# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 205598Orig1s000

# SUMMARY REVIEW

# Division Director Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | (electronic stamp) |
| **From** | Jean-Marc Guettier |
| **Subject** | Division Director Summary Review |
| **NDA/BLA # and Supplement #** | 205598 |
| **Applicant** | Aeterna Zentaris |
| **Date of Submission** | 30 JUNE 2017 |
| **PDUFA Goal Date** | 30 DECEMBER 2017 |
| **Proprietary Name** | MACRILEN |
| **Established or Proper Name** | Macimorelin acetate |
| **Dosage Form(s)** | (b) (4) to be reconstituted for oral solution. The recommended dose is 0.5 mg/kg to be administered orally for a single use |
| **Applicant Proposed Indication(s)/Population(s)** | MACRILEN is indicated for the diagnosis of adult growth hormone deficiency (AGHD). |
| **Action or Recommended Action:** | *Approval* |
| **Approved/Recommended Indication(s)/Population(s)** (if applicable) | *MACRILEN is indicated for the diagnosis of adult growth hormone deficiency (AGHD).* |

| **Material Reviewed/Consulted** OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| **Medical Officer Review** | William Lubas, MD PhD |
| **Statistical Review** | Anna Ketterman, PhD |
| **Pharmacology Toxicology Review** | Jeff Quinn, PhD |
| **OPQ Review** | Martin Haber, PhD, Su Tan, Ph.D. |
| **Clinical Pharmacology Review** | Sze Lau, PhD |
| **OSI** | Cynthia Kleppinger, MD |
| **CDTL Review** | Not applicable |
| **OSE/DRISK** | Joyce Weaver, Pharm D |
| Other | |

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

.

APPEARS THIS WAY ON ORIGINAL

# 1. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

**Benefit-Risk Assessment Framework**

**Benefit-Risk Integrated Assessment**

The applicant seeks to indicate the Macrilen test for the diagnosis of growth hormone deficiency in adults. Macrilen (i.e., the drug product) is a growth hormone secretagogue receptor agonist that is used to test the function of the anterior pituitary gland. For the test, a solution of Macrilen is ingested and the maximum amount of growth hormone (GH) detected in the serum, either 45, 60 or 90 minutes after ingestion, is used to determine whether growth hormone deficiency is present or absent.

Signs and symptoms of adult-onset GH deficiency are non-specific and provocative testing is used to establish the diagnosis. A diagnostic test for this condition should accurately distinguish between patients who stand to benefit from growth hormone replacement (i.e., those with GH deficiency) and individuals who do not (i.e., those without GH deficiency). Inaccurate tests subject individuals to unnecessary risks including those associated with the testing procedure and those associated with the consequence of a wrong diagnosis. The consequence of a falsely positive diagnosis could result in individuals receiving unnecessary therapy and being exposed to the risks of such therapies. The consequence of a falsely negative test could delay the diagnosis of growth hormone deficiency in an individual who could otherwise benefit from therapy.

Currently available diagnostic tests for adult growth hormone deficiency (insulin tolerance test, glucagon stimulation test, and arginine stimulation test) are complicated and challenging to administer, some are poorly tolerated and some can place individuals at risk of serious medical complications. An accurate diagnostic test that is easier and safer to administer than the current gold-standard test (i.e., insulin tolerance test) would be valuable.

The applicant established the effectiveness of the Macrilen test for the diagnosis of adult growth hormone deficiencies in two pivotal studies; AEZS-130-047 and pivotal study AEZS-130-052. In study AEZS-130-047, the applicant established that a Macrilen stimulated maximum serum growth hormone level of either 2.8 or 4.7 ng/mL best discriminated between adults with known growth hormone deficiency and healthy individuals (i.e., both yielded similar area under the ROC curve). A cut-point of 2.8 ng/mL was selected over the cut point of 4.7 ng/mL because it had the highest specificity (i.e., lowest false positive rate and highest positive predictive value and therefore the lowest likelihood of committing a subject to the risks of an unneeded therapy).

In study AEZS-130-052, the applicant compared the diagnostic performance of the Macrilen test (using the 2.8 ng/mL cut point) to the gold standard test (i.e., the insulin tolerance test) using a cross-over design. The population in this study was representative of the spectrum of patients who could be tested in clinical practice (i.e., spanning the range from high to low pre-test probability of disease). The results of AESZ-130-52 demonstrated a high degree of negative agreement between the Macrilen and the insulin tolerance tests (i.e., individuals with a negative ITT also have a negative Macrilen test).

The data in the application provide the substantial evidence necessary to conclude that a positive Macrilen test (i.e., a maximally stimulated serum GH value of 2.8 ng/mL or less) reliably rules in (or confirms) the presence of adult growth hormone deficiency. The test performs slightly less well at reliably ruling out (i.e., excluding) disease [i.e., moderate level of positive agreement with the insulin tolerance test].

