

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211527Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 111091

MEETING MINUTES

Galderma Research and Development, LLC
Attention: Stacie M. Winter
Regulatory Submissions Manager
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Winter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for trifarotene cream.

We also refer to the meeting between representatives of your firm and the FDA on April 4, 2018. The purpose of the meeting was to discuss the content and format of your proposed New Drug Application (NDA).

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

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
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: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: April 4, 2018; 10:30am EST
Meeting Location: FDA White Oak Campus, Building 22

Application Number: IND 111091
Product Name: trifarotene cream
Indication: For the treatment of acne vulgaris in patients 9 years of age and older
Sponsor Name: Galderma Research and Development, LLC

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Kendall Marcus, MD, Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Denise Cook, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Peggy Kriger, PhD, Product Quality Microbiologist, OPF
Vidula Kolhatkar, PhD, Biopharmacology Team Leader, OPQ
Yichun Sun, PhD, CMC Lead, ONDP
Chinmay Shukla, PhD, Clinical Pharmacology Team Leader, DCP III
Luke Oh, PhD, Clinical Pharmacology Reviewer, DCP III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Bei Yu, PhD, Office of Scientific Investigations (OSI) Reviewer, OSI
John McMichael, PhD, Device Team Leader, CDRH/ODE
Peter Petrochenko, PhD, Device Reviewer, CDRH/ODE
Dawn Williams, BSN, Regulatory Project Manager, DDDP

SPONSOR ATTENDEES

Michael Graeber, MD, Senior Medical Advisor
Alessandra Alio, MD, Medical Expert
Nathalie Wagner, Clinical Pharmacokinetics Manager
Kevin Chan, Senior Clinical Project Manager
Kenny Frazier, Head of Global Clinical Development

Palma Seljan, MD, Clinical Safety Physician
Faiz Ahmad, Head of US Biostatistics
Jean-Pierre Etchegaray, Pharmaceutical Development Expert
Bobbi Drais, Head of US Regulatory Affairs Development
Stacie Winter, Regulatory Submission Manager
Bernard Ruty, Toxicology Expert

1.0 BACKGROUND

The purpose of this meeting is to discuss the content and format of the proposed NDA for trifarotene for the treatment of acne vulgaris in patients 9 years of age and older, and the treatment of lamellar ichthyosis.

We have had the following meetings with you:

- February 27, 2018 Guidance
- February 18, 2015 Guidance
- June 11, 2014 Guidance
- April 16, 2014 End of Phase 2
- April 4, 2012 Guidance

We have sent the following correspondences:

- June 13, 2017 Agreed Pediatric Study Plan
- December 29, 2015 Advice
- September 11, 2015 Advice/Information Request
- November 13, 2014 Special Protocol- Agreement (2)
- October 27, 2014 Agreed Pediatric Study Plan
- September 4, 2014 Special Protocol- Request Denied (2)
- August 28, 2014 Advice
- July 31, 2014 Pediatric Study Plan- Written Response
- September 26, 2013 Advice
- May 24, 2013 Advice
- December 26, 2012 Advice/Information Request
- August 31, 2012 Advice/Information Request
- August 22, 2012 Advice/Information Request
- January 12, 2012 Special Protocol- Agreement (carcinogenicity)
- November 7, 2011 IRB Waiver Granted
- October 17, 2011 Advice/Information Request
- July 27, 2011 Advice
- June 8, 2011 Advice

2.0 DISCUSSION

2.1. Regulatory

Question 1:

Does the Agency agree that the development program supports the proposed NDA submission?

FDA Response to Question 1:

Your NDA will consist of the following:

- Four dermal safety Phase 1 studies, to assess the 21-day cumulative irritation (Studies 40055E and 40209), sensitization Study 40190), phototoxicity (Study 40208) and photosensitization (Study 40189) potential of trifarotene cream in healthy volunteers,
- One Phase 1 pharmacokinetic study: to assess the linearity of trifarotene PK profile over potential therapeutic doses in healthy volunteers (Study 40128)
- One QT/QTc study to evaluate the effect of trifarotene on ventricular repolarization under supra-therapeutic conditions (Study 40196)
- One Drug-Drug Interaction Phase 1 study to assess the ability of trifarotene to interfere with systemic levels of hormonal contraception in female healthy volunteers (Study 103918)
- One Phase 2b, dose range study to assess the efficacy and safety of different concentrations of trifarotene cream, tazarotene 0.1% gel compared with vehicle cream in subjects with moderate and severe acne vulgaris (Study 18223)
- Two Maximal usage PK studies (MUSt) to characterize the PK profile of trifarotene under maximal use conditions in 9-17 years old pediatric and adult subjects with acne (Studies 18237 and 40182).
- Two Phase 3 independent well-controlled, pivotal studies (Studies 18251 and 18252) to assess the efficacy and safety of trifarotene 50 μ g/g cream compared with vehicle cream (12-week study duration), and
- One Long-Term (52-week study duration) open label safety study in patients 9 years of age and older with moderate facial and truncal acne vulgaris (Study 18250)

The Agency does agree that these studies are sufficient to support the filing of an NDA of trifarotene 50 μ g/g cream for the proposed indication of topical treatment of acne vulgaris in patients 9 years of age and older.

