

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210566Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 107302

MEETING MINUTES

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

Dear Mr. Heintz:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for halobetasol propionate foam, 0.05%.

We also refer to the teleconference between representatives of your firm and the FDA on June 14, 2017. The purpose of the meeting was to discuss the development program for halobetasol propionate foam, 0.05%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD, FAAD
Acting Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 14, 2017, 9-10am
Meeting Format: Teleconference

Application Number: IND 107302
Product Name: halobetasol propionate foam, 0.05%
Proposed Indication: for the treatment of plaque psoriasis in patients 18 years of age and older
Sponsor Name: Therapeutics, Inc.

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Cristina Attinello, MPH

FDA ATTENDEES

Jill Lindstrom, MD, Deputy Director, DDDP
Nancy Xu, MD, Acting Associate Director for Labeling
David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, DO, MS, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Marilena Flouri, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Yichun Sun, PhD, Acting Quality Assessment Lead, DNDP II, NDPB V
Samata Tiwari, PhD, Review Microbiologist, OPQ/OPF/DMA/BII
Carlos Mena-Grillasca, RPh, Safety Evaluator, DMEPA
Roy Blay, Reviewer, OSI
Robert Meyer, BS, ME, Reviewer/ Mechanical Engineer, CDRH/ODE
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Dan Piacquadio, M.D. CEO (Clinical & Clinical Pharmacology)
Anthony Andrasfay, B.S. Vice President, Clinical Development
Bob Gauthier, M.S. Vice President, Product Development
Wayne Alden IV, B.S. Associate Director of CMC
Andrea Kichura, Ph.D. Manager, Data & Medical Writing Services

Garet Heintz, B.S., RAC Director, Regulatory Affairs

1.0 BACKGROUND

Purpose of the Teleconference:

The purpose of this teleconference is to discuss the planned marketing application for halobetasol propionate foam, 0.05%.

Regulatory Correspondence History:

We have had the following teleconference with you:

- 21 Aug 2013 – End-of-Phase 2

We have sent the following correspondences:

- 26 Feb 2010 – Advice/Information Request Letter
- 09 Jun 2011 – Advice/Information Request Letter
- 19 Jan 2012 – Advice Letter
- 14 Jun 2013 – Advice/Information Request Letter
- 17 Aug 2012 – Advice Letter
- 15 Jan 2014 – PSP Written Response Letter
- 13 May 2014 – SPA Agreement Letter (SPA-1)
- 15 May 2014 – PSP Initial Agreement Letter
- 21 May 2014 – SPA Agreement Letter (SPA-2)
- 15 Oct 2014 – Advice Letter
- 02 Mar 2016 – Advice Letter
- 10 Jan 2017 – PSP Written Response Letter (amended)
- 09 Feb 2017 – PSP Amended Agreement Letter

2.0 DISCUSSION

2.1. Regulatory

Question 16:

At present, TI has not selected a tradename for HBP Foam. Does FDA agree that the proposed proprietary name and trade dress can be submitted during the NDA review, but no later than 90 days prior to the PDUFA goal date, without impacting the NDA review timeline?

FDA Response to Question 16:

If you intend to have a proprietary name for this product, we recommend you submit a request for a proposed proprietary name at the time of NDA submission.

We encourage you to submit your request for FDA review of your proposed proprietary name during the IND phase of your drug development program.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)

2.2. Chemistry, Manufacturing and Controls

Question 1:

The compendial drug substance, halobetasol propionate, is manufactured and supplied by (b) (4)

Does FDA agree that the drug substance specifications, test parameters, and acceptance criteria (i.e., USP) are appropriate and adequate to support filing of an NDA?

FDA Response to Question 1:

(b) (4) However, if the manufacturing process for the API generates impurities that are not included in the USP monograph specifications, these additional impurities should be included in the specification and reported as well.

Question 2:

The commercial production of HBP Foam, (b) (4) will be performed by the Pharmasol Corporation. Additional analytical testing may be performed by (b) (4) Initial scale-up, process development, Phase 3 clinical supply manufacturing, and definitive stability were completed at the (b) (4) batch scale (as described in Section 10.1.2). In anticipation of commercial launch, Pharmasol is preparing to scale-up the current process to (b) (4) batches (with the final commercial scale to be decided). Process validation of three commercial batches at scale will be performed prior to commercialization.

Does FDA agree that the in-process testing and final drug product specifications, rationale for establishing limits, analytical methods, and stability data are appropriate and adequate to support filing of an NDA?

FDA Response to Question 2:

We recommend you add an assay test for the halobetasol propionate (b) (4). The tests listed in the drug product specification appear reasonable. The test methods including their validation studies and acceptance criteria of the drug product specification will be evaluated during NDA review. The amounts of stability data except in-use stability data proposed to be included in the NDA submission appear reasonable to support the filing of your NDA. We recommend you include in-use stability data obtained from stability samples of one of the registration stability batches of the drug product at the end of the proposed expiration dating period (i.e. (b) (4)) in your NDA submission.

Aqueous non-sterile drug products may potentially be contaminated with organisms in the *Burkholderia cepacia* complex (BCC). BCC strains have a well-documented ability to ferment a wide variety of substrates. Further, BCC strains are known to proliferate in the presence of many traditional preservative systems and can survive and even proliferate in product during storage. For a recent review of FDA's perspective on BCC see PDA J Pharm Sci Tech 2011; 65(5): 535-43.

