DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 210566

WRITTEN REQUEST

Therapeutics Inc.
Attention: Garet Heintz, RAC
Director, Regulatory Affairs
9025 Balboa Avenue, Suite 100
San Diego, CA 92123

Dear Mr. Heintz:

Reference is made to your December 30, 2014 Proposed Pediatric Study Request for halobetasol propionate foam, 0.05%.

BACKGROUND:

This study investigates the potential use of halobetasol propionate foam, 0.05% in the treatment of pediatric plaque psoriasis.

Psoriasis occurs in pediatric subjects ages 12 to less than 18 years of age. In the U.S., the annual incidence of psoriasis in patients aged younger than 18 years was estimated to be 40.8 per 100,000. [1] Extrapolation of efficacy from adults to pediatric patients ages 12 to less than 18 years of age for plaque psoriasis is reasonable as disease progression and response to intervention are similar and consistent with other topical products to treat plaque psoriasis. Study in pediatric patients 11 years of age and younger with plaque psoriasis including neonates is not required as part of this Written Request because of a) safety considerations (i.e., the greater risk of HPA axis suppression with high or super-potent corticosteroids), particularly in infants and children less than 12 years of age; and b) the small number of pediatric patients with psoriasis where super-potent topical corticosteroids are a medically appropriate therapy.

To obtain needed pediatric information on halobetasol propionate (HBP) foam, 0.05%, 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)*:

[1] Tollefson MM, Crowson CS, McEvoy MT, et al. Incidence of psoriasis in children: a population based study. J. Amer. Acad. Dermatol. 2010; 62: 979-987.

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 study:*

A formal protocol and statistical analysis plan for the study must be agreed upon with the Agency before initiation of the study.

Study 1:
Multicenter, open-label study with halobetasol propionate foam, 0.05% to determine the pharmacokinetic properties and adrenal suppression potential in pediatric subjects from 12 to less than 18 years of age with plaque psoriasis.

Efficacy in pediatric subjects from 12 to less than 18 years of age will be supported by extrapolation of efficacy from adequate and well controlled studies in adults.

- *Objective of the study:*

To determine the pharmacokinetic properties and adrenal suppression potential of halobetasol propionate foam, 0.05% under maximal use conditions in pediatric subjects from 12 to less than 18 years of age with plaque psoriasis.

- *Patients to be Studied:*

  Age group in which study will be performed:
  Subjects from 12 to less than 18 years of age with greater than 10% body surface area (BSA) involvement.

  Number of patients to be studied:
  At least 20 completed and evaluable subjects. Enrollment should be approximately evenly distributed among ages and males and females and there should be sufficient number of subjects at the lowest ages.

  Representation of Ethnic and Racial Minorities:
  The study 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 (PK) endpoints for the study must include plasma levels of HBP. The PK sampling schedule should be based on available PK concentration time profile for each respective formulation in adults. PK assessment will be conducted as agreed

with the Agency at the time of protocol submission and review prior to initiation of the study.

Safety Endpoints:
Safety outcomes must include: adverse events, local skin reactions, urine pregnancy testing (as applicable), routine clinical laboratory testing, dosing compliance, and extent of exposure. The following adverse events must be actively monitored: HPA axis suppression and local skin reactions including atrophy and development of telangiectasia. HPA axis suppression is assessed via measurement of serum cortisol concentrations after stimulation of the adrenal cortex with cosyntropin (Cortrosyn® tests). HPA axis suppression is defined as a post-stimulation serum cortisol level ≤ 18 μg/dL assessed at the end of study. All adverse events must be monitored until symptom resolution or until the condition stabilizes.

- *Known Drug Safety concerns and monitoring:*

HPA axis suppression is the primary systemic drug specific safety concern. Local skin reactions including atrophy and the development of telangiectasia are the primary local drug specific safety concern.

- *Extraordinary results:*

In the course of conducting this study, 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:
foam

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:*

The study must assess at least 20 completed and evaluable subjects. The report 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*:

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 HBP foam, 0.05% 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.

- *Format and types of reports to be submitted*:

You must submit a full study report (which has not been previously submitted to the Agency) that addresses 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 the report of the study:*

The reports of the above study must be submitted to the Agency on or before February 28, 2020. 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 report of the study 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 study 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, 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 a protocol for the above study 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 this study. 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 study 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 Cristina Attinello, Senior Regulatory Project Manager, at 301-796-3986.

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
11/29/2017