The applicant performed retrospective analyses of data from AESZ-130-52 (b) (4) . These retrospective analyses were performed because the test failed to achieve the desired level of positive agreement with the insulin tolerance test. (b) (4) .

The data in the application also showed that collecting serum growth hormone levels at two time points (45 minutes and 60 minutes) is sufficient for test interpretation and that the test has good repeatability (i.e., a measure of precision). Finally, GH response to stimuli is known to decrease with age and with increasing BMI. There were insufficient individuals older than 65 and with a BMI > 40 kg/m2 to adequately evaluate the performance of the test in these patients.

The safety data in the application show that the risks of the drug, when used as directed, do not outweigh the benefits. Common adverse reactions were found to be generally mild, reversible, and can be managed using product labeling. Data in the resubmission confirmed that Macimorelin has a low proarrhythmic risk when used alone (i.e., the drug prolongs the QT interval by ~ 11 msec). The risk of arrhythmia with the use of Macimorelin may increase if it is combined with other drugs that prolong the QT interval. This risk will be mitigated through labeling by means of a Warning and Precautions which will serve the purpose of informing prescribers of the risk and provide guidance to reduce this potential serious risk by recommending avoidance of Macrilen use with drugs that are known to prolong the QT.

Overall, the data in the application establish that the Macrilen test is sufficiently reliable to rule-in a diagnosis of adult growth hormone deficiency and that the test is easier to perform, better tolerated and is safer than the gold-standard test (i.e., insulin tolerance test). I concur with Dr. Lubas' assessment that the benefits of the drug, in its intended use, clearly outweigh the identified risks and I recommend approval.

**Benefit-Risk Dimensions**

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| **Analysis of Condition** | • The condition targeted by the diagnostic test is adult growth hormone deficiency.<br>• Adult growth hormone deficiency is difficult to diagnose because signs and symptoms associated with the condition occur gradually and are non-specific (e.g., altered body composition, loss of strength, centripetal obesity, dyslipidemia, bone mineral density loss, fatigue, loss of energy, and diminished quality of life).<br>• Replacement of growth hormone with one of the approved recombinant growth hormone products improves the signs and symptoms caused by growth hormone deficiency in adults. Most of the currently marketed recombinant human growth hormone products are indicated for this use (i.e., for the replacement of | An accurate diagnostic test for adult growth hormone deficiency is valuable because it would correctly identify individuals that stand to benefit from recombinant growth hormone replacement therapy from individuals that would not. |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | endogenous growth hormone in adults with growth hormone deficiency). | |
| **Current Treatment Options** | • The most accurate test to confirm the presence of adult growth hormone deficiency available in the United States is the insulin tolerance test.<br>• Although the insulin tolerance test is regarded as the gold-standard test by endocrinologists, the test is complicated and challenging to administer even in the best of circumstances and requires induction of severe hypoglycemia which can place patients at risk of serious medical complications. These factors limit the test's practical utility.<br>• Other available tests for adult growth hormone deficiency (glucagon stimulation test and arginine infusion test) are not as accurate, are also impractical or complicated, can be poorly tolerated and carry risks | An accurate diagnostic test that is easier and safer to administer than the insulin tolerance test would be valuable. |
| **Benefit** | • The applicant has demonstrated that the Macrilen test;<br>○ Correctly discerns between adults with growth hormone deficiency and adults without the condition<br>○ Has a high level of negative agreement with the insulin tolerance test<br>○ Has good test-retest reliability<br>○ Is likely to be more rugged than the insulin tolerance test because it is simpler to administer and therefore less reliant on the operator for proper conduct. This, however, has not been evaluated or quantified.<br>○ The test does not require inducing severe hypoglycemia to work | • The Macrilen test is an accurate means of confirming the presence of adult growth hormone deficiency.<br>• The Macrilen test is reliable, easier to administer and safer than the insulin tolerance test. |
| **Risk and Risk Management** | • Dysgusia (4.5%); dizziness, fatigue, and headache (4%); hunger and nausea (3%); and diarrhea (2%) were the adverse reactions attributed to use of Macrilen.<br>• Macrilen causes a small increase in the QT interval (~10 msec. prolongation) at the therapeutic dose through an unknown mechanism. The effect of Macrilen on the QT is not dose-dependence of the QT effect, occurs after the peak plasma concentration, and is not mediated through blockage of the hERG potassium channel. | • Common adverse reactions are generally mild, reversible, and can be managed using product labeling.<br>• Macimorelin alone carries a low proarrhythmic risk. The risk of arrhythmia may increase if Macimorelin is used concomitantly with drugs known to prolong the QT interval. This risk will be mitigated through labeling (Warning and Precautions) by recommending avoiding use of Macrilen with drugs that are known to prolong the QT (e.g., |