In order to control for the presence of BCC in your product you should consider the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and describe the steps to minimize the risk of BCC organisms in the final drug product. We recommend that potential sources are examined and sampled as process controls. These may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria.
2. Provide test methods and acceptance criteria to demonstrate the drug product is free of BCC. Your test method should be validated and a discussion of those methods should be provided. Test method validation should address multiple strains of the species and cells should be acclimated to the conditions in the manufacturing environment (e.g., temperature) before testing.

As there are currently no compendial methods for detection of BCC, we have provided suggestions for a potential validation approach and some points to consider when designing your validation studies. However, any validated method capable of detecting BCC organisms would be adequate. It is currently sufficient to precondition representative strain(s) of BCC in water and/or your drug product without preservatives to demonstrate that your proposed method is capable of detecting small numbers of BCC. Your submission should describe the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method to include growth medium and incubation conditions. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to insure that the proposed recovery methods are adequate to recover organisms potentially present in the environment. For more information, we refer you to Envir Microbiol 2011; 13(1):1-12 and J. Appl Microbiol 1997; 83(3):322-6.

Please also see response to Question 4 below.

Meeting Discussion:

The sponsor requested exemption from BCC testing based on performing USP 61 and 62 at release, along with AET testing in the stability lots. The Agency noted that due to historical data regarding the adverse effect of BCC in non-sterile aqueous drug products, the testing of BCC is needed. The sponsor stated that (b) (4) they anticipate difficulties performing the modified USP 62. However, the sponsor stated that they plan on trying various strategies to perform the requested tests and will submit the results for the studies as they become available during product development. The Agency acknowledged the sponsor's response.

Question 3:

To characterize the drug product formulation inside the aerosol can, TI conducted a (b) (4) canister stability study in two configurations:

- with the same head-space to fill-volume ratio as the proposed final configuration;
- with the same bulk fill level as the proposed final commercial configuration.

The study, per FDA request, was designed to determine whether the HBP is fully solubilized inside the canister in the presence of the propellant throughout the shelf-life of the product and whether the formulation inside the canister in the presence of the propellant is an emulsion, a suspension, or a solution throughout the shelf-life of the product. The results for 24 months of real-time 25°C/60%RH stability storage demonstrate that the drug substance remains fully solubilized in solution in the presence of propellant and additional details will be provided in Section 3.2.P.2 (Pharmaceutical Development) of the NDA (see also Section 10.1.2.3.4).

Does FDA agree that TI has adequately characterized the drug product in the canister in the presence of propellant?

FDA Response to Question 3:

The characterization studies you performed appear reasonable to support the filing of your NDA.

Question 4:

TI has completed antimicrobial preservative effectiveness testing (b) (4) and confirmed that the formulation is self-preserving in accordance with USP <51> (b) (4) TI has performed microbiological enumeration testing and microbiological testing for specific organisms as part of the registration stability program and performed testing on three batches at the proposed shelf-life (see Section 10.1.2.3.5). Based on these data, (b) (4) TI proposes to remove USP <61> and <62> testing during product release testing and stability testing.

Does FDA agree, pending review of the data, with TI's proposal to remove microbiological testing on release and stability testing for commercial lots?

FDA Response to Question 4:

The proposal to omit microbial testing from the DP release testing and stability testing for commercial lots is acceptable. However, consider adding microbial limits testing at the initial stability testing time point for the first lots in the stability program.

Please note that the NDA submission should also include the data for the AET study performed (b) (4) to confirm that the formulation is self-preserving for this multi-dose drug product.

Question 5:

As agreed with FDA at EOP2, TI has completed controlled extraction testing with the individual container closure components, using a blend of (b) (4) % w/w ethanol and water (to model the drug product formulation) (b) (4)

(b) (4) were also used to perform standard extraction analyses. No analytes extracted from the container closure system that exceeded the analytical evaluation threshold were of a safety or toxicological concern; all were well known and characterized compounds below levels of concern. Additionally, all of the product contacting elements of the container closure system meet FDA food grade requirements for direct contact. Additional details of this testing are described in Section 10.1.2.7.5.

Does FDA agree that the container closure system has been adequately characterized?

FDA Response to Question 5:

Your proposal of not conducting leachable studies appears reasonable based on the information provided in the briefing package. Detailed extractable studies and study reports will be evaluated during NDA review.

The container closure system characterization is incomplete. We recommend the following be provided within the NDA submission:

1. An Instructions for Use (IFU) document which outlines how the canister device should be used, use environments, user profiles, etc.
2. Similar canister device section should be provided which includes:
 - a. An image of the canister if not provided in the IFU.
 - b. A description of how the device produces the intended drug output specifications.
 - c. Conditions for use, expected and worst case, which are acceptable.
 - d. The device verification and validation data to demonstrate that the design of the device will consistently produce the drug output specifications (e.g., foam stiffness, foam collapse, delivered amount) within the specified device performance (e.g., delivery rate, can pressure, leak rate etc.). It is recommended that you provide a traceability Matrix which tabulates device specifications and provides clear references to associated specification verification reports. Verification reports should be provided, and should reiterate the subject specification and include the verification protocol, parameters,

conditions, sample size tested, summarized results etc. All conditions applied and samples sizes should be justified.

- Additional device specifications that should be verified include functionality specifications such as forces to press a feature, remove a cap, delivery rate, etc.
- e. Lot release specifications table, which identifies how and how many, finished device are verified prior to marketing. The acceptance criteria per lot should be included.
- f. Shipping verification which demonstrates devices function as intended after shipping.
- g. Risk analysis associated with the device or component failures and misuse.

