have a torsadogenic effect or to be able to induce Brugada-like arrhythmias.

The mechanism of action for the clinically observed ECG changes however remains unclear. Macimorelin metabolites which have not been characterized or indirect effects (e.g. crosstalk/coupling of the intracellular signalling pathway of the ghrelin/growth hormone secretagogue receptor with cardiac ion channels) could have a role on these effects. The applicant is therefore recommended to further explore the mechanism for the delayed QTc-prolonging effect of macimorelin, e. g. by performing studies of macimorelin metabolites on hERG and Nav1.5 currents or by investigating indirect effects of macimorelin on these currents.

Overall, however the cardiac safety of a single dose administration of oral macimorelin (0.5 mg/kg) performed in patients not at particular risk in an in- or outpatient setting appears acceptable. On the other hand concomitant use with medicinal products that are known to induce torsades de pointes (antipsychotic medicinal products e.g. chlorpromazine, haloperidol, antibiotics (e.g., moxifloxacin, erythromycin, clarithromycin), anti-arrhythmics Class Ia (e.g. quinidine), and Class III (e.g. amiodarone, procainamide, sotalol) should be avoided.

Macimorelin should also be used with caution in patients with pro-arrhythmic condition (e.g., history of myocardial infarction, heart failure or prolonged ECG QTc interval, as defined as QTc > 500 ms). For such patients, ECG controls may be indicated prior to the administration of macimorelin and 1 hour, 2 hours, 4 hours and 6 hours after administration of macimorelin. Finally, in patients with known congenital or acquired long QT syndrome and in patients with a history of torsades de pointes, the use of macimorelin may only be considered in a cardiovascular clinical unit.

Torsades de pointes has also been included in the Risk Management Plan of macimorelin as an important potential risk and will be monitored in the post-authorisation setting through routine pharmacovigilance activities.

No significant effects were found for 0.5 mg/kg oral macimorelin on any other laboratory parameters measured including clinical chemistry, haematology and hormones such as TSH, ACTH, cortisol or prolactin.

2.6.2. Conclusions on the clinical safety

The overall safety database and safety profile of macimorelin is considered acceptable.

The main concern identified through the submitted studies is a QTC interval prolongation of approximately 10ms. Considering that respective warnings have been included in the product information, the product is intended for single use and that the test is performed or supervised by an endocrinologist, this issue is considered to be adequately manageable.

As the mechanism underlying the QT prolongation induced by macimorelin remains unknown, it is recommended that the applicant further investigates possible mechanism for the observed effect.

2.7. Risk Management Plan

Safety concerns

Table 40. Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Torsade de pointes
	False positive diagnosis of growth hormone deficiency in patients with BMI >40 kg/m^2, and in those receiving concomitant CYP3A4 inducers
Missing information	Usefulness of the test during pregnancy and safety for the unborn child during pregnancy

Pharmacovigilance plan

Not applicable.

Risk minimisation measures

Only routine risk minimisation measures are being described for macimorelin as described in the Summary of Product Characteristics (SmPC) and in the package leaflet (PL).

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.12.2017. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of macimorelin acetate with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers macimorelin acetate to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Macimorelin Aeterna Zentaris (macimorelin) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.>

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed indication for Macimorelin Aeterna Zentaris is the diagnosis of growth hormone deficiency (GHD) in adults.

GHD is a heterogeneous disorder that may develop during childhood or adult life, resulting from a variety of causes including structural lesions, genetic abnormalities, trauma, infiltrative diseases, surgery or irradiation to the pituitary gland and/or hypothalamus. In adult patients, no single sign or symptom of so-called Adult GHD (AGHD) is pathognomonic but it is recognized that AGHD leads to increased morbidity (metabolic syndrome, osteoporosis, muscle wasting, and impaired quality of life) and increased incidence of cardiovascular events, a main cause of the increased mortality observed in this population.

3.1.2. Available therapies and unmet medical need

Current published guidelines recommend that evaluation of AGHD be based on clinical findings, medical history and using an appropriate GH stimulation test (GHST) for biochemical confirmation. In patients with ≥ 3 pituitary hormone deficiencies and low serum IGF-I levels and patients with congenital/genetic GHD, the diagnosis of AGHD can be made without requiring stimulatory GH testing.