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| | | chlorpromazine, haloperidol, thioridazine, ziprasidone, moxifloxacin, quinidine, procainamide etc.) |

## 2. Background

On November 4, 2014 Aeterna-Zentaris submitted a New Drug Application (NDA) for Macrilen under section 505(b)(1) of the Food, Drug and Cosmetic Act. Macrilen is a growth hormone secretagogue receptor agonist (also referred to as ghrelin receptor agonist). The dosage form is (b) (4) for oral solution and the proposed dosage is a single, weight-based, dose of 0.5 mg per kilogram. On November 5, 2015 Aeternas-Zentaris was issued a Complete Response Letter because multiple clinical and statistical deficiencies called into question the reliability of the evidence submitted to establish the product's efficacy and safety[1].

To address the deficiencies the applicant was asked to establish the efficacy of Macrilen in a new confirmatory clinical trial and to conduct a dedicated thorough QT study to characterize the effect of macimorelin on cardiac repolarization. In this re-submission, the applicant submits the data and final report for the new confirmatory trial (AEZS-130-052) and for the thorough QT study (AEZS-130-055).

The application has a long regulatory history which has been reviewed previously[2]. The applicant is seeking to indicate Macrilen to diagnose growth hormone deficiency in adults. The drug received orphan designation status (Orphan Designation# 06-2255) for this indication.

## 3. Product Quality

The CMC portion of the application was reviewed by Dr. Haber in the previous review cycle. Dr. Haber reviewed new data on the drug substance manufacturing process in this cycle and continues to recommend approval. Dr. Galliford reviewed new data on the drug product manufacturing process in the resubmission and continues to recommend approval. The Office of Pharmaceutical Quality has also evaluated the manufacturing and testing facilities and recommends approval. Long-term stability data submitted in this cycle of review support the request to grant the product a shelf-life expiry of 48 months when stored between 2-8°C.

The drug substance, macimorelin acetate, is a growth hormone receptor secretagoue (i.e., ghrelin receptor) agonist. It is a small synthetic peptide consisting of two D-tryptophan residues and one amino isobutyric acid group linked in a single chain by two peptide bonds. The drug substance is manufactured by (b) (4). Solubility in the pH range 1-8 is approximately 300 mg/mL. The drug substance specification is standard for a small synthetic molecule and includes the following attributes: macimorelin identity (HPLC, NMR and optical rotation), acetate identity (HPLC), residual solvents, water content, sulphated ash, heavy metals, related substances (specified, unidentified, and total), chiral purity, macimorelin assay

[1] For full details refer to Complete Response Letter in DARRTS dated 11/05/14 (Reference ID: 3653987)
[2] For full details refer to Division Director Memo in DARRTS dated 11/05/14 (Reference ID: 3653916)

(HPLC), acetate assay, and microbial tests. Sufficient drug substance stability data was provided to support the retest period of (b) (4) months at (b) (4). The drug substance is manufactured by (b) (4) and the key intermediate is manufactured by (b) (4).

The drug product is 60 mg macimorelin (or (b) (4) mg of macimorelin acetate) formulated as granules and packaged in (b) (4), to be reconstituted in 120 mL of water to a final concentration of 0.5 mg/mL oral solution. The (b) (4)% overfill (i.e., each (b) (4) contains a total of (b) (4) mg macimorelin) is adequate (b) (4) Excipients are lactose monohydrate, crospovidone, colloidal silicon dioxide, sodium stearyl fumarate and saccharin sodium (b) (4) all are compendial. The manufacturing process involves (b) (4) The drug product specification is standard for the dosage form: identity (HPLC and UV), average filling quantity, assay (HPLC), uniformity of dosage units, degradants (specified, unidentified, and total), concentration after reconstitution, and microbial tests. The drug product is manufactured by Allphamed Pharbil GmbH, Germany.

To use Macrilen, the content of one (b) (4) is dissolved by the health care provider in 120 mL of water. This forms a solution with a concentration of 0.5 mg/mL of macimorelin acetate. The solution is intended for one-time use and is to be used immediately after reconstitution. The dose (i.e., volume of solution) to be administered orally to the patient is based on the patient's body weight and relies on the following formula 0.5 mg of macimorelin acetate per kilogram of body weight. For example, a 100 kg adult would require 0.5 mg * 100 kg or 5 mg (100 mL of solution).

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by Dr. Quinn, the nonclinical pharmacology/toxicology reviewer, that there continues to be no outstanding nonclinical pharmacology/toxicology issues that preclude approval. Please refer to his review for details.

## 5. Clinical Pharmacology

I concur with the conclusions reached by Dr. Lau, the clinical pharmacology reviewer, that there continues to be no outstanding clinical pharmacology issues that preclude approval. The drug's clinical pharmacology has been previously reviewed[3].

