

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206255Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 206255

SUPPL # n/a

HFD # 540

Trade Name SOOLANTRA®

Generic Name ivermectin

Applicant Name Galderma Research and Development

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(2)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 050742 Stromectol (ivermectin)

NDA# 202736 Sklice (ivermectin)

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete

remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1: RD.06.SPR.18170--A phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1% cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel.

Investigation #2: RD.06.SPR.18171--A phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1% cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel.

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1: RD.06.SPR.18170--A phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1% cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel.

Investigation #2: RD.06.SPR.18171--A phase 3 randomized, double-blind, 12-week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1% cream versus vehicle cream in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	!
	!

IND # 076064 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # 076064 YES ☒ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

Investigation #2 !
!
YES ☐ ! NO ☐
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

=====

Name of person completing form: J. Paul Phillips
Title: Regulatory Health Project Manager
Date: 12/19/2014

Name of Office/Division Director signing form: Jill Lindstrom, MD
Title: Acting Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

J P PHILLIPS
12/19/2014

JILL A LINDSTROM
12/19/2014

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206255	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Soolantra Established/Proper Name: ivermectin Dosage Form: cream, 1%		Applicant: Galderma Agent for Applicant (if applicable): N/A
RPM: J. Paul Phillips		Division: Dermatology and Dental Products
NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) BLA Application Type: ☐ 351(k) ☐ 351(a) Efficacy Supplement: ☐ 351(k) ☐ 351(a)		<u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u> - Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. - Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) ☒ No changes ☐ New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: 12/19/2014; 8/6/2014 <i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i>
❖ Actions		
- Proposed action - User Fee Goal Date is <u>01/20/2015</u>		☒ AP ☐ TA ☐ CR
Previous actions <i>(specify type and date for each action taken)</i>		☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		☒ N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 3
(confirm chemical classification at time of approval)

- | | |
|---|---|
| ☐ Fast Track | ☐ Rx-to-OTC full switch |
| ☐ Rolling Review | ☐ Rx-to-OTC partial switch |
| ☐ Orphan drug designation | ☐ Direct-to-OTC |
| ☐ Breakthrough Therapy designation | |

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

- ☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

- REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☒ REMS not required

Comments:

❖ BLAs only: Ensure RMS-BLA Product Information Sheet for TBP and RMS-BLA Facility Information Sheet for TBP have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	☐ Yes ☐ No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes NP exclusivity*- 3 yr. expires 2/7/2015 *Different indication
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☒ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval: 12/19/2014
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
• Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (10/8/2014)
• Original applicant-proposed labeling	☒ Included (12/20/2013)
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	☐ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>)	☒ Included (10/1/2014)
• Original applicant-proposed labeling	☒ Included (7/22/2014)
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
• Most-recent draft labeling	☒ Included (10/1/2014)
❖ Proprietary Name	
• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)	04/10/2014
• Review(s) (<i>indicate date(s)</i>)	03/20/2014
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: ☒ 02/25/2014 DMEPA: ☒ 07/07/2014 DMPP/PLT: ☒ 08/13/2014 OPDP: ☒ 08/12/2014 SEALD: ☒ N/A CSS: ☒ N/A Other: ☒ N/A
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	☒ 02/28/2014 RPM Filing review
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	☒ 08/27/2014
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	☒ Included (12/19/2014)

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm		
• Applicant is on the AIP		☐ Yes ☒ No
• This application is on the AIP		☐ Yes ☒ No
○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)		
○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)		☐ Not an AP action
❖ Pediatrics (<i>approvals only</i>)		
• Date reviewed by PeRC 07/09/2014 If PeRC review not necessary, explain: <u>N/A</u>		
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)		N=20
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)		N/A
❖ Minutes of Meetings		
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)		☒ N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)		☒ 06/12/2013
• EOP2 meeting (<i>indicate date of mtg</i>)		☒ 03/18/2008
• Mid-cycle Communication (<i>indicate date of mtg</i>)		☒ N/A
• Late-cycle Meeting (<i>indicate date of mtg</i>)		☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)		Pre-Phase 3 Mtg 08/10/2011, Type A SPA Mtg 02/09/2009
❖ Advisory Committee Meeting(s)		☒ No AC meeting
• Date(s) of Meeting(s)		N/A
Decisional and Summary Memos		
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)		☒ None
Division Director Summary Review (<i>indicate date for each review</i>)		☒ 12/19/2014
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)		☒ 12/19/2014 (see Signatory Summary Review)
PMR/PMC Development Templates (<i>indicate total number</i>)		☒ None
Clinical		
❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		☒ None
• Clinical review(s) (<i>indicate date for each review</i>)		☒ 02/03/2014 Filing review; 11/05/2014 Final review
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not (<i>indicate date of review/memo</i>)		See Clinical review, pg. 25/ 11/05/2014

