DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077537

WRITTEN REQUEST – AMENDMENT 1

Anacor Pharmaceuticals, Inc.
c/o Pfizer Inc.
Attention: Crystal Browning, MS
Senior Director, Regulatory Affairs
270 Littlefield Avenue
South San Francisco, CA 94080

Dear Ms. Browning:

Please refer to your correspondence dated May 2, 2017, requesting changes to FDA's March 16, 2017 Written Request for pediatric studies for crisaborole.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on March 16, 2017, remain the same. (Text added is underlined. Text deleted is strikethrough.)

> Subjects in the PK cohort ~~and subjects with abnormal renal or hepatic function at baseline~~ must have assessment of propylene glycol systemic levels, lactate levels, calculation of osmolar gap and anion gap at <u>pre-dose on day 8 only</u> ~~each PK sampling timepoint~~.
>
> For all subjects, in addition to the proposed routine laboratory evaluations, laboratory monitoring must include assessment of propylene glycol systemic levels, lactate levels, calculation of osmolar gap and anion gap, at ~~baseline~~ <u>screening</u> and at the end of treatment.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated March 16, 2017, as amended by this letter, must be submitted to the Agency on or before September 30, 2019, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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 addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, 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:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- 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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Omolara Laiyemo, Regulatory Project Manager, at (240) 402-3842.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Complete Copy of Written Request as Amended

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 077537

WRITTEN REQUEST

Anacor Pharmaceuticals, Inc.
Attention: Carmen R. Rodríguez, M.Sc.
Senior Vice President, Regulatory Affairs and Quality
1020 East Meadow Circle
Palo Alto, CA 94303-4230

Dear Ms. Rodriguez:

Reference is made to your 18 Nov 2016 Proposed Pediatric Study Request for Eucrisa (crisaborole) ointment, 2%.

BACKGROUND:

This study investigates the potential use of Eucrisa (crisaborole) ointment, 2% in the treatment of pediatric patients with mild to moderate atopic dermatitis ages 3 months to < 2 years.

Atopic dermatitis (AD) is a common, chronic, inflammatory skin disease that occurs predominantly in children. Atopic dermatitis affects up to 30% of children[1] and an estimated 2% to 3% of adults with 85% of affected individuals showing signs of the disease before 5 years of age. The prevalence of atopic dermatitis among children younger than 3 months of age is lower than other pediatric age groups. Therefore, studies in subjects with atopic dermatitis less than 3 months of age would be impossible or highly impractical.

The sponsor completed trials in adults and children ages 2 years to 16 years and 11 months which supported approval of Eucrisa ointment for the topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older. Because atopic dermatitis occurs in children ages 3 months to < 2 years, it is feasible to conduct studies in this pediatric age group. Although there are safe and effective FDA approved products for the treatment of this disorder, Eucrisa provides an effective treatment option without the safety concerns associated with chronic use of topical corticosteroids or calcineurin inhibitors. Because the clinical presentation and course of atopic dermatitis are similar in all pediatric age groups, efficacy may be extrapolated from adequate and well controlled studies in the pediatric population ages 2 years to 16 years and 11 months.

[redacted] (b) (4)

[1] Bieber, T. Mechanisms of Disease Atopic Dermatitis. N Engl J Med 2008; 358:1483-94.

(b) (4)

To obtain needed pediatric information on crisaborole, 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 nonclinical toxicology data, the following studies must be conducted prior to the start of the clinical study described in this written request.

  Study 1:
  Pilot dose oral (gavage) range-finding study in juvenile rats (1 week of age at the start of dosing).

  This study will assess a range of oral gavage doses and evaluate the toxicokinetics to compare potential toxicity and exposures with crisaborole in studies of older rats. The results from this dose range-finding study will be used to determine the appropriate dose range to use in the systemic juvenile rat toxicology study (Study 2).

  Study 2:
  Systemic toxicology study in juvenile rats (1 week of age at the start of dosing).

  The route of administration in this study will be determined based on the results from the pilot dose range-finding study in juvenile rats and must be agreed upon with the Agency. This toxicology study will assess clinical observations, food consumption, body weight, motor activity, acoustic startle habituation, macroscopic and limited microscopic pathology evaluations, and toxicokinetics. The protocol must be agreed upon with the Agency before initiation of the study.

- *Clinical study:*

  Multicenter, open-label PK and safety trial with crisaborole to determine the safety and pharmacokinetics in pediatric subjects from 3 months to less than 2 years of age with mild to moderate atopic dermatitis.

  Efficacy in pediatric subjects from 3 months to less than 2 years of age will be supported by extrapolation of efficacy from adequate and well controlled studies in the pediatric population ages 2 years to 16 years and 11 months.

