DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204410

WRITTEN REQUEST

Actelion Clinical Research, Inc.
Attention: Cheryl Czachorowski
Director, US Drug Regulatory Affairs
1820 Chapel Avenue West, Suite 300
Cherry Hill, NJ 08002

Dear Ms. Czachorowski:

Reference is made to your January 22, 2016, Proposed Pediatric Study Request for Opsumit (Macitentan), received on January 27, 2016.

BACKGROUND:

Study AC-055-312 investigates the potential use of macitentan in the treatment of children diagnosed with pulmonary arterial hypertension (PAH) from age ≥ 1 month to < 18 years. The primary objective of the study is to evaluate macitentan in comparison to standard of care for delaying disease progression in children with PAH. Neonates under 1 month of age are excluded from this written request, as persistent pulmonary hypertension in the newborn (PPHN) has a different etiology.

There are no products approved for PAH in this population. PAH is a rare disease and all approved products have Orphan Designation and are exempt from the requirements for pediatric studies under PREA. For this reason, it is important to utilize the exclusivity incentive under BPCA to request pediatric studies.

This Written Request contains a mixture of requirements (where failure to comply would be expected to lead to denial of pediatric exclusivity) and advice; we highlight the requirements to make them unambiguous.

To obtain needed pediatric information on macitentan, the Food and Drug Administration (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 studies*: Based on review of the available non-clinical toxicology, no additional nonclinical studies are required to support the clinical studies described in this Written Request.

- *Clinical study:* Efficacy in patients aged at least 1 month but less than 18 years cannot be fully extrapolated and will be determined by the study outlined in this Written Request. This will be

a multicenter, open-label, randomized, parallel-group, group-sequential, event-driven study to assess the efficacy, safety, and pharmacokinetics (PK) of macitentan versus standard of care (SoC) in children with PAH.

Children ≥1 month and <2 years of age will only be enrolled once sufficient PK data are available in a PK substudy in older children (described below) and subsequent PK modeling has been performed to allow for selection of the appropriate daily dose in the 1-month to 2-year age group. You must submit the PK modeling and sampling plan to the Agency prior to initiating dosing in this age group. A justification for the selected doses should be provided and the selected doses should be agreed upon with the Agency prior to initiating the study in this age group. If the dosing justification in this age group is based on exposure matching, modeling and simulation should be conducted to demonstrate similarity in the exposure of macitentan and its active metabolite ACT-132577 for the proposed dosing.

To support dose selection for patients <2 years, you must characterize the PK of macitentan and its active metabolite ACT-132577 in a subpopulation of the macitentan arm (up to 40 subjects distributed over the ages of ≥2 years and <18 years) at Day 14 (steady state).

You should enroll a minimum of 10 children under the age of 2 years. A minimum of 8 children under the age of 2 years should be included in a PK substudy to characterize PK in this age group.

Representation of ethnic and racial groups: Differences in response to treatment have not been observed in adults of different ethnic and racial groups. You should make trial participation equitable by race and ethnicity.

Efficacy endpoints: The primary objective of the study is to evaluate macitentan in comparison to standard of care (SoC) for delaying disease progression in children with pulmonary arterial hypertension (PAH).

The primary efficacy endpoint will be time to the first of the following disease progression events occurring between randomization and end-of-study (EOS):

1. Death (all causes)
2. Atrial septostomy or Potts' anastomosis, or on lung transplant list
3. Hospitalization due to worsening PAH, excluding hospitalizations that are elective, routine, or clearly attributable to appearance/worsening of comorbidities (e.g., pneumonia)
4. Clinical worsening of PAH (from baseline) defined as:
    a) one of these:
        i. Worsening in WHO functional class (FC)
        ii. New occurrence or worsening of syncope or at least 2 PAH symptoms (i.e., shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue)
        iii. New occurrence or worsening of signs of right heart failure not responding to oral diuretics
    b) and need for or initiation of new PAH-specific therapy (e.g., endothelin receptor antagonists, PDE5i, prostanoids, soluble guanylate cyclase stimulators), intravenous diuretics, or continuous oxygen use.

An independent Clinical Event Committee (CEC) will adjudicate all potential disease progression events reported by investigators (conditions defined in the CEC Charter) in a blinded fashion. The date of the first CEC-confirmed disease progression event will be used for the primary time-to-event efficacy variable.