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	☒ N/A
❖ Risk Management - REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) - REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) - Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)	N/A N/A ☒ None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	☒ 07/07/2014 NAI letter 07/22/2014 NAI letter 08/01/2014 VAI letter 08/01/2014 Inspection summary
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	☒ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	☒ 02/06/2014 Filing review; 08/29/2014 Final review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	☒ No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	☒ 02/06/2014 Filing review; 10/03/2014 Final review
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	☒ 02/03/2014 Filing review 08/04/2014 Final review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	☒ None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	☒ 05/07/2014 Final review 07/01/2014 review addendum
❖ ECAC/CAC report/memo of meeting for protocol review	☒ 01/25/2007
❖ ECAC/CAC report/memo of meeting for final report review	☒ 06/23/2014
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	☒ None requested

Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	☒ No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	☒ 02/10/2014 Filing review; 10/21/2014 Final review
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	01/31/2014 Filing review, 03/07/2014 Final review N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	☒ 02/20/2014 OC Filing review ☒ 08/28/2014 Biopharm Final review
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review, pg. 122/ 10/21/2014
☐ Review & FONSI <i>(indicate date of review)</i>	N/A
☐ Review & Environmental Impact Statement <i>(indicate date of each review)</i>	N/A
❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) <i>(only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵)</i>	Date completed: 8/14/2014 ☒ Acceptable ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) <i>(original and supplemental BLAs)</i>	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed (per review)

⁵ i.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☒ No changes ☐ New patent/exclusivity (<i>Notify CDER OND IO</i>)
• Finalize 505(b)(2) assessment	☒ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☐ Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	☒ Done
❖ Ensure Pediatric Record is accurate	☒ Done
❖ Send approval email within one business day to CDER-APPROVALS	☒ Done

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

/s/

J P PHILLIPS
12/19/2014

From: Phillips, J. Paul
Sent: Tuesday, October 07, 2014 2:19 PM
To: 'CLARK Elaine'
Cc: Gould, Barbara; Williams, Dawn
Subject: RE: NDA 206255 - Soolantra (ivermectin) - Labeling Response

Ms. Clark,

Please see the attached draft labeling for NDA 206255 with a few additional FDA edits in track changes. We ask that you respond by Friday, 10/10/2014.



NDA 206255 draft
PI_10-7-14.docx

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: CLARK Elaine [<mailto:Elaine.CLARK@galderma.com>]
Sent: Wednesday, October 01, 2014 3:30 PM
To: Phillips, J. Paul
Cc: Gould, Barbara; Williams, Dawn
Subject: NDA 206255 - Soolantra (ivermectin) - Labeling Response

Hello Paul,

Attached are courtesy copies of our response to FDA most recent proposal to the PI and IFU, accepting all edits, indicating our agreement with the proposal. In addition, we have made the correction to add the parentheses around the established name on the container and carton labeling as requested. Formal NDA amendment submission of all labeling, including new artwork mockups reflecting this change for all size configurations, was just submitted via the electronic submissions gateway, so you should see it this afternoon. Please do not hesitate to contact me if there are any questions or if you need further information.

Best regards,
Elaine

Elaine M. Clark
Sr. Director, US Regulatory Submissions
Galderma Laboratories, L.P.

14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (817) 720-1040
mobile (b) (6)
e-mail Elaine.clark@galderma.com

From: Phillips, J. Paul [<mailto:Paul.Phillips@fda.hhs.gov>]
Sent: Tuesday, September 30, 2014 12:49 PM
To: CLARK Elaine
Cc: Gould, Barbara; Williams, Dawn
Subject: RE: NDA 206255 - Soolantra (ivermectin) Package Insert - Question re Revision

Ms. Clark,

Please see the attached draft labeling for NDA 206255 Soolantra with FDA edits in track changes.

Also see the below comment regarding the carton/container labeling.