The biochemical diagnosis of severe GHD is straightforward. Partial GHD is at present not a well-defined clinical entity in adults. Because in the absence of suggestive clinical circumstances there is a significant false-positive error rate in the response to a single GH stimulation test (GHST), 2 independent GHST are recommended before making this rare diagnosis. The presence of a low IGF-I increases the likelihood that the diagnosis is correct. However, normal IGF-I does not exclude GHD.

The insulin tolerance test (ITT) is currently considered the “gold standard” test for evaluation of AGHD, but requires adequate hypoglycaemia (blood glucose <40 mg/dL) for interpretability of the results. In patients in whom an ITT cannot be performed (patients with ischemic heart disease or seizures, and in the elderly), the glucagon stimulation test (GST) is a safe alternative and has been assessed against the ITT in evaluating GH reserve. The L-ARG+GHRH test is essentially the arginine test with improved diagnostic accuracy by combining it with a potent priming agent (a GHRH analogue) in one test. Unfortunately, GHRH is not widely available.

Due to the potential safety issues associated with hypoglycemia, a subject undergoing the ITT requires close medical supervision over 3 to 4 hours until recovery of normal blood glucose levels. Moreover, it is reported to be an unpleasant and uncomfortable experience by most of the tested subjects.

All GH stimulation tests (GHST) have limitations with regard to performance characteristic (sensitivity, specificity and/or reproducibility). Testing for confirmation of AGHD should only be performed if there is a high pretest probability, and with the intention to treat if the diagnosis is confirmed.

3.1.3. Main clinical studies

Study 052 was the pivotal Phase III study. It was an open-label, randomized, multicentre, multinational, 2-way crossover study. The primary objective was to validate the use of single dose oral macimorelin (0.5

mg/kg) as growth hormone stimulation test (GHST) for the diagnosis of AGHD, using the insulin tolerance test (INTT) as comparator GHST.

Study subjects were assigned to 4 groups of descending likelihood of having AGHD (Group A: high likelihood of GHD, Group B: intermediate likelihood, Group C: low likelihood, Group D: healthy controls).

The co-primary endpoints were 1) Percent of Negative Agreement and 2) Percent of Positive Agreement. Overall agreement was a key secondary endpoint.

The predefined evaluation was based on a cut-off value of peak serum GH of 2.8 ng/mL for the macimorelin stimulation test (MAC) that was derived from the results of study 047. For the ITT, a cut-off point of 5.1 ng/mL was predefined and agreed by the CMHP during a scientific advice procedure. A peak GH value below the cut-point was considered 'test positive', a value above the cut-off 'test negative'.

The performance of the GHST with macimorelin (MAC) was considered to be acceptable if the lower bound of the two-sided 95% confidence interval (or lower bound of the one-sided 97.5% confidence interval) for the primary efficacy variables was 75% or higher for 'percent negative agreement', and 70% or higher for the 'percent positive agreement'.

Serum GH concentrations were determined 30, 45, 60 and 90 min post-dose.

Two tests were performed in a part of the subjects in order to assess repeatability.

The primary efficacy analysis set of study 052 comprises 140 subjects.

3.2. Favourable effects

Macimorelin at a single oral dose of 0.5 mg/kg body weight increased GH serum concentrations with a peak between 45 and 60 min post-dose. The increase was inversely related to the likelihood of having AGHD. Macimorelin induced approximately 1.4-fold higher GH concentrations than were obtained with the ITT.

At the predefined cut-off values for peak serum GH of 2.8 ng/mL for MAC and 5.1 ng/mL for ITT, respectively, the negative agreement between MAC and ITT was within the predefined margins (lower; upper 95% CI): 93.94 (85.20; 98.32) (one of two co-primary endpoints successful) and overall agreement was 83.57 % (76.38; 89.29).

Highly consistent effects were observed in the repeatability assessment. In 34 subjects there was a positive agreement in 16, a negative agreement in 16 and discrepant results in 2 subjects when the predefined cut-off points of GH were used.

Additional analyses indicated that it is generally sufficient to take samples at 45 and 60 min post-dose. In order to detect also rare late responders, an additional 90 min post-dose time point is recommended.