## 6. Clinical Microbiology

There are no outstanding clinical microbiology issues that preclude approval.

## 7. Clinical/Statistical-Efficacy

[3] For full details refer to Division Director Memo in DARRTS dated 11/05/14 (Reference ID: 3653916)

Drs. Lubas and Ketterman have reviewed the efficacy data and recommend approval. I agree that the applicant has provided the substantial evidence of effectiveness necessary to support approval. The evidence was provided from data derived from trial AEZS-130-047, previously reviewed[4], and data from new trial AEZS-130-052 submitted with the re-submission.

Briefly, the Macrilen test was developed to test the function of the anterior pituitary gland in people who may have growth hormone deficiency. The drug product works by stimulating the release of growth hormone from the anterior pituitary gland and the maximum amount of growth hormone detected in the serum 45 to 90 minutes after Macrilen is ingested is used to determine whether the anterior pituitary functions normally.

To recap what has been stated in the statistical and primary clinical reviews, the applicant demonstrated the utility of the test;

1. By establishing the maximum, stimulated, serum growth hormone cut point that best discriminates between adults with growth hormone deficiency from those without using data from trial AEZS-130-047

2. Then, using this established cut point, by comparing the performance of the test versus the gold-standard test (i.e., insulin tolerance test) in the intended use population[5] in trial AEZS-130-052 (i.e., new efficacy study submitted with the resubmission).

*Cut point used for the Macrilen Test*

A maximum, stimulated, serum growth hormone of **2.8 ng/mL** was selected as the cut point for the test based on a determination of the greatest area under the receiver operating characteristic (ROC) curve from data generated in study AEZS-130-047. Accordingly, maximum, stimulated, serum growth hormone levels that fall **below** 2.8 ng/mL denote the **presence** of adult growth hormone deficiency (i.e., **Positive Macrilen Test**) and those **at or above** 2.8 ng/mL denote the **absence** of growth hormone deficiency (i.e., **Negative Macrilen Test**). The specific threshold was also selected because it yielded the least false positive results[6] (i.e., wrongly concluding that a person without adult growth hormone deficiency has the condition and initiating lifelong replacement therapy when this is not needed). Another threshold (i.e., 4.7 ng/mL) that yielded an equally large area under the curve was not selected because it was associated with > 20% likelihood of a false positive results[7]. The selected cut-off point favored specificity over sensitivity because wrongly committing someone to unneeded therapy was judged a worse outcome than failing to diagnose a subject when an alternative gold-standard test exists.

*Cut point used for the comparator (Insulin Tolerance Test)*

[4] For full details refer to Division Director Memo in DARRTS dated 11/05/14 (Reference ID: 3653916)
[5] i.e., a population spanning the spectrum of high to low pre-test probability of adult growth hormone deficiency
[6] 82% sensitivity and 90% specificity
[7] 90% sensitivity and 79% specificity

A maximum, stimulated, serum growth hormone of **5.1 ng/mL** on the insulin tolerance test was selected as the cut point for the insulin tolerance test based on a report from the literature [8]. Accordingly, maximum, stimulated, serum growth hormone levels that fall below 5.1 ng/mL on this test denote the presence of adult growth hormone deficiency (i.e., Positive Insulin Tolerance Test) and those at or above 5.1 ng/mL denote the absence of growth hormone deficiency (i.e., Negative Insulin Tolerance Test). The authors report that this threshold had 96% sensitivity and 92% specificity.

***Description of the New Pivotal Efficacy Study in Resubmission: AEZS-120-052***

In the resubmission, the applicant submitted new trial AEZS-130-052, a multicenter, multinational, open-label, randomized, single dose, two way, cross over study whose primary objective was to compare the performance of the Macrilen Test (i.e., using the 2.8 ng/mL threshold) to the "gold-standard test[9]" in 4 groups of 140 adult subjects selected to span the spectrum of clinical likelihood of having growth hormone deficiency (GHD). The groups were divided as follows;

**Group A: High Likelihood of Growth Hormone Deficiency** (N=38):

- Structural hypothalamic or pituitary lesions and low IGF-1[10], and/or
- Three or more pituitary hormone deficiencies and low IGF-1, or
- Childhood onset GHD with structural lesions and low IGF-1

**Group B: Intermediate Likelihood of Growth Hormone Deficiency** (N=37):

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

**Group C: Low Likelihood of Growth Hormone Deficiency** (N=40):

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

**Group D: Healthy Controls** (N=25):

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

Although Dr. Ketterman states in her review that the intended population is mostly those individuals belonging to group B and C, I do not agree with her assessment. In practice, it may be difficult to precisely ascertain which category a patient who may be referred to the test belongs to (i.e., A vs. B or C vs. D) as signs and symptoms are subtle and medical history isn't always known or accurately relayed to the healthcare provider. It is not a stretch to think that the test will be administered to subjects across all four categories. Second, even if sufficient

[8] The Journal of Clinical Endocrinology & Metabolism, Volume 87, Issue 5, 1 May 2002, Pages 2067–2079

[9] Using the established threshold for this test.