Meeting Discussion:

The Agency requested the sponsor submit a stand-alone document which demonstrates the finished device's function as intended throughout the expiration time, and after foreseeable preconditions are applied, reliably.

The Agency recommended the engineering analysis be summarized using a traceability matrix which lists critical features and specifications which are used to control parameters. Associated with each feature and specification should be a verification report which clearly shows that within such specifications the device functions as intended. Some specifications or features may be justified through engineering tools, such as dimensional stack up analysis or component analysis.

In addition to verifying specifications and device features, the documentation provided should explain how finished devices are verified prior to release. The Agency recommended that the explanation identify the Lot Release verification process, and the sample size per feature verified per Lot. Justification as to why only select features are verified was recommended, as well as the sample size used.

In response, the sponsor stated testing was completed during the aerosol can development process to ensure the device sprayed foam as needed. The sponsor stated they were not expecting to provide the noted device analysis, and stated they will provide a summarized report within the NDA, but would appreciate if the documentation can be revised based on interactive questions during the review.

The Agency stated the provided report should identify critical functions which are needed to ensure the foam is consistent, and should identify how such functions are verified. The Agency noted that if there are additional questions they can be asked and worked through interactively during the review process.

2.3. Pharmacology/Toxicology

Question 6:

A series of six nonclinical toxicology studies have been completed with HBP Foam. These include dermal and ocular irritation studies in rabbits, a sensitization study in guinea pigs, a 4-week dermal toxicity study in minipigs, a 4-day dosing feasibility study in rats using vehicle material, and a 13-week dermal toxicity study in rats. All but the 13-week repeat-dose rat study evaluated a formulation that contained minor differences from the to-be-marketed formulation

(b) (4)

The 13-week rat study utilized the final to-be-marketed formulation.

As agreed at the EOP2 meeting, TI has completed the required studies to demonstrate safety of HBP Foam. Does FDA agree that no additional nonclinical studies on HBP Foam are needed to support the NDA?

FDA Response to Question 6:

We agree that no additional nonclinical studies on hbp foam are needed to support the NDA.

Question 7:

A right-of-reference to both ULTRAVATE® (halobetasol propionate), 0.05% NDAs (19-967 [Cream] and 19-968 [Ointment]) has been secured and TI intends to include the study reports for the following toxicity studies that supported the ULTRAVATE® NDA approvals: (b) (4)

A listing of the contents and summaries of the legacy reports to be included in Module 4 of the pending NDA submission is provided in Section 9.3.

Does FDA agree that the inclusion of the above-listed nonclinical toxicology studies on HBP in the Ultravate Ointment and Cream NDAs, in addition to the nonclinical HBP Foam studies, in the planned HBP Foam NDA provides adequate data to support the proposed prescribing information as presented in the draft labeling text (see Section 6)?

FDA Response to Question 7:

We agree that the inclusion of the above-listed nonclinical toxicology studies on hbp in the Ultravate ointment and cream NDAs, in addition to the nonclinical hbp foam studies, in the planned hbp foam NDA provide adequate data to support the proposed prescribing information as presented in the draft labeling text.

Question 8:

Since the nonclinical pharmacology and pharmacokinetics (excluding toxicokinetics) for HBP are well established, the Sponsor plans to include only written summaries of the information from the ULTRAVATE® NDAs and will not be preparing tabulated summaries to cover electronic Common Technical Document (eCTD) sections 2.6.3 and 2.6.5 in the NDA submission. Does FDA agree with this approach?

FDA Response to Question 8:

Since the nonclinical pharmacology and pharmacokinetics (excluding toxicokinetics) for hbp are well established, we agree that only written summaries of the nonclinical pharmacology and pharmacokinetics information from the ULTRAVATE® NDAs can be provided in the electronic Common Technical Document (eCTD) sections 2.6.3 and 2.6.5 of the NDA submission.

Meeting Discussion:

The sponsor clarified that the written summaries will be provided in sections 2.6.2 and 2.6.4 of the NDA submission.

2.4. Clinical/Biostatistics

Question 9:

As detailed in [Table 41](#), the completed clinical studies with HBP Foam include all the required studies to demonstrate safety and efficacy of HBP Foam. Based on this, does FDA agree that no additional safety or efficacy clinical studies on HBP Foam are needed to support the NDA?

FDA Response to Question 9:

You have conducted the following clinical studies: VCA, HRIPT, HPA axis suppression/PK, two Phase 2 trials, and three Phase 3 trials. The two initial Phase 3 trials were conducted under a SPA. You have requested a waiver for conducting human phototoxicity and photocontact allergy studies based on lack of significant absorption in the visible UV spectrum. You have also requested a waiver for conducting studies in pediatric subjects age 11 years and younger.

Your vasoconstrictor assay (study 122-0551-101) was conducted with an older formulation and the results were inconclusive. We communicated this to you at the time of End of Phase 2 meeting. Provide a justification in the NDA to support applicability of this study.

Your development program appears reasonable to support filing. The adequacy of the safety and efficacy data to support the NDA will be a review issue.

Question 10:

In total, 680 subjects have been exposed to HBP Foam and more than half (399/680; 59%) of those subjects were treated for the indicated dermatologic condition: plaque psoriasis. HBP Foam has demonstrated a safety profile similar to the other marketed formulations of HBP, 0.05% (ULTRAVATE ® Cream, Ointment, and Lotion) and other high to super-high potency topical corticosteroids and no unanticipated drug-related safety events were identified in multiple clinical trials. Please see [Section 10.3](#) for further information.