Carton/Container

- Please add parenthesis around the established name "ivermectin" as were present in the original labels.

We ask that you respond by 10/3/2014.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: CLARK Elaine [<mailto:Elaine.CLARK@galderma.com>]
Sent: Monday, September 29, 2014 10:43 AM
To: Phillips, J. Paul
Subject: NDA 206255 - Soolantra (ivermectin) Package Insert - Question re Revision

Hello Paul,

I just left you a voicemail message in response to your question you left me in voice message last week while I was traveling. I am very sorry I did not get the message until just today, but I

understand the question you raised regarding the package insert edits we made and the point regarding the less than or equal symbol.

You are correct that in the NDA Module 2.7.4 in Table 29, the term “skin burning sensation” appears at 1.0%, while “skin irritation” is present at 0.9%. The reasoning behind Galderma switching the symbol to greater than equal to 1% from the original less than or equal to 1% was related to rounding up to 1% (and usually we have events at greater than equal to 1% in other labeling). However as you are quite correct that for Soolantra neither event actually appears at greater than or equal to 1%, we are perfectly fine maintaining the original less than equal to 1% symbol. I have just confirmed this with our pharmacovigilance department as well.

I hope this is clear, but please do not hesitate to contact me if you have any questions. Apologies again for the delayed reply and we look forward to receiving your response to our proposal.

Best regards,
Elaine

Elaine M. Clark

Sr. Director, US Regulatory Submissions
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (817) 720-1040
mobile (b) (6)
e-mail Elaine.clark@galderma.com

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

/s/

J P PHILLIPS
10/07/2014

From: Phillips, J. Paul
Sent: Friday, September 05, 2014 3:05 PM
To: CLARK Elaine (Elaine.CLARK@galderma.com)
Cc: Gould, Barbara; Williams, Dawn
Subject: NDA 206255 Soolantra (ivermectin) draft labeling

Ms. Clark,

Please see the attached draft labeling for NDA 206255 Soolantra (ivermectin) with FDA edits in track changes.



NDA 206255
(Soolantra)_PI_F...



NDA 206255
(Soolantra)_IFU_...

Below are FDA comments regarding your proposed carton/container labels.

Carton and Container Labels (all package sizes)

1. Consider revising the presentation of the established name from all-caps (i.e. IVERMECTIN) to lower case (i.e. ivermectin) to improve readability of the name. Words set in lower case are easier to read than the rectangular shape that is formed by words set in all capital letters.
2. After implementing item number 1 above, ensure the presentation of the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2).
3. Consider relocating the strength statement “1%” to appear below the established name to help increase the readability of this information.
4. Revise the (b) (4) used for the presentation of the active ingredient, dosage form, and strength statements to a darker color. As currently presented it is difficult to read, especially on the smaller labels.
5. Increase the prominence of the statement “To open tube...” by bolding, increasing the font size, or using a color font. Although the concept of push and turn to open a child-resistant container closure system is common for bottles, it is still unusual for tubes. Therefore, highlighting this information might help facilitate the patient’s use of the product.

Container

We are unclear where the graphic (i.e. diamond cluster in a semi-circle) will be presented on the 2 g (b) (4). Please verify that the placement of the graphic on the 2 g (b) (4) does not represent intervening matter. We recommend that the proprietary name and the established name not be separated by placement of intervening matter that, in any way would detract, obfuscate, or de-emphasize the established name of the product, or obscure the relationship between the proprietary name and the established name. We acknowledge that the graphic is presented on other carton and container labels (e.g., the 5 g (b) (4)), and we do not have comments on those presentations.

Carton

For consistency with other product carton and container labels, we recommend adding important material information from the DOSAGE AND ADMINISTRATION section of the PI. For example, please consider adding the following language to the "Usual Dosage" section: "Apply to the affected areas once daily. See package insert for complete prescribing information."

We ask that you respond **by September 17, 2014**.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@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/

J P PHILLIPS
09/05/2014

From: Phillips, J. Paul
Sent: Tuesday, September 30, 2014 1:49 PM
To: 'CLARK Elaine'
Cc: Gould, Barbara; Williams, Dawn
Subject: RE: NDA 206255 - Soolantra (ivermectin) Package Insert - Question re Revision

Ms. Clark,

Please see the attached draft labeling for NDA 206255 Soolantra with FDA edits in track changes.