Statistical considerations: We accept your premise of an expected 35% reduction in events and designing for alpha = 0.05 in one study as the basis for extending the claim to pediatric patients. One hundred and eighty-seven primary endpoint events are needed to reject the null hypothesis with an overall power of 80% and alpha=0.05 assuming an alternative hazard ratio of 0.65.

If you decide to conduct an interim analysis, the interim analysis should be carried out with at least 131 events (~70% of events). If this analysis includes a provision to stop early for effectiveness, then an appropriate alpha adjustment is required and should be agreed upon with the Division. If this analysis can only be used to stop for futility, no alpha adjustment is necessary, but stopping for futility because the event rate is lower than expected will not be considered responsive to the Written Request.

Unless you are able to conclude that the trial shows significant treatment effect at the interim analysis or conclude that the trial will not be able to demonstrate a significant treatment effect with 187 events, accrual will continue until the final number of events is observed.

Treatment groups: Subjects will be randomized 1:1 to macitentan or to SoC. Only PDE-5 inhibitors are allowed as background PAH-specific medication.

Subjects randomized to the macitentan arm will be treated as follows:

- Subjects with no PAH-specific therapy at randomization will receive macitentan as monotherapy.
- Subjects on PDE-5 inhibitor monotherapy at randomization will receive macitentan as add-on therapy on top of the PDE-5 inhibitor.
- Subjects on monotherapy such as ERA or oral/inhaled prostanoid monotherapy at randomization will receive macitentan as monotherapy.
- Subjects on PDE-5 inhibitor in combination with another PAH-specific therapy at randomization will receive the combination of macitentan and the PDE-5 inhibitor.

Subjects randomized to SoC can receive PAH non-specific treatment and up to two PAH-specific medications as per local practice. In addition:

- Subjects only on PAH non-specific medications at randomization continue on their medications.
- Subjects on PDE-5 inhibitor and/or on other PAH-specific treatment (such as ERA, or inhaled/oral prostanoids) at randomization continue on their medications.
- For all subjects, PAH-specific therapy (excluding macitentan and i.v./s.c. prostanoids) defined as SoC at randomization can be initiated.

Dose adjustment to reach the targeted dose or sequential introduction of combination therapy is allowed as prescribed at randomization.

Study follow-up: Subjects in the SoC arm should be discouraged from initiating open-label macitentan. Other appropriate drugs may be given as clinically-indicated. Follow all patients who stop study drug treatment for vital status until the end of the trial; do not conduct the study in regions where determination of vital status cannot be reasonably assured.

Safety Endpoints: Safety outcomes must include the following:

- Adverse events
- Vital signs
- Tanner stage
- Height, weight

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

An Independent Data Monitoring Committee (IDMC) must review data at regular intervals according to the IDMC charter. The IDMC has overall responsibility for safeguarding the interests of subjects by monitoring safety and efficacy data obtained in the study and making appropriate recommendations based on the reported data. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *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:*Macitentan, open-label, is administered once daily via the oral route. Macitentan is provided as dispersible tablet formulation of the following dosage strengths: 0.5 mg, 2.5 mg and 5 mg. Daily dosage depends on the body weight category of the subjects and will be adjusted during the study as needed. The dosage for pediatric patients should be selected to target systemic exposures of macitentan and its active metabolite that have been observed in adults at the approved dose of 10 mg.

  Use an age-appropriate formulation in the study 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, 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*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrates that macitentan is safe and effective, or whether such study results are inconclusive in the studied pediatric population, the labeling must include information about the results of the study. 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.

- *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.

  Although not currently required, we request that study data 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 the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

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 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.

- *Summary of post-marketing experience:* 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 FDA's Guidance for Industry "Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)", available at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm346564.pdf . You are encouraged to contact the reviewing Division for further guidance.

- *Timeframe for submitting reports of the study:* Reports of the above studies must be submitted to the Agency on or before April 12, 2021. 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 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. 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 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the 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 at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes 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 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 Public Health Service Act (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 at www.ClinicalTrials.gov.

If you have any questions, call Wayne Amchin, RAC, Regulatory Project Manager, at 301-796-0421.

Sincerely,

{See appended electronic signature page}

Ellis Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
04/13/2016