In accordance with §314.50(f)(2) and recent precedents for similar products, we intend to only include case report forms (CRFs) for all patients who experienced a serious or severe AE, and for all Phase 2 and 3 patients (i.e., subjects with plaque psoriasis) that discontinued the study for any reason (see [Section 9.6](#)). Does FDA agree?

FDA Response to Question 10:

Yes. This is acceptable.

Question 11:

In addition to the HPA/PK and the Phase 2 pilot efficacy studies, three Phase 3 studies to determine the safety and effectiveness of HBP Foam in patients with plaque psoriasis have been completed. Study #122-0551-305 and Study # 122-0551-306 were conducted as per the SPA Agreement Letters received from FDA; Study # 122-0551-310 had an identical study design to

the other Phase 3 studies. Two of the three Phase 3 studies met the primary efficacy endpoint with significantly more subjects achieving “treatment success” in the HBP Foam group (306: 25%; 310: 31%) versus the VEH Foam group (306: 4%; 310: 7%) at Day 15 ($p < 0.001$). The third Phase 3 study was directional consistent to the two pivotal studies, with more subjects achieving “treatment success” in the HBP Foam group (305: 18%) versus the VEH Foam group (305: 10%) but the study results did not reach statistical significance (see [Section 10.3.2 for further information](#)).

Given that two of the Phase 3 studies met the conditions specified in the SPA Agreement for the pre-specified primary endpoint, we believe that these studies are adequate to support the submission of an NDA. Does FDA agree?

FDA Response to Question 11:

Your proposal appears reasonable for the filing of an NDA.

Question 12:

TI plans to provide raw datasets (as described in Section 9.5) and analysis datasets, including define.xml documentation, for the pivotal and supportive Phase 3 clinical studies (306, 310, and 305), the supportive Phase 2 studies (202 and 203), and the integrated analyses of safety and efficacy. The raw datasets will be modeled in accordance with the CDISC Study Data Tabulation Model (SDTM) Implementation Guide: Human Clinical Trials which comprises Version 3.1.3 of the Submission Data Standards. The analysis data sets will be modeled in accordance with the CDISC Analysis Data Model (ADaM), Version 2.1. All SDTM and ADaM datasets will be submitted in SAS transport form (.xpt). Does FDA Agree with this plan?

FDA Response to Question 12:

Your proposal to submit datasets according to CDISC formatting is acceptable.

The Multiple Imputation (MI) approach is one of your sensitivity analyses in your Phase 3 trials to investigate the impact of the handling of missing data, which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, submit the SAS code used to implement MI. In addition, submit the SAS code used to analyze these datasets.

For the analysis datasets, we have the following comments:

- Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.
- The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For

ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Question 13:

TI plans to provide raw datasets in transport form (.xpt) for the Phase 1 VCA (Study 101) and HRIPT (Study 108) studies. These datasets will not be in SDTM format. Does FDA Agree with this plan?

FDA Response to Question 13:

Your proposal appears acceptable. See response to Question 9.

Question 14:

The ISS will present the relevant safety summaries for each of the seven clinical studies, as well as, a pooled analysis including all Phase 2 and Phase 3 studies. The safety summaries for the Phase 1 studies (Studies 101 and 108), which enrolled healthy subjects with limited exposure to HBP Foam (<1 g) will be presented for the individual studies. The safety results of the Phase 2 and 3 studies (Studies 202, 203, 305, 306, and 310), which enrolled adults with plaque psoriasis and exposed to HBP Foam for two weeks (approximately 50-60 grams per week) will be presented individually and pooled as described in the draft statistical analysis plan (SAP) provided in Section 8.

The ISE will include individual and integrated summaries of the supportive Phase 2 efficacy study (Study 203) and the three Phase 3 studies (Pivotal Studies 306 and 310 and the supportive Study 305). The three Phase 3 studies were conducted using identical protocols. The supportive Phase 2 efficacy study (Study 203) was similar to the Phase 3 studies with regards to baseline disease characteristics, dosing regimens, study methodology, and efficacy endpoints that were measured using essentially the same severity disease scale.

A draft SAP, which summarizes the statistical methods and analyses to be performed for the integrating studies described above, is provided in Section 8.

Does FDA agree with the Sponsor's proposal for the pooling of studies to be included in the ISS and ISE and the statistical analyses to be conducted?

FDA Response to Question 14:

You propose that your ISS contains pooled analyses of all Phase 2 and Phase 3 trials (202, 203, 305, 306, and 310). We recommend also including pooled analyses that do not include trials 202 (an open-label trial) and 203, designed to be of shorter duration (2 weeks or 1 week if psoriasis has cleared at Day 8) than the Phase 3 trials.

It should be noted that the objective of the integrated summary of efficacy (ISE) is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim

based on pooling data from the individual trials. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials demonstrating replication of study finding.

Question 15:

Provided in Section 6 is a draft product labeling (package insert) with annotations to data and /or information to support the proposed draft labeling text. The package insert conforms to the Physician Labeling Rule (PLR) [REDACTED] (b) (4)

In addition to the primary efficacy endpoint, does FDA agree that the secondary endpoints are meaningful to the prescriber and thus acceptable for inclusion in the Clinical Studies section of the label?