[10] Insulin-like growth factor 1

data from the clinical history allows one to conclude with reasonable certainty that a patient belongs to category A for example, most insurers will ask for confirmation of the diagnosis of adult growth hormone deficiency by use of provocative testing prior to approving growth hormone replacement therapy for patients. Therefore, this applicant evaluated the correct intended use population (i.e., the spectrum of individuals who could potentially be subject to the test in clinical practice). Refer to primary statistical and medical reviews for the complete set of inclusion and exclusion criteria.

*Description of Testing Procedures Used in AEZS-120-052*

Trial AEZS-120-052 relied on a cross-over design. Each participant underwent the two procedures and served as their own control. The two procedures were the Macrilen test (novel procedure) and the Insulin tolerance test (i.e., control procedure). Each test is described below.

*Macrilen Test*

To conduct the Macrilen test, subjects were fasted for at least 8 hours prior to the test and were administered a 0.5 mg/kg body weight dose of Macrilen. Blood samples were collected in fasted subjects pre-dose, and 30, 45, 60, and 90 minutes (+/- 5 minutes time window) following Macrilen administration, to assay for serum growth hormone concentration using a valid bioassay.

*The Insulin Tolerance Test (i.e., the Gold Standard Test)*

To conduct the insulin tolerance test, the same subjects were fasted for 8 hours prior to the test and throughout the sampling period. Insulin was administered intravenously at 0.10 U/kg (0.15 U/kg in subjects with a BMI > 30 kg/m2) and blood glucose was monitored using capillary whole blood every 10 minutes for the first 60 minutes until occurrence of neuroglycopenia (e.g., confusion, sensation of warmth, weakness, or fatigue). When clinical signs of severe hypoglycemia were achieved, a plasma glucose measure was obtained to confirm biochemical hypoglycemia (i.e., 40 mg/dL). An additional insulin bolus of 0.05 U/kg could be administered if the target glucose value of < 40 mg/dL was not reached AND neuroglycopenia was not observed within the first 45 minutes of the test. Blood samples were collected for serum GH pre-dose, and 15, 30, 45, 60, 90 and 120 minutes (+/- 5 minutes window) following insulin administration to assay for serum growth hormone concentration using a valid bioassay.

*Oversight of Testing Procedure Quality*

Each subject included in the analysis was required to have undergone both tests. Both tests had to be performed in accordance with the protocol mandated instructions. A data review committee, blinded to test results, was responsible for evaluating the quality of the testing procedure and was charged with designating the test as either “evaluable” or “non-evaluable” prior to allowing release of growth hormone data from the central lab. Only tests whose

conduct was of sufficient quality to be deemed "evaluable" by the review committee were used in the analysis. Reasons for designating a test "non-evaluable" was most commonly due to problems related to inadequate conduct for example, problems with blood sampling (missing or erroneous timing), failure to reach neuroglycopenia (insulin tolerance test), or vomiting during the procedure (macimorelin test). More insulin tolerance tests compared to Macrilen tests were categorized as "non-evaluable" confirming that this test is challenging to conduct.

*Pre-specified Primary Analysis*

The primary analysis in this cross-over study was performed on a modified Intent-to-Treat Population which included all randomized subjects with an "evaluable" macimorelin test and an "evaluable" insulin stimulation test (i.e., each subject served as their own control, subjects with only one "evaluable test" out of the two had either no test or control procedures and were therefore rightly excluded from the analysis).

For the primary analysis, results obtained on the insulin tolerance test were used as the benchmark to evaluate the performance of the Macrilen test. The reviewers refer to this benchmark as a "non-reference" standard (i.e., versus a "reference" standard) because data on the insulin tolerance test cannot determine with 100% certainty the presence or absence of adult growth hormone deficiency. When the benchmark used for comparison is a "non-reference" standard, performance (i.e., accuracy measure) is reported as "percent positive agreement" and "percent negative agreement'" rather than specificity and sensitivity as one would do if the true presence or absence of disease were known.

Peak serum GH achieved after dosing with either insulin or macimorelin was to be used to determine test positivity or negativity (see above description on cut-offs used to determine positivity and negativity).