Question 2:

Does the Agency agree with the proposed format and content of the submission?

FDA Response to Question 2:

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

- A cover letter should be provided as a separate document from the Reviewers Guide
- Providing Table of Contents in 2.1, 3.1, 4.1 and 5.1, is not necessary in the eCTD structure. Please provide a reviewer's aid instead.

- 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.
- Do not provide placeholders for sections that will not be submitted (e.g. 4.2.1.4 Pharmacodynamic Drug Interactions, N/A, 4.2.2.6, 5.3.1.1.etc.,).
- Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Case Report Forms 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". Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>
- Regarding use of the m5-3-7 heading element, FDA does not use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml.
- Please make sure you provide Table of content, bookmarks and hyperlinks for documents more than five pages, long. The Briefing Package did not have a Table of Contents and some sections were not hyperlinked.

Question 3:

The Sponsor proposed to provide the Agency with all references cited in Module 2 of the proposed NDA. All other references cited in Module 1, 3, 4 and 5 as well as references cited in clinical study reports will be provided upon request. Does the Agency agree?

FDA Response to Question 3:

Yes, we agree.

Question 4:

Does the Agency agree that, as no safety signals were detected in the Phase 2 studies, the Sponsor considers that the post-marketing safety surveillance of Trifarotene can be accomplished according to 21 CFR 314.80 in combination with the patient package insert, and does not believe a formal REMS program will be required?

FDA Response to Question 4:

From the information that you have provided in your briefing package, it would appear that a REMS program will not be required for your drug product. However, the final determination will be made after the review of the NDA is complete.

2.2 Chemistry, Manufacturing and Controls (CMC)

There are no CMC questions in your briefing package. However, we have the following comments on your NDA submission:

Drug Product:

We recommend you add a test for globule size of the cream, dose accuracy per actuation, and actuation force to your drug product specification. Provide results of in-use stability study conducted on stability samples of representative time points of the long-term stability study. Additionally, provide results of extractable and leachable studies on the container closure systems of the drug product.

Meeting Discussion:

The sponsor proposed only to conduct the test of globule size on 3 future commercial batches of their drug product, and not to include the test in the drug product specification. The Agency replied that the test should be included in the drug product specification and be conducted at release and during stability studies.

Quality Microbiology:

The specified microbiological tests, methods and acceptance criteria provided in the IND amendment submitted June 28, 2017 appear to be acceptable; however, note that the acceptability of the drug product release and stability specifications will be determined at the time of potential NDA submission.

Regarding the (b) (6) it is acknowledged that the drug product release and stability specification includes (b) (6) testing. (b) (6)

See ICH Q1a Stability Testing of New Drug Substances and Products.

In preparation for NDA submission, please consider that 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 review of FDA's perspective on BCC, see *PDA J Pharm Sci Tech* 2011; 65(5): 535-43.

To control for the presence of BCC in your product, FDA recommends the following:

1. Identify potential sources for introduction of BCC during the manufacturing process and 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. Implement test methods and acceptance criteria to demonstrate the drug product is free of BCC. At the time of NDA submission, your test methods 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. At the time of NDA submission, a description of the preconditioning step (time, temperature, and solution(s) used), the total number of inoculated organisms, and the detailed test method including growth medium and incubation conditions should be provided. It is essential that sufficient preconditioning of the organisms occurs during these method validation studies to ensure 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.

Biopharmaceutics:

- We recommend that you develop an *in vitro* release test (IVRT) methodology and propose *in vitro* release acceptance criteria (range) for your drug product to be used systemically at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format (e.g. MS Excel) as described below:

Chamber ID: # (identify each cell assignment)

Sample volume removed: mL

Diffusion cell area: cm²

Time (min, hr, etc.)	Sq. rt. Time	Concentration in Cell (µg/mL)	Amount in Cell (µg)	Cumulative Amount in Cell (µg)	Cumulative Diffusion (µg/cm ²)
T1					
T2					
T3					
T4					

T5					
Tn					

- Also, along with the proposed *in vitro* release specification, include the IVRT method development and validation report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:
 - a. Diffusion apparatus
 - b. Receptor medium selection
 - c. Membrane selection
 - d. Sampling time points
 - e. Temperature
- The IVRT method validation report should contain (but is not limited to) the following validation components:
 - a. Linearity and Range
 - b. Accuracy/Precision and Reproducibility
 - c. Mass Balance
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability
- The IVRT method's sensitivity, specificity, selectivity and robustness should to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.