FDA Response to Question 15:

Secondary endpoints regarding plaque elevation, scaling and erythema are components of the primary endpoint. For secondary endpoints to appear in labeling, they need to be prespecified and adjusted for multiplicity, in addition to being clinically meaningful. The precise content of eventual product labeling will be determined during review of the complete NDA application.

Question 17:

Due to the extensive marketing experience and well established safety profile of topical drug products containing HBP, 0.05% (ULTRAVATE® Cream, Ointment and Lotion, and the numerous generic equivalents), together with the 680 subject exposures to HBP Foam, we do not believe there is a need to develop additional risk management plans (e.g., medication guide or formal REMS program) beyond the safety information contained in the product labeling. Does FDA concur?

FDA Response to Question 17:

Pending review of the safety database, labeling appears adequate to convey the risks and benefits of the product. We do not anticipate a need for additional risk management plans.

Question 18:

TI submitted an Agreed iPSP to the IND on 17 April 2014 (Serial No. 0032), which was subsequently amended and agreed to by FDA on 10 January 2017 (Serial No. 0061). Does FDA agree that a reference to the Agreed Amended iPSP is sufficient to satisfy the PREA requirements and no additional information is needed to support the NDA?

FDA Response to Question 18:

In the agreed upon iPSP, you request a partial waiver from conducting clinical studies in the pediatric population (birth to 11 years of age) for HBP Foam, 0.05%. A formal decision by the FDA about granting a waiver and/or deferral of required pediatric assessments will not be made until approval of the marketing application; the information contained in an agreed iPSP will be considered in review of any requests for waiver and/or deferral submitted in the application.

Additional Comments

1. In your NDA, submit all bioanalytical method validation as well as bioanalysis reports for review for the parent, any metabolites and cortisol levels. Also provide information to support long term storage stability of all pharmacokinetic samples as well as cortisol samples. You should also submit the results of incurred sample reanalysis for review.
2. Submit all PK data sets in XPT format.

2.5. Administrative

Question:

TI will submit the NDA in accordance with the eCTD and intends to follow the latest submissions standards for all components of the NDA as described in Section 9 (see also [Appendix 1](#), which provides a preliminary index of the planned NDA in the eCTD format). Since this will be TI's first electronic NDA submission, TI welcomes any feedback regarding the proposed index structure, hierarchy, and format from FDA.

FDA Response to Question:

From a technical standpoint (not content related) yes, the proposed index structure, hierarchy, and format for the planned NDA is acceptable. However, please see additional comments below:

- For archival purposes, also submit a pdf file of any document submitted in word (e.g. 1.14.1.3). When word documents are submitted, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.
- Providing Table of Contents in 4.1 is not necessary in the eCTD structure however, a reviewer's guide will be helpful and it could be placed in m1.2 (cover letter section).
- Study Tagging Files (STF) file is required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs) and datasets. Please refer to [The eCTD Backbone File Specification for Study Tagging Files 2.6.1 \(PDF - 149KB\) \(6/3/2008\)](#) and Study Data Standards Resources, for datasets, located here:- <https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>.
- Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report form need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Do not use 5.3.7 as a heading element in the index.xml.

3.0 ADMINISTRATIVE COMMENTS

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of May 5, 2017, the following submission types: **NDA, ANDA, and BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:

Site number

Principal investigator

Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

Number of subjects screened at each site

Number of subjects randomized at each site

Number of subjects treated who prematurely discontinued for each site by site

Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection

Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:

Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated

Subject listing for treatment assignment (randomization)

Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued

Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

By subject listing, of AEs, SAEs, deaths and dates

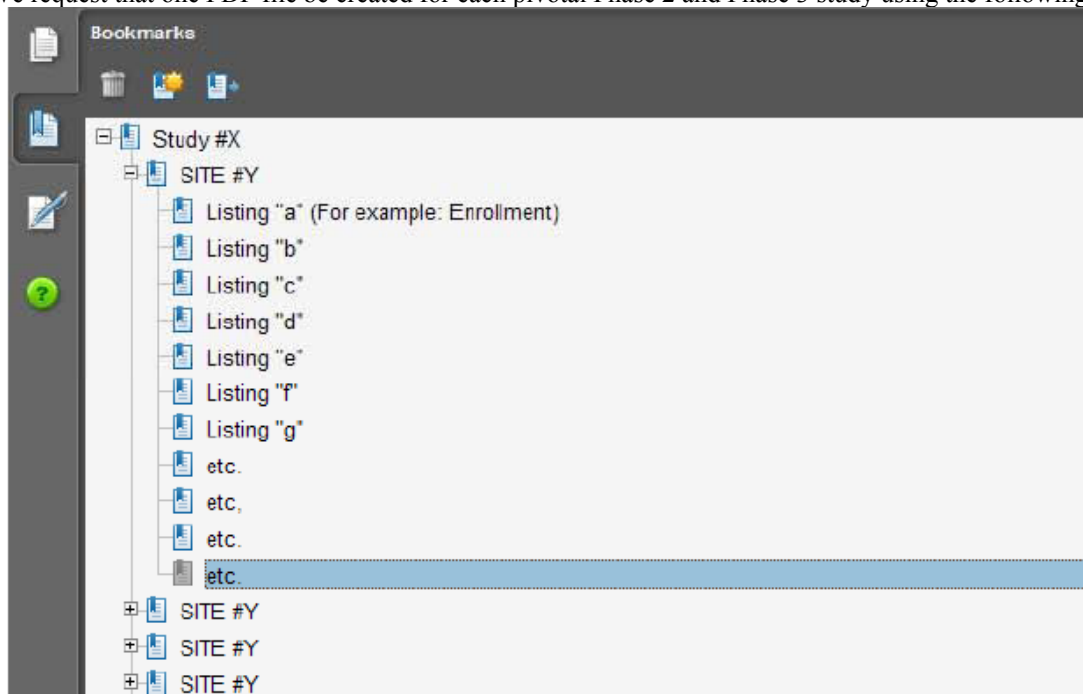
By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.