The two endpoints (i.e., co-primary) used in the pre-specified primary analysis were;

1. **Percent Negative Agreement:** That is, the proportion of subjects with a negative insulin tolerance test (i.e., those without disease per the "gold-standard" test) who also have a negative macimorelin test. For the applicant to win on this endpoint the applicant had to demonstrate that the lower bound of the two-sided 95% confidence interval around the estimate for percent negative agreement was 75% or higher. Subjects who have a negative insulin tolerance test but a positive macimorelin would receive unnecessary therapy.

2. **Percent Positive Agreement:** That is, the proportion of subjects with a positive insulin tolerance test (i.e., those with disease per the "gold-standard" test) who also have a positive macimorelin test. For the applicant to win on this endpoint the applicant had to demonstrate that the lower bound of the two-sided 95% confidence interval around

the estimate for percent negative agreement was 70% or higher. It should be noted that the threshold for a positive test

The two primary endpoints can be calculated as follows (Source; Table 2 in Dr. Ketterman's review);

| | | Non-reference Standard (ITT) | |
|---|---|---|---|
| Macimorelin Test | | + | – |
| | + | A | B |
| | – | C | D |
| Total | | A+C | B+D |

Percent Positive Agreement [%]=100% x A/(A+C)
Percent Negative Agreement [%]=100% x D/(B+D)
Percent Overall Agreement [%]=100% x (A+D)/(A+B+C+D)

Two-sided 95% Clopper-Pearson confidence intervals for all calculated measures of agreement were provided.

Overall agreement and sensitivity and specificity of the macimorelin test using Group A and D and repeatability were designated secondary endpoints. These are discussed in Dr. Lubas and Ketterman's review and will not be discussed here.

***Results***

Demographics and baseline characteristics are presented in Tables 3 through 8 in Dr. Ketterman's review. Subjects ranged in age from 18 to 66 years old (mean 40.6 years). Subjects in groups A and B were slightly older (mean age 42.4 and 40.6 years old) than subjects in groups C and D (mean age 34.8 and 39.2 years old). Although age may have a modifying effect on the growth hormone response observed after stimulation[11], the differences in age observed in this study are small and would not be expected to have an impact. The mean BMI overall was 27 $kg/m^2$ and was approximately the same among all four groups. Although large differences in BMI could influence the growth hormone response observed after stimulation[12], the magnitude of the difference in BMI observed in this study are also relatively small and not expected to have an impact on result interpretation. Gender distribution was balanced among groups A, B, and D (40% female to 60% male). Group C however had more male subjects (80%). Study subjects were from the EU (77%) and the US (22%). Most of the subjects from the US

[11] GH response to stimulation may decline with age but no normative data to support this is available.

[12] GH response in the insulin tolerance test and Macrilen test may decline with increasing BMI.

were in the intermediate likelihood of disease groups (B and C). Group D consisted entirely of subjects recruited in Poland.

The results for the pre-specified primary analysis in the 140 individuals who underwent both tests are shown below and it can quickly be gleaned from the raw data that negative agreement of the macimorelin test with the insulin tolerance test is higher than positive agreement.

**Table 1. ITT and MAC outcomes for All subjects (source Table 11 in Dr. Ketterman's review)**

| | | ITT test | | |
|---|---|---|---|---|
| MAC test | | + | - | |
| | + | 55 | 4 | 59 |
| | - | 29 | 62 | 81 |
| | | 74 | 66 | |

*Results for Negative Agreement*

The applicant demonstrated that 94% (95% Confidence Interval: 85%, 98%) of patients who had a negative test following insulin induced hypoglycemia (i.e., a maximum serum GH response following stimulation of the anterior pituitary with insulin induced hypoglycemia of > or = to 5.1 ng/mL) also had a negative test with Macrilen stimulation (i.e., a maximum serum GH response following stimulation of the anterior pituitary with Macrilen of > or = to 2.8 ng/mL). The lower bound of the two sided 95% confidence interval for the estimate of negative agreement (i.e., 85%) was above the pre-specified margin of 75%.

To succinctly summarize, there is high concordance between a negative result on the insulin tolerance test and a negative result on the Macrilen test. The negative result on the benchmark test (i.e., the insulin tolerance test) was the standard used (and agreed upon) to represent the normal response. The high negative agreement observed between the two tests suggests that the likelihood of a false positive with the Macrilen test is low. That is, it is unlikely that an individual will be wrongly diagnosed as having adult growth hormone deficiency by the Macrilen test when, in fact, they do not have the condition. In other words, the great majority of positive tests with Macrilen are true positives and the test is therefore useful at ruling in the condition in patients with signs and symptoms of growth hormone deficiency.