Meeting Discussion:

The sponsor proposed only to conduct in vitro release test on 3 future commercial batches of drug product, and not to include the test in the drug product specification. The Agency will evaluate the results and the decision will be based on the totality of the data provided.

The Sponsor asked if they needed to provide a dose accuracy per actuation specification given that the device is not a metered dose pump. The Agency stated if the Sponsor provides a justification that a dose accuracy specification is not clinically relevant based on the risk of possible variable delivery by the pump then this may be acceptable.

The Sponsor stated they will evaluate and implement a method for measuring actuation force for future commercial batches. The Sponsor stated (b) (4) The Agency stated that this is acceptable.

It is unclear what device constituent parts you intend to pursue as the commercial to-be-marketed version of your product. The comments below pertain to the (b) (4) pump device

referenced in the briefing package and also provide general recommendations for device constituent parts of combination products.

It is recommended that you refer to the eCTD Technical Conformance Guide published in September 2016

(<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf>) when determining the location of the following information within your submission.

For more information regarding cGMP requirements for combination products please refer to the FDA guidance titled guidance for industry and FDA staff: *Current Good Manufacturing Practice Requirements for Combination Products* issued in January 2017 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>).

Provide the following information to support the device constituent parts of the combination product in a future marketing application:

- 1) A complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device. This should also include engineering drawings and detailed descriptions of the individual device constituent components.
- 2) Detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, in which you explain the mechanical drug delivery mechanisms of your device constituent for it to achieve its intended use.
- 3) A complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product. Be sure to identify the essential performance requirements of your device. The essential performance requirements of any device constituent parts are the design outputs necessary for your device constituent to safely and effectively achieve the product's intended use. The essential performance requirements of the device should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, and design of the constituent parts of the combination product. Your design requirements and essential performance requirements should consider the desired level of reliability of the product and level of risk associated with failure to meet the essential performance requirements.

For (b) (4) pumps, we expect the essential performance requirements to include, at a minimum, the following:

- Pump Delivery (dose accuracy per actuation)
- Actuation Force

- 4) Design verification documentation. Verification testing documentation may include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design requirements of the device. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should conduct testing to verify the essential performance requirements of the combination product with the to-be-marketed version of the device constituent and the intended product; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended product (i.e. fluid characteristics, viscosity, etc.). Valid justifications for any test results not being able to pass its acceptance criteria should be provided, if applicable. Furthermore, you should utilize enough device constituent test samples that will be statistically relevant for your performance testing.
- 5) Design validation documentation. Design validation documentation should be performed to ensure that the device constituent parts of the combination product meet the intended use of the combination product. Design validation documentation may be in the form of clinical studies with the to-be-marketed presentation of the device, bridging studies that successfully validate the to-be-marketed presentation of the device constituent through clinical and/or bench top studies of the essential performance requirements of the device constituent in the context of the intended use of the combination product, literature review regarding the use of the to-be-marketed device constituent presentation in the context of the intended use of the combination product, human factors studies, and/or simulated actual-use studies. It is highly recommended that you conduct clinical studies with the to-be-marketed presentation of the combination product and capture any device constituent failures/malfunctions as part of the clinical study protocol to successfully validate the device constituent parts of the combination product.
- 6) Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.).
- 7) Biocompatibility evaluation. You should provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA guidance titled *Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process* – Guidance for Industry and Food and Drug Administration Staff issued in June 2016

(<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf>) for more details.

- 8) Stability and shelf-life testing. You should provide documentation that ensures the final finished combination product maintains its essential performance requirements up to the labeled date of expiry.
- 9) Shipping studies. You should provide documentation that ensures that the final finished combination product maintains its essential performance requirements after actual or simulated shipping.
- 10) Lot release specifications. Provide the lot release specifications associated with the device constituents of the combination product, including all essential performance requirements.
- 11) It is recommended that a traceability matrix is provided to ensure each design requirement has been adequately verified and validated. The following is an example traceability matrix for the essential performance requirements of the device constituent as a summary of the testing completed to support the device constituents of the combination product:

Essential Performance Requirement	Specification	Verification	Validation	Shelf Life / Stability (Y/N)	Shipping / Transportation (Y/N)	Lot Release Testing (Y/N)
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- 12) As the owner of the combination product it is expected that you maintain the requirements for your product within your marketing application. If you intend to refer to documentation (e.g. verification testing) held within another submission and/or master file be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.