By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

JILL A LINDSTROM
06/21/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107302

MEETING MINUTES

Therapeutics, Inc.
Attention: Rebecca K. Tong
Senior Director, Regulatory Affairs
9025 Balboa Avenue, Suite 100
San Diego, CA 92123

Dear Ms. Tong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (halobetasol propionate) Foam, 0.05%.

We also refer to the teleconference between representatives of Therapeutics and the FDA on August 21, 2013. The purpose of the meeting was to discuss the development program for (halobetasol propionate) Foam, 0.05%.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Barbara Gould, Chief Project Management Staff at (301) 796-4224.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Teleconference Type: B
Teleconference Category: End of Phase II

Teleconference Date and Time: August 21, 2013 @ 9:00 a.m.

Teleconference Information:

(b) (4)

(b) (4)

Application Number: IND 107302
Product Name: (halobetasol propionate) Foam, 0.05%
Proposed Indication: For the treatment of plaque psoriasis
Sponsor Name: Therapeutics, Inc.

Meeting Chair: Susan J. Walker, MD
Meeting Recorder: Barbara Gould

FDA ATTENDEES

Susan Walker, MD, FAAD, Director, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Tatiana Oussova, MD, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP 3
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Caroline Strasinger, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Roy Blay, PhD, Reviewer, DGCAB
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES

Dan Piacquadio, MD, CEO (Clinical & Clinical Pharmacology)
Mary Beth Ferdon, MD, Sr. Director, Data Management & Statistics
(b) (4) Pharm/Tox Consultant
Bob Gauthier, MS, Vice President, Product Development (CMC)
Tony Andrasfay, BS, Vice President, Clinical Development
Rebecca Tong, MS, Sr. Director, Regulatory Affairs
Hutch Humphreys, MS, Assoc. Director, Regulatory Affairs

Purpose of the Teleconference:

To discuss development program for (halobetasol propionate) Foam, 0.05%

Regulatory Correspondence History

We have sent the following correspondences:

- 26 Feb 2010 – Advice/Information Request Letter
- 09 Jun 2011 – Advice/Information Request Letter
- 19 Jan 2012 – Advice Letter
- 14 Jun 2013 – Advice/Information Request Letter
- 17 Aug 2012 – Advice Letter

Chemistry, Manufacturing and Controls (CMC)

Drug Substance:

Question 1:

Does the Agency agree that the drug substance specifications, test parameters and acceptance criteria are appropriate and adequate to support the Phase 3 program and NDA submission?

Response:

The drug substance specification shown on page 24 of 233 of the briefing package is reasonable to support Phase 3 clinical development. The adequacy of a specification to support NDA submission will be determined in the NDA review.

Drug Product:

Question 2:

Does the Agency agree that the drug product specifications, rationale for establishing limits and the analytical methods are appropriate and adequate to support the Phase 3 program and NDA submission?

Response:

They are inadequate to support Phase 3 clinical development. We have the following comments regarding the drug product specification to support Phase 3 clinical development:

1. The acceptance criterion of the assay test should be tightened to (b) (4) % of the label claim.
2. An acceptance criterion of (b) (4) is not acceptable for Phase 3. Replace it with a meaningful description or a numeric value/range.
3. Add the following tests with appropriate acceptance criteria to drug product release specification (b) (4)

4. Add the following tests with appropriate acceptance criteria to drug product stability specification [REDACTED] (b) (4)

Meeting Discussion:

The sponsor proposed to run microbial limits testing at 6, 12, 18 and 24 month at room temperature. The Agency agreed with the sponsor proposal.

5. Structure the related substances specification as recommended by ICH Q3B.
6. We may have other comments for the specification if the active ingredient is not fully solubilized in the formulation inside the can in the presence of propellant.

The adequacy of a specification to support NDA submission will be determined in the NDA review.

Question 3:

Does the Agency agree that the overall CMC plans and stability program are adequate to support the Phase 3 program and the NDA?

Response:

They are inadequate to support Phase 3 development mainly due to inadequate drug product specification. The characterization of the formulation inside the aerosol can is also inadequate. We recommend that you determine (1) whether the active ingredient is fully solubilized inside the can in the presence of the propellant throughout the shelf-life of the product, and (2) whether the formulation inside the can in the presence of the propellant is an emulsion, a suspension or a solution throughout the shelf-life of the product. The information that supports your determination will need to be included in Section 3.2.P.2 Pharmaceutical Development of the proposed NDA.

In the NDA submission include both upright and inverted orientations in the registration stability protocol and a separate in-use stability study. The evaluation of extractables should be performed on individual formulation-contacting packaging components [REDACTED] (b) (4). If warranted, chemical identities of potential major extractables should be determined and monitored in the registration stability batches.

Meeting Discussion:

The sponsor proposed to retest random samples of used product returned from Phase 3 trials.

The Agency indicated that the sponsor should provide the amounts remaining in the can so that we can ensure that the test is adequate to assess partially used product.

Regarding the extractable testing, the sponsor proposes to use ethanol and water [REDACTED] (b) (4). The Agency agrees with this approach.