Based on patients with high likelihood of disease and healthy controls, sensitivity and specificity were 0.87 % (0.72; 0.96) and 0.96 % (0.80; 1.00) respectively.

3.3. Uncertainties and limitations about favourable effects

The second co-primary endpoint, i.e. positive agreement, did not meet the predefined acceptance margins. At the predefined cut-off of 2.8 ng/mL the positive agreement between MAC and ITT was (lower; upper 95% CI): 74.32 (62.84; 83.78). This was mainly due to the fact that some of the ITT positive subjects were not categorized as positive by the MAC. Therefore, the MAC appears to be more

conservative in diagnosing AGHD by reducing the risk of false positive results and unnecessary treatment. This is the key expectation for a GHST.

The cut-off of the ITT had been predefined at 5.1 ng/mL, which is higher than the cut-off of 3.0 ng/mL as proposed by a consensus guideline for the diagnosis and treatment of adults with GH deficiency (Ho KKY et al, 2007). When using the lower cut-off point for ITT, post-hoc calculations provided by the applicant showed that the CIs for positive and negative agreement were within the ranges that were predefined for the primary endpoints, indicating that the study might have been positive if this cut-off point would have been used for the ITT.

The cut-off of 2.8 ng/mL was based on calculations derived from study 047. The transferability of the results to study 052 was not established since different GH assays were used in both trials.

Stimulated GH concentrations are known to be reduced with obesity. This was also confirmed in the dataset provided by the applicant. No subjects with BMI >40 kg/m^2 were included in the pivotal study 052. Thus, diagnostic performance of the MAC in subjects with BMI >40 kg/m2 has not been established.

During the transition period from late puberty to full adult maturation, cut-off values of 5-6 ng/mL for ITT are suggested by guidelines. The data from study 052 do not allow determination of a valid cut point for the MAC during the transition period but MAC and ITT showed similar performance in subjects between 18 and 25 years

3.4. Unfavourable effects

A total of 377 subjects were treated with the MAC during clinical development studies, which included a total of 254 subjects in two studies (047 and 052) investigating the diagnostic use for AGHD.

The most common adverse reactions associated with the MAC (greater than 1% incidence in all macimorelin-treated subjects in two diagnostic studies were dysgeusia (7%) and headache, diarrhoea, nausea, and fatigue (each 2%). The rate of dysgeusia was lower after a taste masking formulation was used.

ECG related adverse events occurred in 7 of 254 subjects (2.76%) exposed to an oral macimorelin dose of 0.5 mg/kg during studies AEZS-130-047 and AEZS-130-052.

The thorough QT study and PK/PD study 054 revealed that macimorelin elicits a prolongation of the QTc interval in the ECG of around 10ms. The effect was highest at three to four hours after dosing and was seen at all macimorelin doses including the dose intended for diagnostic use.

When comparing Adverse Events (AEs) of the Macimorelin test with the insulin tolerance test (ITT) based on the Phase 3 studies 047 and 052, 126 AEs occurred in 27% of subjects following the Macimorelin GH stimulation test compared with 761 AEs in 96.2% of subjects following insulin tolerance test (ITT).

The Insulin Tolerance test (ITT) was associated with a broad spectrum of symptoms related to hypoglycaemia including hyperhidrosis (67%), somnolence (36%), hunger (29%), feeling hot (28%), dizziness (27%), fatigue (27%), asthenia (19%), tremor (16%), nausea (13%), cardiac palpitations (11%), headache (10%), tachycardia (9%), dry mouth (8%) and thirst (8%) as the most frequent adverse events.

It is concluded that the Macimorelin GH stimulation test was associated with significantly less side effects when compared with the Insulin Tolerance test (ITT).

3.5. Uncertainties and limitations about unfavourable effects

The mechanism by which QT-prolongation occurs following macimorelin administration is unknown. According to the summary as provided in the documentation *in vitro* studies did not reveal acute or delayed effects of macimorelin on hERG channels or Nav1.5 currents. It is possible that macimorelin metabolites and indirect effects (e.g. crosstalk/coupling of the intracellular signaling pathway of the ghrelin/growth hormone secretagogue receptor with cardiac ion channels) could be involved but further studies would be required to elucidate this mechanism.

