IND 104504
NDA 207947
NDA 214275

WRITTEN REQUEST

Actelion Pharmaceuticals Ltd.
c/o: Janssen Research & Development, LLC
Attention: Rhoda Maddonni, MS
Associate Director, Global Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560

Dear Rhoda Maddonni:

Reference is made to your April 8, 2025, Proposed Pediatric Study Request for Uptravi (selexipag).

These studies investigate the potential use of selexipag in the treatment of children (2 to <18 years old) with pulmonary arterial hypertension.

BACKGROUND:

Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension, is defined as a mean pulmonary arterial pressure greater than 20 mmHg, an indexed pulmonary vascular resistance of ≥ 3 WU x m^2 with a normal pulmonary capillary wedge pressure (≤ 15 mmHg). The most common etiologies of PAH in pediatric patients are idiopathic PAH, heritable PAH, congenital heart disease-associated PAH, and persistent pulmonary hypertension of the newborn.[1]

PAH is a rare disease in children with an incidence of 4-10 cases per million children per year and a prevalence of 20-40 cases per million children.[2] In neonates, however, the most common etiology of pulmonary hypertension is persistent pulmonary hypertension of the newborn (PPHN) which resolves in most neonates and is not associated with genetic factors.[3] Studies will not be requested in pediatric patients less

[1] Sullivan RT, Raj JU, Austin ED. Recent Advances in Pediatric Pulmonary Hypertension: Implications for Diagnosis and Treatment. Clin Ther. 2023 Sep;45(9):901-912. doi: 10.1016/j.clinthera.2023.07.001.
[2] Kwiatkowska J, Zuk M, Migdal A, Kusa J, Skiba E, Zygielo K, Przetocka K, Werynski P, Banaszak P, Rzeznik-Bieniaszewska A, Surmacz R, Bobkowski W, Wojcicka-Urbanska B, Werner B, Pluzanska J, Ostrowska K, Waldoch A, Kopec G. Children and Adolescents with Pulmonary Arterial Hypertension: Baseline and Follow-Up Data from the Polish Registry of Pulmonary Hypertension (BNP-PL). J Clin Med. 2020 Jun 3;9(6):1717. doi: 10.3390/jcm9061717.
[3] Steinhorn RH. Neonatal pulmonary hypertension. Pediatr Crit Care Med. 2010 Mar;11(2 Suppl):S79-84. doi: 10.1097/PCC.0b013e3181c76cdc.

than 2 years of age, including neonates, for this reason and also because intestinal intussusception was observed in some dogs within 4 weeks of dosing with selexipag in the 39-week juvenile toxicity study and in the repeat-dose general toxicity studies. Intussusception is a frequent cause of intestinal obstruction and bowel necrosis in children less than 2 years of age.[4]

Current PAH therapies that are indicated in pediatric patients include bosentan, which is approved in children ≥ 3 years of age with idiopathic or congenital PAH to improve pulmonary vascular resistance, and sildenafil which is approved in children ≥ 1 year of age with PAH (World Health Organization (WHO) Group 1) to improve exercise capacity and pulmonary hemodynamics. All approved products for PAH have Orphan Designation. Thus, these products are exempt from the requirements for pediatric studies under the Pediatric Research Equity Act (PREA). For this reason, it is important to utilize the exclusivity incentive under Best Pharmaceuticals for Children Act (BPCA) to request pediatric studies.

To justify a pediatric extrapolation approach using NT-proBNP as a bridging biomarker and to provide an assessment of the efficacy of selexipag in the treatment of PAH, you must submit analyses of data from clinical trials in pediatric PAH that assess the efficacy and safety of selexipag in the treatment of PAH. These clinical trials must analyze the reduction of NT-proBNP from baseline to the specific timepoints of interest depending on the study. You must also submit the results from Study 3 (below) which was previously conducted, outside the United States. The study includes NT-proBNP data and hemodynamic data (indexed pulmonary vascular resistance) to support pediatric extrapolation of efficacy of selexipag using NT-proBNP.

To obtain needed pediatric information on selexipag, 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 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.

[4] Roeyen G, Jansen M, Hubens G, Vaneerdeweg W, Eyskens E. Intussusception in infants: an emergency in diagnosis and treatment. Eur J Emerg Med. 1999 Mar;6(1):73-6.