Pharmacology/Toxicology

Question 4:

Does the Agency agree that the nonclinical studies completed and planned with the HBP Foam, 0.05% along with the previously conducted nonclinical studies that supported the approvals of Ultravate Cream (NDA 019-967) and Ointment (NDA 019-968), to which TI has a right of reference, are sufficient to support Phase 3 clinical development and an NDA submission for HBP Foam, 0.05%?

Response:

To support the safety of the to-be-marketed HBP Foam formulation (338-13-6), four studies have been completed with a precursor formulation (b) (4): a dermal irritation study in rabbits (b) (4) Study # 0420LT28.012); an *in vivo* eye irritation study in rabbits (b) (4) Study # 0421LT28.004); a guinea pig sensitization study (b) (4) Study # 0424GT28.005); and a 28-day dermal toxicity study in minipigs (b) (4) Study # 1246-009). The optimization of the tested precursor formulation (b) (4) to the to-be-marketed formulation (338-13-6) (b) (4) This change is considered toxicologically inconsequential and acceptable results from Agency review of the nonclinical studies conducted with the precursor formulation will support the safety of the to-be-marketed formulation.

If the planned 13-week dermal range-finding study to be conducted with the to-be-marketed formulation indicates that a 2-year dermal carcinogenicity study is feasible, then a carcinogenicity protocol will be required to be submitted to the IND. Acceptable results from these studies in combination with the nonclinical studies that supported the approval of Ultravate Cream (NDA 19967) and Ultravate Ointment (NDA 19968) are sufficient to support Phase 3 clinical development and an NDA submission for HBP Foam, 0.05%.

Question 5:

In the NDA for HBP Foam, 0.05%, TI intends to include all final study reports and related information for those nonclinical studies conducted with the HBP Foam formulations under IND 107,302. All other nonclinical data and information required for the NDA will be referenced to the nonclinical studies previously reviewed by the Agency for the approvals of NDA's 019-967 and 019-968 (Ultravate Cream and Ointment). Does the Agency agree with this proposal?

Response:

No. Ultravate Cream (NDA 19967) and Ultravate Ointment (NDA 19968) were approved in December, 1990 and the nonclinical study reports are not readily accessible to the reviewer. Submit complete pharmacology and toxicology information (*i.e.*, full study reports for pivotal nonclinical studies) in Module 4 of the NDA planned for the HBP Foam, 0.05% formulation.

The sponsor agreed to submit study reports (b) (4) in Module 4 of the NDA.

Question 6:

Does the Agency agree that the outline provided for the proposed 13-week dermal range-finding study (to define potential doses for a 2 year rat dermal carcinogenicity study) in rats is adequate (including the dosing frequency and proposed doses)?

Response:

The outline provided proposes daily dermal dosing for 13 weeks with two dose levels, the clinical concentration (0.05%) and the maximum feasible concentration (MFC; (b) (4) %).

Given the known sensitivity of rodents to dermal corticosteroids, the MFC is unlikely to be tolerated during extended testing. The Agency recommends conducting the range-finding study with three dose levels achieved by maintaining a uniform dose volume and varying the concentration to determine a maximum tolerated dose of halobetasol propionate in the foam vehicle. It is acceptable to conduct dermal carcinogenicity studies with exposures below those expected clinically.

Meeting Discussion:

The sponsor proposed doses for the 13 week dermal range finding study. The Agency requested that the sponsor submit their study report with a rationale for dose selection to the IND.

Question 7:

It is possible that prolonged treatment (e.g., 13 weeks or longer) of rats with the HBP foam formulation may produce significant adverse effects that could compromise the health of the animals such that the conduct of a carcinogenicity study is not possible. If the results of the 13-week dermal range-finding study in rats present such a scenario, the Sponsor plans to request a waiver from conducting a 2-year dermal carcinogenicity study with HBP. Does the Agency agree that a decision about the feasibility of conducting the 2-year dermal carcinogenicity study will be made following completion of the 13-week dermal range-finding study in rats and evaluation of the results by the Agency and the Sponsor?

Response:

Yes. Submit the study report from the 13-week dermal range finding study conducted with HBP Foam formulation (three concentrations) with either a proposed protocol for the 2-year dermal carcinogenicity study as a Special Protocol Assessment (see Guidance for Industry, May 2002) or, if the data suggest that the conduct of a carcinogenicity study is not feasible, a waiver request. The Agency will review and respond to a Special Protocol Assessment within 45 days.

Question 8:

Based on the lack of significant absorption in the UV-visible region (290 to 700nm) for the HBP Foam formulation under development, the Sponsor is planning to request a waiver from conducting a nonclinical phototoxicity study. Does the Agency agree that a waiver request is appropriate based on the lack of significant absorption?

Response:

Yes, a waiver request from conducting a nonclinical phototoxicity study is appropriate based on the lack of significant absorption in the UV-visible region (290 to 700 nm). You should submit the waiver request with supporting data to the IND for review.

Clinical/Biostatistics/Clinical Pharmacology

Question 9:

In the Phase 3 program, TI intends to conduct two adequate, well-controlled studies of identical design. For these Phase 3 studies, does the Agency agree that the following are appropriate and adequate to support the NDA, the indication, and the labeling of the drug product?