*Results for Positive Agreement*

The applicant demonstrated that 74% (95% confidence interval: 63%, 84%) of patients who had a positive test following insulin-induced hypoglycemia (i.e., a maximum serum GH response following stimulation of the anterior pituitary with insulin induced hypoglycemia of < 5.1 ng/mL) also had a positive test with Macrilen stimulation (i.e., a maximum serum GH response following stimulation of the anterior pituitary with Macrilen < 2.8 ng/mL). The lower bound of the two sided 95% confidence interval for the estimate of negative agreement (i.e.,

63%) was below the pre-specified margin of 70%. The sponsor therefore did not meet this specified co-primary endpoint (demonstrating that the estimated lower bound of the 95% CI around positive agreement was > 70%)

To succinctly summarize, there is moderate concordance between a positive result on the insulin tolerance test and a positive result on the Macrilen test. A positive result on the benchmark test (i.e., the insulin tolerance test) was the standard used (and agreed upon) to represent disease (i.e., adults with growth hormone deficiency). The moderate level of positive agreement observed between the two tests suggests that the likelihood of a false negative result with the Macrilen test is also moderate. That is, it is possible that up to 37% of individuals (i.e., the estimate defined by the lower bound of the 95% CI) could be categorized as normal by the Macrilen test when, in fact, they have disease (at least per the results of the insulin tolerance test).

The six subjects with discordant results (i.e., a positive insulin tolerance and a negative Macrilen test) had maximum Macrilen stimulated serum growth hormone level between 3.16 and 4.74 ng/mL during the trial (low levels when compared to the normal mean response). Two subjects belonged group A (high pre-test probability), three to group B (intermediate pre-test probability) and one to Group C (low pre-test probability).

*Discussion related to the failure to meet the pre-specified positive agreement threshold*

The sponsor did not meet one of the two co-primary endpoints (demonstrating that the estimated lower bound of the 95% CI around positive agreement was > 70%) and believes that the pre-specified cut point of 2.8 ng/mL derived from ROC analyses of data generated in study AEZS-130-047 may not have been optimal. The sponsor agrees with the FDA's assessment of this study in stating that data derived from study AEZS-130-047 may not have been 100% reliable. The population in this study was to be comprised of patients with a prior established diagnosis of growth hormone deficiency (true positives) and matched healthy control subjects (true negatives) but for some subjects with disease, details of the diagnoses turned out to be incorrect or unreliable. It follows logic that a cut point established from possibly unreliable data may be erroneous.

(b) (4)

The differences in maximum GH response between the two stimuli are described in the table below and in figure 4 of Dr. Ketterman's review. Incidentally and unrelated, the table also shows that the variability in maximum response (i.e., coefficient of variation) for the two tests are about the same suggesting precision for the two tests are about the same.

**Table 2: Descriptive Statistics for Maximum Serum Growth Hormone Response Elicited by Severe Hypoglycemia (Rows 1-5; GH ITT test) and Macrilen (Rows 6-10; GH MAC test). Source Table of Dr. Ketterman's Review.**

| Group | Label | N | Median | Minimum | Maximum | Mean | Std Dev | Coeff of Variation |
|---|---|---|---|---|---|---|---|---|
| All | GH ITT test | 140 | 4.4 | 0.1 | 40.5 | 7.2 | 8.9 | 123.8 |
| A | GH ITT test | 38 | 0.1 | 0.1 | 6.2 | 0.5 | 1.3 | 246.2 |
| B | GH ITT test | 37 | 1.2 | 0.1 | 31.9 | 3.5 | 6.2 | 176.4 |
| C | GH ITT test | 40 | 9.7 | 0.4 | 40.5 | 13.4 | 9.7 | 72.7 |
| D | GH ITT test | 25 | 10.3 | 2.1 | 33.2 | 12.9 | 7.5 | 58.4 |
| All | GH MAC test | 140 | 6 | 0.1 | 61.2 | 10.1 | 12.3 | 121.5 |
| A | GH MAC test | 38 | 0.1 | 0.1 | 8.6 | 0.9 | 2 | 213.7 |
| B | GH MAC test | 37 | 2 | 0.1 | 27 | 5.2 | 6.5 | 125.1 |
| C | GH MAC test | 40 | 14.5 | 0.7 | 61.2 | 19.2 | 15.5 | 80.8 |
| D | GH MAC test | 25 | 16.1 | 2.2 | 34.6 | 16.6 | 7.4 | 44.4 |

Based on these results, it would be logical to assume that the test using the more potent stimulus (i.e., Macrilen) should have a cut point at least as high, if not higher, than the cut point used for the less potent stimulus (i.e., hypoglycemia). (b) (4)

The sponsor performed a series of post-hoc analyses using data from study AEZS-120-052 for multiple cut points higher than 2.8 ng/mL and examined positive agreement, negative agreement, overall agreement, reproducibility, sensitivity and specificity for these exploratory cut points. Based on this post-hoc examination, higher cut points yield more favorable positive agreement and overall agreement. Results for some of these post-hoc analyses (i.e., for cut points between 2.8 and 6.1 ng/mL) are shown below. Data for subject RS01-06 was omitted from these analyses. This subject had a documented compliance issue with the first of two macimorelin tests [i.e., macimorelin was undetectable in serum during the first test and caused a false positive result].