Meeting Discussion:

The sponsor asked why this pump is considered a device. The Agency noted that this container closure system meets the regulatory definition of a device and therefore would be considered a device constituent of the combination product. The sponsor stated that they do not consider the container closure system a device and noted that it does not deliver a metered dose.

The Agency clarified that we consider the (b) (6) pump has functionality and delivers the drug product and it would be considered device and combination product. The Agency stated that this is consistent with devices having very similar functionalities.

The sponsor asked about further information regarding request for designation (RFD) regarding the combination product designation. The Agency referred the Sponsor to the RFD process through the Office of Combination Products, which is detailed online. The Agency also commented that if they would like to dispute the classification of the container closure as a device they can submit a request for classification to the Office of Combination Products and receive feedback from the respective Centers jurisdictional officers.

The Sponsor asked a question regarding the location of device related information and the use of a Master File. The Agency reiterated the written comments provided to the Sponsor with regards to the information required to be included in the NDA as the combination product owner as well as what information can be referenced to under a Master File.

2.2. Nonclinical

To enable us to conduct the statistical review of the dermal mouse carcinogenicity study and the oral rat carcinogenicity study, submit the SAS tumor data sets (tumor.xpt) for each carcinogenicity study to your NDA. Follow the standard format, indicated below, for preparing the data.

Table 1: FDA Biostatistics Data Format Sheet

Tumor Dataset For Statistical Analysis^{1,2} (tumor.xpt)				
Variable	Label	Type	Codes	Comments
STUDYNUM	Study number	char		3
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	4

DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	⁴
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

¹ Each animal in the study should have at least one record even if it does not have a tumor.

² Additional variables, as appropriate, can be added to the bottom of this dataset.

³ ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

⁴ A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

⁵ Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

Question 5:

Does the Agency agree with the proposal to submit SEND data only for pivotal non-clinical studies performed with CD5789 cream (DP) and with CD5789 drug substance?

FDA Response to Question 5:

Yes, we agree.

2.3. Clinical Pharmacology/Clinical

Question 6:

Does the Agency agree that the clinical pharmacokinetic assessment for CD5789 50 µg/g cream is adequate to support an indication in subject with acne vulgaris 9 years of age and older?

FDA Response to Question 6:

We acknowledge that you completed two maximal use pharmacokinetic (PK) studies; one in pediatric subjects between 10 and 17 years of age and the other one in adult subjects. In addition to this, you obtained additional PK assessments in a subgroup of pediatric population (10 years of age and older) in the Phase 3 long-term safety study. Since you have not assessed PK in any 9 year old subjects, we note that you conducted a physiologically based PK modeling to simulate systemic exposure in pediatric population.

The available data appears to support filing of your NDA; however, the adequacy of data will be a review issue and will be determined at the time of your NDA submission following a detailed review of your study reports and associated bioanalytical method validation and bioanalysis reports.

We recommend you to submit PK data in SAS transport format in your NDA and you should also clearly provide data to support long-term storage stability of the PK samples and incurred sample reanalysis reports.

Meeting Discussion:

The Agency recommended the sponsor to adequately address the drug-drug interaction potential in their NDA.

Question 7:

Does the Agency agree that, in accordance with 21 CFR 314.50 (f), the Sponsor proposes to provide in the NDA only the individual subject's CRFs for all subject who (i) died during the studies, (ii) experienced SAE during the studies, or (iii) discontinued from the studies due to an AE. They will be included in section 16.3.

FDA Response to Question 7:

Yes, the Agency does agree. However, we reserve the right to request any additional CRFs as necessary during the conduct of the review.

2.4. Clinical/Biostatistics

Question 8:

Does the Agency agree that the ISS/ISE will be summarized in the respective M2 sections and only supportive data will be provided in M5?

FDA Response to Question 8:

This proposal is reasonable.

Question 9:

Does the Agency agree with the proposed dataset submission plan?

FDA Response to Question 9:

Your proposal to submit datasets for Studies 18250, 18251, and 18252 using SDTM 3.2 and ADaM 1.0 formats is acceptable. Submit the datasets in SAS transport format (.xpt). Ensure that the analysis datasets include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study reports.

As we noted in our Written Responses Letter dated 2/27/2018, your ISS pooling strategy appears reasonable. However, it is not clear from your briefing package whether you intend to submit the datasets for your Phase 1 and Phase 2 studies only as components of "Pool 2" and "Pool 3" or whether you will also submit datasets for each study separately. At a minimum, submit the complete datasets for the Phase 2 (acne) and PK studies individually.

Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variables used) and descriptions of the codes used in factor variables.

Because the protocols specified handling missing data using multiple imputation, clarify how you intend to submit the datasets. We recommend submitting the observed-case datasets along with complete statistical programs for conducting the multiple imputation through all stages of the analyses, so that the full analyses can be conducted from the observed-case datasets. Also include any additional statistical programs for non-standard or model-based analyses.

Meeting Discussion:

The sponsor confirmed they will submit the data sets for the acne phase 2 dose ranging study and the 2 maximal use PK studies separately.

The sponsor inquired whether the code fragments included in the SAP for the multiple imputation analyses would be sufficient. The Agency clarified that full executable programs are requested.

Include the study protocol, all protocol amendments, the statistical analysis plan, and an annotated copy of the case report form as well as the other required elements for the clinical trials.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 1, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

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 Pedsdrugs@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>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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 items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications (available at the following links)

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf>

<https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>

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 ORA investigators who conduct those inspections. 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.

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

/s/

KENDALL A MARCUS
04/09/2018



IND 111091

MEETING MINUTES

Galderma Research and Development, LLC
Attention: Elaine Clark
Sr. Director, Regulatory Submissions
14501 North Freeway
Forth Worth, TX 76177

Dear Ms. Clark:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (trifarotene) cream.

We also refer to the meeting between representatives of your firm and the FDA on April 16, 2014. The purpose of the meeting was to discuss the development program for (trifarotene) cream.

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

If you have any questions, call Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Tatiana Oussova, MD, MPH
Deputy Director for Safety
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: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: April 16, 2014; 10:30 a.m. ET
Meeting Location: FDA WO Bldg. 22/room 1313

Application Number: IND 111091
Product Name: (trifarotene) cream
Proposed Indication: treatment of acne vulgaris
Sponsor Name: Galderma Research and Development, LLC

Meeting Chair: Tatiana Oussova, MD
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Denise Cook, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
An-Chi Lu, MS, PharmD, Clinical Pharmacology Reviewer, DCP3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Acting Deputy Director, ODE III
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Belainesh Robnett, MS, Regulatory Health Project Manager, DDDP
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Matthew Leoni, MD, Development Project Leader
Vasant Manna, MD, Medical Advisor
Michel Poncet, Senior Statistical Expert
Min Yao, Senior Statistics Manager
Nathalie Wagner, Clinical Pharmacokinetics Manager
Sandrine Antoniotti, Pharmaceutical Development Coordinator

Guy Bouvier, Pre-Clinical Development Manager
Orla Duffy-Roger, Regulatory Affairs Project Manager
Elaine Clark, Senior Director, US Regulatory Submissions

Purpose of the Meeting:

To discuss the development program for (trifarotene) cream

Regulatory Correspondence History

We have had the following meeting with you:

- 04/04/2012: Type C (guidance) meeting

We have sent the following correspondences:

- 09/26/2013: Adv/IR letter
- 05/24/2013: Adv/IR letter
- 12/26/2012: Adv/IR letter
- 08/31/2012: Adv/IR letter
- 08/22/2012: Adv/IR letter
- 01/12/2012: Exec CAC meeting minutes and recommendations for Nonclinical SPA
- 11/07/2011: IRB Waiver Granted letter for foreign study site
- 10/17/2011: Adv/IR letter
- 07/27/2011: Adv/IR letter
- 06/08/2011: Adv/IR letter

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Agency agree to [REDACTED] the proposed control strategy for these starting materials?

(b) (6)

Response:

Yes, we agree provided that the following information for the starting materials will be referenced to a DMF with a letter of authorization or provided in the proposed NDA:

1. Name and address of suppliers of starting materials
2. Brief description of synthetic routes with flow charts.
3. Reagents and solvents
4. In-coming specifications and validated analytical methods
5. Batch analysis
6. Impurity profile, and impurity carry-over potential
7. Vendor qualification program for starting material suppliers
8. Commitment to submit a prior approval supplement for significant changes made to the starting materials (e.g., new supplier, changes in process, etc.).

Meeting Discussion:

The sponsor indicated they would submit items 1-8 in a DMF prior to NDA submission. Items 1-6 will be submitted to the IND as a CMC amendment.

Question 2:

Does the Agency agree that the dosage form of the drug product is a cream?

Response:

We acknowledge your statements that the formulation is an emulsion, and that the product is a non-pourable semi-solid. However, examination of a representative sample is necessary before we can agree with your statements and make a preliminary recommendation regarding the dosage form. The final decision on the dosage form is made in the NDA review after we examine a sample which is representative of the commercial batches.