- *Clinical studies:*

  Study 1: Phase 2, prospective, multicenter, open-label, single-arm study to investigate the safety, tolerability, and pharmacokinetics of selexipag in children with PAH

  - *Study Objectives:*

    - To confirm the selexipag starting dose(s) for Study 2 by confirming similar exposure to that of the effective dose in the adult population.

  - *Subjects to be Studied:*

    - *Age groups to be studied:*
      - Subjects ≥ 2 and < 18 years of age

    - *Number of subjects to be studied:*
      - At least 45 subjects, followed for 16 weeks with the following breakdown by age:
        - Cohort 1: ≥ 12 to < 18 years of age: 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles
        - Cohort 2: ≥ 6 to < 12 years of age: 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles
        - Cohort 3: ≥ 2 to < 6 years of age: 20 enrolled participants to obtain at least 15 participants with evaluable PK profiles

    Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

  - *Study endpoints:*

    - Primary efficacy endpoint must be:
      - Model-based exposure ($AUC_{\tau,ss,combined}$) of selexipag and the active metabolite, ACT-333679 corrected for their potencies.
    - Key secondary endpoints must include:
      - Area under the plasma concentration-time curve over one dosing interval at steady state ($AUC_{\tau,ss}$), maximum plasma concentration ($C_{max,ss}$), and the time at which $C_{max,ss}$ is observed ($t_{max,\ ss}$) for selexipag and ACT-333679.
      - Trough concentration of selexipag and ACT-333679 at steady state ($C_{trough,ss}$).

- Additional endpoints must include:
  - Plasma NT-proBNP, the absolute value and the percent of baseline at each time point of assessment during the 12 weeks of up-titration and the maintenance period from Week 12 to Week 16. You should also provide assessments of this endpoint as available during the maintenance period after Week 16.
  - Time to first of the following disease progression events occurring between first study drug dose and 7 days after end of treatment:
    - death (all causes)
    - atrial septostomy or Potts' anastomosis, or registration on lung transplant list
    - hospitalization due to worsening PAH excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (e.g., pneumonia)
    - clinical worsening from baseline of PAH defined as the need for, or initiation of new PAH-specific therapy or intravenous diuretics or continuous oxygen use AND one of the following:
      - worsening in WHO functional class
      - new occurrence or worsening of syncope
      - new occurrence of at least 2 PAH symptoms (shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue),
    - new occurrence of worsening of signs of right heart failure not responding to oral diuretics.

- *Safety Endpoints/Monitoring:* The protocol must include a plan for the monitoring of the following:
  - Clinical signs and symptoms known to be adverse reactions to selexipag including arthralgia, diarrhea, flushing, headache, jaw pain, myalgia, nausea, and vomiting.
  - Adverse events, serious adverse events (SAEs), deaths (all causes).
  - Adverse events leading to premature discontinuation of study treatment.
  - Treatment-emergent marked ECG and laboratory abnormalities.
  - Change from baseline in laboratory variables.
  - Change from baseline in vital signs, height, body mass index, and sexual maturation (Tanner Stage).
  - The protocol must include plans for monitoring all adverse events until symptom resolution or until the condition stabilizes.

Study 2: Phase 3, randomized, multicenter, double-blind, placebo-controlled, parallel-group study with an open-label extension period (OLEP) to assess the efficacy and safety of selexipag as add-on to standard of care in children aged ≥ 2 to <18 years with PAH (WHO group 1).

- *Study Objectives:*
  - To evaluate whether the addition of selexipag to standard of care treatment delays disease progression in children with PAH in comparison to placebo.

- *Subjects to be Studied:*
  - *Age groups to be studied:*
    - Subjects ≥ 2 and < 18 years of age
  - *Number of subjects to be studied:*
    - At least 120 subjects must be treated for 24 weeks in the double-blind treatment period with the following breakdown by age:
      - Cohort 1: ≥ 12 to < 18 years of age: minimum 31 in each arm
      - Cohort 2: ≥ 6 to < 12 years of age: minimum 25 in each arm
      - Cohort 3: ≥ 2 to < 6 years of age: minimum 4 in each arm

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  - *Double-blind treatment period*
    - Primary efficacy endpoint must be:
      - Time to disease progression from randomization up to 7 days after study treatment discontinuation. Disease progression must be defined as the first occurrence of any of the following components:
        - death (all causes)
        - atrial septostomy or Potts' anastomosis, or registration on lung transplant list
        - hospitalization due to worsening PAH excluding hospitalizations that are elective, routine or clearly attributable to appearance/worsening of comorbidities (e.g., pneumonia)