**Table 3: Effect of Varying the Macrilen Growth Hormone Cut Point on Positive, Negative, and Overall Agreement with the results of the Insulin Tolerance Test**

| MAC GH cut- off point | Core study analysis Agreement between MAC and ITT (*N=139*) | | | | | | MAC Reproducibility M-core vs M-rep.; (*N=33*) | | ROC analysis for MAC *Groups A+D only (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 (%) | (%) | (%) |
| 2.80 | 95.38 | **87.10** | 74.32 | 62.84 | 84.17 | 77.02 | **96.97** | **84.24** | 87 | **96** |
| 4.60 | 95.38 | **87.10** | 81.08 | **70.30** | 87.77 | **81.14** | **93.94** | **79.77** | **92** | **96** |
| 5.10 | 93.85 | **84.99** | 82.43 | **71.83** | 87.77 | **81.14** | **93.94** | **79.77** | **92** | **96** |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 6.10 | 92.31 | **82.95** | 86.49 | **76.55** | 89.21 | **82.83** | 87.88 | 71.80 | **95** | **92** |

(b) (4)

(b) (4)

the data in the application clearly establishes that a maximally stimulated serum GH level of 2.8 ng/mL on the Macrilen test can be used to reliably confirm or rule-in the presence of disease. The test has utility in that regard and should be approved for that purpose given the multiple issues with currently available alternatives.

Dr. Ketterman also performed analyses to determine which timepoints elicited the highest serum growth hormone levels and determined, from theses analyses, that three time points were sufficient for the interpretation of test result (45, 60 and 90 minutes). The highest serum GH levels at either the 45, 60 or the 90 minute timepoints should be used for results interpretation. Dr. Ketterman also verified that the test was repeatable (i.e., a measure of test precision). Dr. Ketterman examined the results across various subgroups. These provide limited useful information given the small number of subjects in each subgroup. Finally, it is known that GH response to stimulation decreases with advancing age and increasing body mass index (BMI). Regarding age, the were not data in the application on subjects above 65 years of age. With regards to BMI, there were 15 subjects with a BMI between 35 and 40 kg/m2 and no subjects with a BMI above 40 kg/m2. Absence of efficacy data in these age and BMI subgroups will be noted in appropriate sections of labeling.

## 8. Safety

Safety findings for the resubmission have been reviewed by Dr. Lubas (refer to Section 7.3 of his review). The number exposed to Macrilen and the extent of exposure in the clinical program were appropriate given that adult growth hormone deficiency is a rare disorder and that the intended use is for a single administration.

In the original submission, a morbidly obese control (i.e., 365 lbs) who received a relatively high absolute single Macrilen dose experienced a QTc prolongation of 61 milliseconds uto a maximum prolongation of 501 milliseconds and newly inverted T wave. There were features of the case that suggested Macrilen could have contributed the QT prolongation (high dose, temporal relationship) and confounding medications. The applicant was asked to perform a thorough QT study to adequately characterize the effect of macimorelin on cardiac repolarization in the Complete Response Letter.

The applicant included the results of the thorough QT study in the resubmission and these were reviewed by Dr. Johannsen from the QT interdisciplinary review team. In the study, macimorelin was observed to prolong the QTc interval by ~ 10-11 msec. These findings are consistent with observations made in the single ascending dose (SAD) study. Based on the totality of the evidence, macimorelin is expected to prolong the QTc interval at the therapeutic dose of 0.5 mg/kg via an unknown mechanism (i.e., not mediated through the hERG channel). From these data it is possible to conclude that macimorelin carries a proarrhythmic risk, albeit low, when it is used by itself but that the risk may increase if the drug is combined with other drugs that prolong the QT. The reduce the risk the drug should not be used with drugs that prolong the QT.

## 9. Advisory Committee Meeting

Efficacy and safety issues identified in the application did not rise to the level of requiring the input from an advisory panel. Therefore, no advisory committee was convened.

## 10. Pediatrics

Refer to Dr. Lubas' review

## 11. Other Relevant Regulatory Issues

Refer to Dr. Lubas' review

## 12. Labeling

Refer to the label in the approval letter.

## 13. Postmarketing

- Postmarketing Risk Evaluation and Mitigation Strategies

No safety issues rising to the level of requiring a risk evaluation and mitigation strategy was identified in the application. Safety issues will be handled through appropriate labeling.

- Other Postmarketing Requirements and Commitments

None

---

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

---

/s/

---

JEAN-MARC P GUETTIER
12/05/2017

MARY T THANH HAI
12/05/2017
Concur with Division recommendation