You can submit a sample to the IND for a preliminary evaluation of dosage form. You will need to submit samples again to the NDA during the NDA review.

Question 3:

Does the Agency agree on the excipient functionalities?

Response:

No, we disagree. (b) (6)

You should assign the function of an excipient based on physicochemical properties of the excipient.

Additional Comments

1. Clarify whether you have applied for a USAN name for the proposed drug substance.
2. Clarify whether you plan to use the Phase 3 manufacturing facility for the commercial scale manufacture. If they are different facilities, a bridging study may be needed. SUPAC-SS contains examples for bridging studies.

Meeting Discussion:

The sponsor clarified they would be starting the process for applying for a USAN name. The sponsor also stated they will use the same manufacturing facility for both Phase 3 and commercial manufacturing of drug product.

Pharmacology/Toxicology

Question 4:

The Sponsor considers that the combination of the extensive safety data base already generated for trifarotene, the proposed additional studies and the knowledge of retinoids in general adequately support continued clinical development and the filing of a marketing application for this new formulation intended for the topical treatment of acne vulgaris in subjects (b) (4)

(b) (4)

Does the Agency agree with this proposal?

Response:

It is noted that some of the submitted nonclinical studies have not induced apparent dose-limiting toxicity at any dose that was evaluated. As noted in the ICH M3(R2) document, "*Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*", doses providing a 50-fold margin of exposure (i.e., the ratio of the $AUC_{\text{nonclinical}}$ for the high-dose animals to the AUC_{clinical} for patients under conditions of maximum exposure equals at least 50) generally are considered acceptable as the maximum dose for acute and repeated-dose toxicity studies in any species. On this basis, it appears likely that the pivotal toxicology studies that involved oral dosing may be considered to be acceptable (contingent upon definitive Agency review of the relevant Clinical Pharmacology data, and that analysis of those data confirms that the systemic exposures achieved in those nonclinical studies constituted an acceptably large multiple of the maximum exposure that may be observed in patients). To support Phase 3 clinical trials, dose-limiting toxicity generally should be identified in at least one species when using the 50-fold margin of exposure as the limit dose. None of the repeated-dose toxicity studies currently submitted appear to involve clearly dose-limiting toxicity. However, according to the summary in the briefing document, dose-limiting toxicity was observed in chronic toxicity studies involving oral dosing of both rats and dogs. It is noted that reports of the following studies, which were discussed in the briefing document, have not been submitted to the IND:

1. CD5789: 26-week oral (gavage) toxicity study in the Wistar rat followed by a 6-week recovery period, study No. RDS.03.SRE12863.
2. CD5789: 39 week oral (gavage) toxicity study in the Beagle dog followed by a 8-week recovery period, study No. RDS.03.SRE.12864.
3. CD5789 cream: 13-week topical (dermal application) administration toxicity study in the Gottingen minipig, study No. RDS.03.SPR.12852.
4. CD5789 cream: 9 month topical (dermal application) administration toxicity study in the Gottingen minipig followed by a 4 week treatment free period - CREAM B, study No. RDS.03.SPR.12875.

We request that reports of pivotal nonclinical studies be submitted when available; draft reports should suffice in support of an IND. Presumably, review of those studies will confirm that dose-limiting toxicity was observed in oral repeated-dose toxicity studies.

In regard to the studies "CD5789: Fertility toxicity study by the oral route (gavage) in the rat (Segment I)", study No. RDS.03.SRE.12759, and "CD5789: Pre and Postnatal development study by the oral route (gavage) in the Wistar rat (Segment III)", study No. RDS.03.SRE.12758, it is noted that no evidence of toxicity or stress was observed at any dose evaluated in those studies. As noted in the ICH S5A guidance, "*Detection of Toxicity to Reproduction for Medicinal Products*", some minimal toxicity is generally expected to be induced in the high-dose "dams"

(animals) in reproductive toxicity studies. To help ensure that adequate data are available to support filing of a NDA, it is recommended that data from study No. RDS.03.SRE.12759 and study No. RDS.03.SRE.12758 be supplemented with data from similar studies that involve higher dosages that are consistent with the ICH guidance.

It is noted that qualification of the primary metabolites is ongoing (as mentioned in your question 8). The adequacy of the available data to achieve this purpose will be considered upon submission of your completed analysis.

The available nonclinical data appear adequate to support the proposed Phase 3 clinical development.

Meeting Discussion:

The sponsor stated that they intend to submit to their IND an analysis of data from a 26 week oral rat study along with their rationale for why they feel this will adequately address the deficiencies raised by the FDA regarding the reproductive toxicology data.

Clinical/Clinical Pharmacology/Biostatistics

Question 5:

Does the Agency concur with the target population (b) (6) with acne vulgaris on the face and trunk?