- a. overall protocol design
- b. targeted patient population
- c. the maximum dose of up to (b) (4) grams/week, with a treatment duration of up to two (2) weeks
- d. primary and secondary efficacy endpoints
- e. sample size
- f. statistical analysis plan
- g. safety parameters and monitoring plan

Response:

You propose to conduct Phase 3 trials in 280 subjects (randomized 1:1 to HBP foam and vehicle) 18 years of age and older. Key inclusion criteria include the diagnosis of stable psoriasis with IGA score of at least 3 (moderate), affecting 2-12% of BSA. IGA will be assessed on a 5-point scale where 0=clear, 1=almost clear, 2=mild, 3=moderate and 4=(b) (4). Treatment will be applied twice daily for two weeks.

The primary efficacy endpoint will be the proportion of subjects who achieved “treatment success” (defined as IGA score of 0 or 1 with at least a 2-grade decrease in severity score relative to baseline). Secondary efficacy endpoint will be the proportion of subjects who achieved “treatment success” (score of 0 or 1 with at least a 2-grade decrease in severity) for each of the clinical signs of psoriasis (scaling, erythema, and plaque elevation). The treatment groups will be compared at day 15 using CMH test stratified by analysis center.

We have the following comments regarding your submitted Phase 3 protocol:

1. The overall trial design is acceptable.
2. Clarify your proposed treatment duration of “up to two weeks” in the protocol. The treatment period should be defined as two weeks followed by an efficacy assessment on day 15.
3. The primary endpoint, defined as the proportion of subjects who achieved “treatment success,” (defined as IGA score 0 to 1 with at least a 2-grade decrease in severity score relative to baseline) is acceptable.

The Agency recommends that you revise your IGA scale to a 5-point scale where the grades are non-overlapping and sufficiently defined to appropriately and unambiguously represent each severity grade on the scale. Grade 4 should represent “severe” and not (b) (4) grade as you propose.

Meeting Discussion

The sponsor agreed to refine the IGA scale for the Phase 3 trials.

4. It is acceptable to use the severity of psoriasis clinical signs dichotomized to “treatment success” as secondary endpoints.
5. Note that there appears to be inconsistencies in your Phase 2 trial results. Your definition of success, ODS score of 0 or 1, should also equate to an erythema score of 0 or 1; however, the results of the Phase 2 trial appears to be inconsistent for these two assessments, which might impact estimate of treatment effect to be used for powering Phase 3. In addition, it appears that the two investigators were not consistent in the assessment of these endpoints for a subject. These issues should be discussed in your NDA submission and the investigator inconsistencies should be resolved prior to your Phase 3 trials.
6. You proposed to investigate center-to-center variability for pooled centers. However, as the pooling process could mask center effects, you are encouraged to also investigate center-to-center variability prior to pooling.
7. You plan to impute missing data for the primary endpoint using the Multiple Imputation (MI) approach that uses a logistic regression model containing treatment and plaque elevation as covariates to impute missing data. It is not clear which plaque elevation evaluation (time-point) will be used and what you will do if this value is also missing. The protocol should pre-specify the complete details about MI, including the number of imputations and seeds to ensure the results are not data driven. In addition, the protocol should specify how missing data for the secondary endpoints will be handled.
8. The spectrum and timing of safety evaluation appears adequate. Your proposal to actively assess application site reactions for teleangiectasia, skin atrophy, burning/stinging and folliculitis and report them as mild, moderate or severe is acceptable.

Question 10:

(b) (4)

Does the agency agree with this

approach?

Response:

(b) (4)

Considering halobetasol foam potency, PK profile and HPA axis suppression rates seen in adult PK trial 122-0551-202, the request for pediatric waiver in subjects 0-12 years of age seems reasonable. A waiver request should be included in the Pediatric Study Plan along with the proposed age groups and your rationale based on supporting data.

A final decision regarding a waiver will not be made until after the request is reviewed by the Pediatric Review Committee as mandated by the Food and Drug Administration Amendment Act.

Question 11:

Given the minimal irritation observed with HBP Foam, 0.05% in the completed nonclinical and clinical studies, the extensive safety database of HBP and excipients in the drug product, and the proposed human RIPT study with the HBP Foam in approximately 230 healthy volunteers, the Sponsor is planning to request a waiver from conducting a 21-day cumulative irritation study in humans. Does the Agency agree with this approach?

Response:

Yes. Your product represents a new formulation of HBP. Although nonclinical studies and clinical trials may not show irritation, the irritancy potential of the final to-be-marketed formulation should be established in humans. Cumulative irritation testing can be combined with sensitization testing in a single trial, with the induction phase serving to detect cumulative irritation.

Question 12:

Based on the lack of significant absorption in the UV-visible region (290 to 700nm) for the HBP Foam formulation under development, the Sponsor is planning to request a waiver from conducting phototoxicity and photocontact allergy studies with the HBP Foam in humans. Does the Agency agree that a waiver request is appropriate based on the lack of significant absorption?

Response:

See Question #8.

Based on the report of 270-700 nm Wavelength Scan of Halobetasol Propionate foam 0.05% dated 7/5/2013, it is appropriate to request the waiver from conducting phototoxicity and photoallergenicity testing in humans.

Question 13:

Does the Agency agree that the clinical studies completed and planned with HBP Foam, 0.05%, with data subject to review, are adequate to support an NDA submission for this product?

Response:

Yes. This plan appears reasonable.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. You are encouraged to request a Pre-NDA Meeting at the appropriate time.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting held on or after November 6, 2012. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and

any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

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/s/

STANKA KUKICH

10/02/2013

Signing for Susan Walker, Division Director