NDA 205598
IND 154015

WRITTEN REQUEST

Aeterna Zentaris Inc.
U.S. Agent for Aeterna Zentaris GmbH
Attention: Patricia Zahn
Director of Admin. Services
315 Sigma Drive, Suite 302D
Summerville, SC 29486

Dear Patricia Zahn:

Reference is made to your Written Request for pediatric studies for Macrilen (macimorelin acetate), dated February 27, 2020, and amended on October 7, 2022, March 8, 2024 (corrected on April 25, 2024), and September 3, 2024. That Written Request is now expired therefore we are issuing this new Written Request that extends the timeframe for reporting studies.

These studies investigate the potential use of macimorelin acetate in the diagnosis of growth hormone deficiency (GHD) in children of 2 years and older. Short stature is often the most common presenting feature of GHD in children, and therefore most children are not diagnosed until after the age of 2 years. The diagnosis of GHD is very rare in children < 2 years old, including neonates, and these patients are not present in sufficient numbers to enable participation in clinical trial(s). In addition, congenital GHD which presents with hypoglycemia, prolonged hyperbilirubinemia, microphallus, and serum GH concentration that does not reach above 5 mcg/L during the first week of life does not require GH stimulation testing to make the diagnosis.

BACKGROUND:
Macrilen (macimorelin acetate), a growth hormone (GH) secretagogue receptor agonist, was approved on December 20, 2017, for the diagnosis of adult GHD. Childhood onset of GHD is a rare disorder with an estimated prevalence of 1/4,000 to 1/10,000. Lack of growth hormone secretion results in short stature which if left untreated will result in significantly decreased adult height. Treatment with GH requires daily injections for many years. Given the cost and morbidity associated with daily injections it is important to identify children who are most likely to benefit from GH therapy. Current consensus guidelines recommend two different GH stimulation tests (GHSTs) to assist with the diagnosis for pediatric patients with suspected GHD and without a clear clinical presentation. In general, children with a known hypothalamic or pituitary defect and deficiency in at least one other pituitary hormone do not need GH stimulation to establish the diagnosis. However, for all other pediatric patients in which the diagnosis is less certain, abnormal results from two different GH stimulation tests are

recommended. Currently available GHSTs use arginine, glucagon, insulin or clonidine to provoke GH secretion. None of these GHSTs has been validated in prospective clinical trials in pediatric patients with suspected GHD. These tests can be associated with a greater risk of hypoglycemia. In addition, certain individual tests require intravenous or intramuscular injection. The macimorelin acetate test is an oral test that has been associated with a favorable safety profile in adult studies. The test requires four blood samples collected during the 90-minute test.

To obtain needed pediatric information on macimorelin acetate, FDA is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies):*

  Based on review of the available nonclinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this Written Request.

- *Clinical studies:*

  Study 1: A single dose, pharmacokinetic (PK) and pharmacodynamic (PD) study to determine the dose of macimorelin acetate in pediatric patients 2 to 18 years of age for GH stimulation testing in suspected GHD.

  Study 2: A single-dose diagnostic efficacy and safety study of macimorelin acetate in pediatric patients 2 to 18 years of age with suspected GHD to determine the sensitivity and specificity associated with different cut-off points for stimulated GH levels. The study will also evaluate standardly available GHSTs to assess assay sensitivity and specificity.

- *Study Objectives:*

  Study 1: To investigate the PK, PD, safety, and tolerability of macimorelin acetate after ascending single oral doses of macimorelin acetate in pediatric patients with suspected GHD

  Study 2: To determine the diagnostic efficacy of macimorelin acetate, (i.e., specificity and sensitivity of specific cut off points in the diagnosis of GHD in pediatric patients with suspected GHD), based on the area under the ROC curve

- *Patients to be Studied:*

Study 1: At least 24 patients must be studied; at least 8 patients per each of 3 dose groups with at least 3 patients per dose cohort being pre-pubertal (Tanner Stage I) and at least 3 patients per dose cohort being pubertal (Tanner Stage II-IV). You must also enroll at least 2 patients less than or equal to 9 years of age in each dose group. The protocol must include that Tanner staging will be assessed in each patient.

Study 2: At least 100 patients must be studied with at least 40 patients being pre-pubertal (Tanner Stage I) and at least 20 patients being pubertal (Tanner Stage II-IV). To ensure stable estimation of sensitivity, at least 25 GHD present and at least 25 GHD absent patients (by adjudication) should be included in the study. You must also enroll at least 25 patients less than or equal to 9 years of age. The protocol must include that Tanner staging will be assessed in each patient.

- *Study endpoints:*

  ☐ PK and PD endpoints must include the following:

  Study 1: AUC, Cmax, Tmax, and t1/2 of macimorelin acetate in plasma and stimulated growth hormone concentrations (Cmax and Tmax) in serum.

  ☐ Primary efficacy endpoint(s):

  Study 2: area under the receiver operating characteristic curve (ROC AUC) assuming the outcome of GHD status adjudication by the Central Consensus Committee as the “true” GHD status.

  ☐ Key secondary efficacy endpoints should include:

  Study 2:

  (1) Sensitivity for the macimorelin acetate GHST for the selected cutoff

  (2) Specificity for the macimorelin acetate GHST for the selected cutoff

  (3) Percentage overall agreement between the outcome of the macimorelin acetate GHST and the combined outcome from the 2 standard GHSTs for the selected cutoff

- *Safety Endpoints/Monitoring:*

  ☐ The protocol must include a plan for monitoring of the following known drug safety concerns:

ECG monitoring to assess for the potential for QTc prolongation.

Adverse event monitoring must be included in the protocol and agreed upon by the Agency.

- *Statistical information, including power of study(ies) and statistical assessments:*

  The primary hypothesis is "AUC ≤0.70" against the alternative that "AUC > 0.70". The lower bound of the one-sided 97.5% confidence interval of the AUC will be estimated and the null hypothesis will be rejected if this lower bound is greater than 0.70. The AUC must be estimated non-parametrically using the trapezoidal area under the empirical ROC plot.

  The sample size must provide at least 90% power to reject the null hypothesis.

  Details on how to handle missing data as well as statistical methods for determining and assessing the final GHST cut-off must be provided in the SAP and must be agreed upon with the division before database lock.

The following information pertains to all clinical studies in the Written Request.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  - *dosage form: granules for oral solution*
  - *route of administration: oral*
  - *regimen: single dose*

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

(1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
(2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
(3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that macimorelin acetate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation.

In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and the guidance addendum.[1] You are encouraged to contact the reviewing Division for further guidance.

For studies started after December 17, 2017, study data must be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on FDA.gov[2] and referenced in the guidance for industry *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before January 31, 2026. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm
[2] https://www.fda.gov/media/154109/download

when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the FD&C Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

(1) the type of response to the Written Request (i.e. complete or partial response);
(2) the status of the application (i.e. withdrawn after the supplement has been filed or pending);
(3) the action taken (i.e. approval, complete response); or
(4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[3]

If you wish to discuss any amendments to this Written Request, submit your proposed changes using strikethrough and underline (Text added is underlined. Text deleted is strikethrough.) and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be

[3] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the PHS Act, you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found on the Clinical Trials website.[4]

If you have any questions, contact Julie Van der Waag, Director, Project Management Staff, at (301) 796-1280 or julie.vanderwaag@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Lisa B. Yanoff, MD
Deputy Director
Office of Cardiology, Hematology,
Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

[4] www.ClinicalTrials.gov

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LISA B YANOFF
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