  A formal protocol for this study must be agreed upon with the Agency before initiation of the study.

- *Objective of the study:*

To determine the safety and pharmacokinetics of Eucrisa (crisaborole) ointment, 2% in pediatric subjects from 3 months to less than 2 years of age with mild to moderate atopic dermatitis. A subset of subjects will be studied under maximal use conditions.

- *Patients to be studied:*

  - *Age group in which study will be performed*:
    Subjects from 3 months to less than 2 years of age with mild to moderate atopic dermatitis with at least 5% treatable body surface area (%BSA) excluding the scalp.

    In the subset of subjects to be evaluated for pharmacokinetics of crisaborole under maximal use conditions, subjects should have moderate atopic dermatitis and at least 35% treatable percent body surface area (% BSA) excluding the scalp.

  - *Entry Criteria*
    - Inclusion criteria
      - Investigator's static global assessment (ISGA) Score of Mild (2) or Moderate (3) at Baseline/Day 1
      - Subject meets one of the following:
        - PK cohort: has moderate atopic dermatitis and at least 35% treatable % BSA, excluding the scalp, and adequate venous access to permit repeated PK sampling;
        - Non-PK cohort: has mild to moderate atopic dermatitis and at least 5% treatable % BSA, excluding the scalp.

    - Exclusion criteria
      - Has a history of:
        - angioedema or anaphylaxis.
        - hyperactive airway disease requiring corticosteroid therapy.
        - significant active systemic or localized infection, including known actively infected AD.
        - biologic therapy including intravenous immunoglobulin (IVIG) at any time prior to study.
        - treatment for any type of cancer.
        - previous treatment with crisaborole

- *Number of patients to be studied:*
  At least 100 completed subjects to be evaluated for safety and at least 16 completed subjects to be evaluated for pharmacokinetics of crisaborole under maximal use conditions.

- *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:*

  Pharmacokinetic endpoints:
  The pharmacokinetic endpoints must include the mean steady state C_{max} of AN2728 (parent), AN7602 (metabolite), and AN8323 (downstream metabolite). Conduct PK sampling at steady state in at least 16 subjects ages 3 months to less than 2 years of age with moderate atopic dermatitis.

  Safety endpoints:
  Safety outcomes must include adverse events, local skin reactions, clinical laboratory assessments, weight, height/length, and extent of exposure. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

  Adverse events
  The following adverse events must be actively monitored for the duration of the study based on the known adverse event profile of crisaborole and on the potential for adverse events associated with exposure to propylene glycol which is contained in the product formulation:

  - Hypersensitivity reactions
  - Application site pain
  - Adverse events associated with propylene glycol toxicity:
    -neurologic adverse events (CNS depression; seizures);
    -cardiovascular adverse events.

  Laboratory monitoring:
  For all subjects, in addition to the proposed routine laboratory evaluations, laboratory monitoring must include assessment of propylene glycol systemic levels, lactate levels, calculation of osmolar gap and anion gap, at ~~baseline~~ screening and at the end of treatment.

  Subjects in the PK cohort ~~and subjects with abnormal renal or hepatic function at baseline~~ must have assessment of propylene glycol systemic levels, lactate levels, calculation of osmolar gap and anion gap at pre-dose on day 8 only~~each PK sampling timepoint~~.

- *A Data Monitoring Committee (DMC) must be employed.*

- *Known drug safety concerns and monitoring:*
  Hypersensitivity reactions are the primary drug specific safety concern. Other safety concerns are related to local skin reactions which include application site pain. Parents/caregivers should be queried for the development of these adverse events in pediatric subjects at every visit.

  Propylene glycol toxicity is a theoretical concern to address because the drug product contains 9% propylene glycol. The potential for propylene glycol toxicity should be evaluated with laboratory monitoring (propylene glycol levels, lactate levels, bicarbonate, creatinine,

calculation of osmolar gap and anion gap) and parents/caregivers queried for signs and symptoms indicating neurologic or cardiovascular adverse events.

- *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:* ointment
  - *route of administration:* topical
  - *regimen:* twice per day

  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.

- *Statistical information, including power of study(ies) and statistical assessments:*
  This study must assess at least 100 completed and evaluable subjects. The reports should include summary statistics for all safety and pharmacokinetic assessments as agreed with the Agency at the time of protocol submission and review prior to initiation of the study.

- *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 crisaborole 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. You are encouraged to contact the reviewing Division for further guidance.

  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.

- *Timeframe for submitting reports of the study(ies):*
  Reports of the above studies must be submitted to the Agency on or before September 30, 2019. 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(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. 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 Omolara Laiyemo, Regulatory Project Manager, at 240-402-3842.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
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/

JULIE G BEITZ
07/05/2017