3.6. Effects Table

Table 41. Effects Table for Macimorelin Aeterna Zentaris for the diagnosis of growth hormone deficiency (GHD) in adults (data cut-off: 28 November 2016).

Effect	Short Description	Unit	Macimorelin	Uncertainties/ Strength of evidence	References
Favourable Effects					
Negative agreement MAC-ITT	Using pre-defined cut-points for MAC and ITT (2.8 and 5.1 ng/mL, respectively)	% (95%CI)	93.94 (85.20-98.32)	Predefined margins met	AEZS-130- 052
Positive agreement MAC-ITT	Using pre-defined cut-points for MAC and ITT (2.8 and 5.1 ng/mL, respectively)	% (95%CI)	74.32 (62.84-83.78)	Predefined margins not met When using 3.0 ng/mL as cut-off point for ITT, high sensitivity and specificity 0.87 (0.72; 0.96) and 0.96 (0.80; 1.00) respectively but only exploratory analysis as one co-primary endpoint failed in the primary analysis	
Effect	**Short Description**	**Unit**	**Treatment**	**Uncertainties/ Strength of evidence**	**References**
Unfavourable Effects					
Abnormal ECG	ECG related adverse events	N (%)	7 (2.76%)	2 SAEs (in one patient) Mean QT prolongation of ≈10 ms observed 3-4 hours in a TQT and a PK/PD study at 0.5, 1.0 and 2.0 mg/kg macimorelin Underlying mechanism of action remains unclear	AEZS-130-047 AEZS-130-052 AEZS-130-054 AEZS-130-055

Abbreviations: MAC: Macimorelin; ITT: Insulin tolerance test; ECG: electrocardiogram, TQT: Thorough QT study; PK: pharmacokinetic; PD: pharmacodynamic, SAE: Serious Adverse Event

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients with a high likelihood of having disease based on patients´ history and clinical diagnostic work-up often don´t need a GHST. For those with an intermediate likelihood of having disease that are considered for treatment usually two tests are performed. Currently, the ITT is the preferred test despite tolerability and safety issues associated with its use, and reports of false positive results. Avoiding over-diagnosing is a key expectation for a test for ADGH since unnecessary treatment should be avoided. When using the proposed cut-point of 2.8 ng/mL, the MAC fulfils this expectation.

Based on the results from the submitted pivotal trial, MAC has a sufficiently high negative agreement rate with the INTT, indicating high reliability that a MAC positive patient has indeed GH deficiency but also that the MAC is helpful in avoiding unnecessary treatment.

The main concern with macimorelin relates to cardiac safety. ECG related adverse events were observed in the two clinical trials. The thorough QT study revealed a time-dependent prolongation of the QTc interval in the ECG occurring approximately four hours after macimorelin administration. Considering that respective warnings have been included in the product information, the product is intended for single use and the test is performed or supervised by an endocrinologist, this issue is considered to be adequately manageable.

3.7.2. Balance of benefits and risks

In the context of an overall workup for suspected AGHD, macimorelin can be used to reliably confirm AGHD and thus enable initiation of treatment with GH replacement therapy which is known to have significant beneficial effects on body composition, physical performance and psychological well-being in these patients. By using a cut point of 2.8 ng/mL for peak GH concentrations, the MAC will prevent unnecessary exposure to GH.

The benefit to patients in both cases outweighs the risk of a small prolongation of the QT interval, especially as the product will be used once and under medical supervision. Appropriate labelling is in place to further minimize the risk.

When compared with the ITT there were advantages of the MAC regarding tolerability and the requirement for re-testing of patients. The number of tests evaluable at first try was higher with MAC (153 out of 154) than with the ITT (130 out of 157). MAC was associated with a lower rate of AEs and there was a clear patient preference for the MAC. The vast majority of subjects would choose the MAC if they would need to undergo another GHST in the future.

3.8. Conclusions

The overall B/R of Macimorelin Aeterna Zentaris for the diagnosis of AGHD is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Macimorelin Aeterna Zentaris is favourable in the following indication:

- diagnosis of growth hormone deficiency (GHD) in adults

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that macimorelin acetate is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

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