Response:

The Agency recommends that the target population consists of subjects 9 years old and older.

Question 6:

The Sponsor seeks concurrence on the following aspects of the pivotal Phase 3 study design and statistical points:

- a) Information on the secondary efficacy objective of truncal acne could be included as descriptive data in the clinical section of the labeling
- b) Statistical Approach to the Analyses of the Primary and Secondary Efficacy Endpoints for both Pivotal Studies
- c) Handling of Japanese and Non-Japanese Population

Does the Agency agree with this approach?

Response:

- a) Evaluation of the efficacy of your drug product in a subset of acne vulgaris dependent on location such as you suggest in this instance, “truncal acne” must be evaluated in the same manner as the primary efficacy endpoint. Thus, for labeling purposes in the clinical section of the labeling, success of your product to treat truncal acne must be based on the same 3 efficacy endpoints:
 - i. An IGA of clear or almost clear with a 2 grade improvement
 - ii. Change in inflammatory lesion counts at Week 12

iii. Change in non-inflammatory lesion counts at Week 12

In addition, propose minimal lesion count necessary for the evaluation of truncal acne under inclusion criteria.

b) Statistical Approach

- (1) Your protocols should include additional details regarding the proposed randomization. Protocol RD.06.SPR.18252 states only that randomization will be stratified by center. Protocol RD.06.SPR.18251 states only that subjects will be assigned treatments using a pre-defined randomization sequence. You should provide sufficient details about any stratification plans and information regarding any planned IVRS/IWRS systems or other methods of randomization. Including stratification by center (or assigning complete blocks to centers) is recommended.
- (2) You have not clarified whether all subjects (with the exception of Japanese subjects in RD.06.SPR.18252) will be enrolled in the U.S. or whether subjects from other countries will be enrolled. If subjects from other countries will be enrolled, you should specify the expected proportion of subjects who will be enrolled outside the U.S.
- (3) Your protocol should specify the expected number of centers. We recommend designing the program so that a minimum of 8-10 subjects are enrolled at each center so that center effects and any treatment-by-center interactions can be interpreted. In case some centers cannot meet the minimum enrollment, we recommend including a proposal in the protocol for combining small centers into analysis centers.
- (4) Your primary endpoints are Clear or Almost Clear on the IGA (corresponding to at least 2 grades improvement), change in inflammatory lesions, and change in non-inflammatory lesions at Week 12. We recommend including percent reduction in inflammatory and non-inflammatory lesions as supportive endpoints.
- (5) Although we recognize that your definition of PGA (truncal) response: ‘at least a 2-grade improvement in PGA’ is functionally equivalent to achieving ‘clear or almost clear (with at least 2 grades improvement) on the PGA’ due to requirement that all subjects have a score of 3 at baseline, we recommend using the latter terminology to be consistent with the primary endpoint IGA success definition, and to reduce ambiguity in how to handle any subjects who might be enrolled in violation of this inclusion criterion.
- (6) You have provided only limited information on your proposed handling of missing data (multiple imputation (primary) and LOCF (sensitivity)). You should provide additional details about your multiple imputation model in the protocol, such as the number of imputations, the imputation and analysis models you will use, etc. You should also propose at least one additional sensitivity analysis that uses different assumptions to ensure that the conclusions are not driven by the method of handling missing data.
- (7) You have justified your sample size calculations using only estimates for the IGA endpoint, noting that “the success rate is known to drive the sample size,” Although in many cases the success rate does require a larger sample size than the change in lesion count endpoints, we recommend including in your protocol justification based on estimates of the lesion count changes from your Phase 2 studies, rather than relying on a general assumption.
- (8) Your primary analysis population is the ITT population, defined as all randomized subjects. In addition to the primary ITT population, we recommend defining a per protocol population in the protocol as a supportive analysis population.

c) Handling of Japanese and non-Japanese populations.

It is not clear in Protocol RD.06.SPR.18252 whether the primary analysis will be based on the all-subjects or non-Japanese-subjects populations. We recommend using the all-subjects population as the primary analysis population. Note that if statistical significance for all primary endpoints is not achieved for the primary population, then you cannot rely on results from the non-Japanese population unless you have pre-specified an appropriate multiplicity adjustment or approach.

In addition, your Phase 3 pivotal placebo-controlled trials should include laboratory monitoring of subjects at baseline and end of treatment at a minimum.

Meeting Discussion:

The sponsor agreed to include 9 year old subjects, agreed to minimum baseline lesion counts for truncal acne, and agreed to a lesion count assessment in addition to a PGA assessment for truncal acne. A claim on the truncal region is a secondary endpoint. The FDA stated that labeling for the secondary endpoint in the clinical studies section would be data driven.