        - clinical worsening from baseline of PAH defined as the need for, or initiation of new PAH-specific therapy or intravenous diuretics or continuous oxygen use AND one of the following:
            - worsening in WHO functional class
            - new occurrence or worsening of syncope
            - new occurrence of at least 2 PAH symptoms (shortness of breath/dyspnea, chest pain, cyanosis, dizziness/near syncope, or fatigue),
            - new occurrence of worsening of signs of right heart failure not responding to oral diuretics.
    - Key secondary endpoints must include:
        - Change in $\log_2$(NT-proBNP) from baseline to Week 24 ($\log_2$(Week 24/Baseline)).
        - Time to first clinical event committee (CEC) confirmed hospitalization or death due to PAH occurring from randomization.
    - Pharmacokinetic (PK) endpoints must include:
        - Trough plasma concentrations of selexipag and the active metabolite, ACT-333679, at steady state.

- *Safety Endpoints/Monitoring:* For both the randomized controlled portion and the OLEP, the protocol must include a plan for the monitoring of the following:
    - Clinical signs and symptoms known to be adverse reactions to selexipag including arthralgia, diarrhea, flushing, headache, jaw pain, myalgia, nausea, and vomiting.
    - Adverse events, serious adverse events (SAEs), adverse events leading to premature discontinuation of study treatment.
    - Change in vital signs, body weight and height as agreed upon in the protocol.
    - Change in sexual maturation (Tanner stage) as agreed upon in the protocol.
    - Treatment-emergent ECG abnormalities, marked laboratory abnormalities as agreed upon in the protocol.
    - The protocol must include plans for monitoring all adverse events until symptom resolution or until the condition stabilizes.

- Disease progression must be adjudicated by a blinded clinical event committee (CEC).

Study 3: Phase 2, multicenter, uncontrolled, open-label study of selexipag-exposed Japanese subjects (≥2 and <15 years).

- *Study Objectives:*
  - To provide additional data that were previously collected on the use of selexipag in the treatment of children with PAH.

- *Subjects Studied:*

  - *Age groups studied:*
    - Subjects ≥2 and <15 years of age

  - *Number of subjects studied:*
    - A minimum of 6 subjects followed for 16 weeks

  Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  - Primary efficacy endpoint was:
    - Change in the indexed pulmonary vascular resistance (PVRi) at rest from baseline to Week 16.
  - Key secondary endpoint was:
    - Change in NT-proBNP concentration from baseline to Week 16.

- *Safety Endpoints/Monitoring:* The protocol must have included a plan for the monitoring of the following:
  - Clinical signs and symptoms known to be adverse reactions to selexipag including arthralgia, diarrhea, flushing, headache, jaw pain, myalgia, nausea, and vomiting.
  - Adverse events and serious adverse events (SAEs).
  - Laboratory abnormalities, ECG-related abnormalities, changes in vital signs, and growth parameters.

Statistical information, including statistical assessments:

For Study 1 and Study 2:
You must have a pre-specified, detailed statistical analysis plan appropriate for the study design and outcome measures. FDA must agree to the statistical analysis plans prior to the supplemental new drug application (sNDA) submission.

In each study-specific statistical analysis plan, you must include details of the statistical methods for the analysis of the endpoints of time to disease progression and reduction of NT-proBNP from baseline to Week 28 (Study 1) or Week 24 (Study 2) with plans for handling intercurrent events and missing data in the primary analysis using an estimand framework, as appropriate.

You must perform subgroup analyses for the primary efficacy endpoint of Study 2 (time to disease progression) with subgroups defined by a prespecified baseline NT-proBNP cut-off threshold. The NT-proBNP cut-off threshold must be agreed to by FDA.

For Study 3:
You must submit a detailed statistical analysis plan including study power information and conduct descriptive analyses of the change in PVRi and change in NT-proBNP concentration.

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*: Tablets

  - *Route of administration*: Oral

  - *Regimen*: Dosing regimen must be as agreed in each protocol

    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 selexipag 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. Your submission must include the postmarketing adverse event reports for selexipag available to you prior to December 20, 2024. 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.[5] 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[6] 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 August 29, 2025. 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

[5] 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
[6] https://www.fda.gov/media/154109/download

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.[7]

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

[7] 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.[8]

If you have any questions, please contact Brian Cooney, Regulatory Project Manager, via telephone at (301) 796-0886 or email at brian.cooney@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hylton Joffe, MD
Director
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

[8] 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/

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