The sponsor clarified that only the second trial will enroll Japanese subjects and they do not intend to make an efficacy claim for the Japanese population. The sponsor indicated they will enroll subjects from the European Union to make this a global trial.

The sponsor will provide details about the Multiple Imputation procedure and will propose an additional approach as a sensitivity analysis for handling missing data. The sponsor clarified that the primary analysis would be conducted on the all-subjects population. The sponsor agreed to include laboratory monitoring of subjects at baseline and end of treatment.

Question 7:

The clinical pharmacokinetics of trifarotene (CD5789) was extensively investigated in five clinical studies including two maximal use PK studies on subjects with Acne vulgaris and three studies on healthy volunteers. Overall, 229 subjects provided evaluable PK profiles. Of these, clinical pharmacokinetic of CD5789 was evaluated under maximal use conditions in the targeted population using the to-be-marketed formulation in 35 pediatric subjects (10 to 17 years old) and in 39 adult subjects.

The Sponsor seeks agreement that no further pharmacokinetic studies are required to support the safety of the to-be marketed formulation applied once daily in subjects with acne vulgaris.

Response:

Based on the summary information submitted in this meeting package, the completed pharmacokinetic trials appear adequate to characterize the PK of CD5789 50 µg/g cream in subjects with acne vulgaris 10 years of age and older.

Pharmacokinetic data are not available for subjects 9 years of age and should be provided to support an indication in subjects 9 years of age and older.

Meeting Discussion:

The sponsor plans to assess pharmacokinetics in subjects 9-11 years of age in their Phase 3 trial(s).

Question 8:

Does the agency agree with the adequacy of the assessment of human circulating metabolites?

Response:

Based on the information submitted in this meeting package, your plans appear reasonable. The assessment should be done with validated bioanalytical methods.

Question 9:

In addition to in vitro and in vivo assessment of cardiac safety, the Sponsor conducted a thorough QT (TQT) study in accordance with ICH E14 guidance to investigate effect of trifarotene (CD5789) on ventricular repolarization. This study was conducted under supratherapeutic exposure and demonstrated the absence of effect on ventricular repolarization.

Does the agency agree with adequacy of this study to support the New Drug Application (NDA) submission?

Response:

The final study report with the raw data of your TQT study will need to be submitted to the Agency for review before a determination can be made on its adequacy. Until that time, subjects in your Phase 3 trials will need periodic ECG monitoring.

Question 10:

Considering the results of three in vitro metabolism and drug interaction studies carried out with trifarotene and the very low plasma concentrations found after topical application of the to-be-marketed formulation in humans, it is concluded that chronic topical application of trifarotene cream has no potential to cause clinically significant drug-drug interactions. Therefore, the Sponsor deems that it is unnecessary to perform further in vivo drug-drug interaction studies.

Does the Agency concur with this proposal?

Response:

Based on the information submitted in this meeting package, your proposal regarding potential drug interaction with the parent compound appears reasonable. However, we note that you have not conducted in vitro studies to assess the potential for drug-drug interaction for the metabolites. Provide scientific rationale for not conducting drug interaction studies for the metabolites.

Question 11:

Based on the results of the Phase 2 study conducted under IND 111091 and the proposed Phase 3 studies and Long Term Safety, the Sponsor considers that the overall proposed clinical development plan will be adequate to support registration of trifarotene cream for topical treatment of '*acne vulgaris*'. A pre-specified inclusion criterion will be the presence of acne on

the face and trunk. Therefore labeling will specify that trifarotene will be applied as a thin layer to the affected areas of the face and/or trunk.

Does the Agency concur with this proposal?

Response:

The Dosage and Administration section of the labeling for trifarotene cream will be data driven (see response to Question 6).

Question 12:

The New Drug Application (NDA) will be submitted pursuant to 505(b)(1) of the Federal Food, Drug & Cosmetic Act and will contain full reports of investigations of safety and effectiveness of trifarotene.

Does the Agency concur with this approach and with the pediatric plan as discussed with the pediatric Committee in Europe (PDCO) and presented in Appendix 9 of this End of Phase 2 Briefing Package?

Response:

You should re-submit your proposed initial Pediatric Study Plan (iPSP) as a separate submission within 60 days following this End-of-Phase 2 meeting. The FDA will review and comment on your iPSP at that time.

See additional comments and guidance below under PREA Requirements.

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. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue

early in development.

5. You are encouraged to request a Pre-NDA Meeting at the appropriate time.
6. 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. 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>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](#).

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

/s/

TATIANA OUSSOVA
04/30/2014