NDA 206255 draft
PI_9-30-14.docx



NDA 206255 draft
IFU_9-30-14.docx

Also see the below comment regarding the carton/container labeling.

Carton/Container

- Please add parenthesis around the established name “ivermectin” as were present in the original labels.

We ask that you respond by 10/3/2014.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: CLARK Elaine [<mailto:Elaine.CLARK@galderma.com>]
Sent: Monday, September 29, 2014 10:43 AM
To: Phillips, J. Paul
Subject: NDA 206255 - Soolantra (ivermectin) Package Insert - Question re Revision

Hello Paul,

I just left you a voicemail message in response to your question you left me in voice message last week while I was traveling. I am very sorry I did not get the message until just today, but I understand the question you raised regarding the package insert edits we made and the point regarding the less than or equal symbol.

You are correct that in the NDA Module 2.7.4 in Table 29, the term “skin burning sensation” appears at 1.0%, while “skin irritation” is present at 0.9%. The reasoning behind Galderma

switching the symbol to greater than equal to 1% from the original less than or equal to 1% was related to rounding up to 1% (and usually we have events at greater than equal to 1% in other labeling). However as you are quite correct that for Soolantra neither event actually appears at greater than or equal to 1%, we are perfectly fine maintaining the original less than equal to 1% symbol. I have just confirmed this with our pharmacovigilance department as well.

I hope this is clear, but please do not hesitate to contact me if you have any questions. Apologies again for the delayed reply and we look forward to receiving your response to our proposal.

Best regards,
Elaine

Elaine M. Clark

Sr. Director, US Regulatory Submissions
Galderma Laboratories, L.P.

14501 North Freeway

Fort Worth, TX 76177

phone (817) 961-5492

fax (817) 720-1040

mobile (b) (6)

e-mail Elaine.clark@galderma.com

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

/s/

J P PHILLIPS
09/30/2014



NDA 206255

INFORMATION REQUEST

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following information request. We request a written response by COB September 15, 2014, in order to continue our evaluation of your NDA.

Revise the Regulatory Specification table in Section 3.2.P.5.1 for (ivermectin) cream, 1% to include the test and acceptance criterion for Ivermectin Release Rate as agreed to in the amendment dated June 27, 2014.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, PhD
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE

09/11/2014

Chief, Branch IV



NDA 206255

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Galderma Research and Development, LLC
Attention: Elaine Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated and received December 20, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (ivermectin) cream, 1%.

On August 4, 2014, we received your major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is January 20, 2015.

In addition, we are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by October 22, 2014.

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

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Acting Deputy Director for Safety
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

KENDALL A MARCUS
08/19/2014



NDA 206255

INFORMATION REQUEST

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a written response by COB August 13, 2014, in order to continue our evaluation of your NDA.

Your proposed IVRT acceptance criteria (range) of (b) (4) is too wide. We acknowledge that you set your specification limits based on the individual release rates for each batch tested. However, the IVRT specification limits will be based on mean ivermectin release rates for each batch per the SUPAC-SS guidance. Based on the data you have submitted for all batches tested (including the data submitted on August 4, 2014), we recommend you accept (b) (4) as your regulatory IVRT acceptance criteria (range) for your drug product. The recommended IVRT acceptance range is based on the overall mean of the mean release rates that you reported for each clinical and commercial batch tested $\pm$ the standard deviation (b) (4)

Should you need to change the IVRT acceptance criteria (range) during post-approval, submit a request with justification to the Agency for review.

We request acknowledgement of your acceptance of the recommended IVRT acceptance criteria, and your concurrence to revising the IVRT acceptance criteria based on release data collected over 12 months.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, PhD
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE

08/12/2014

Chief, Branch IV



NDA 206255/SDN 1

INFORMATION REQUEST

Galderma Research and Development, LLC
Attention: Elaine M. Clark
Senior Director, US Regulatory Submissions
14501 North Freeway
Fort Worth, TX 76177

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted December 20, 2013, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We have the following request for information:

Develop patient labeling (such as Instructions for Use) to inform patients on the operation of the child-resistant container closure system for ivermectin 1% cream.

We ask that you respond by July 23, 2014 to the above request.

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

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JILL A LINDSTROM
07/11/2014



NDA 206255

(E)CAC – FINAL REPORT

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

Dear Ms. Clark:

Please refer to your new drug application (NDA) pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

Our (Executive) Carcinogenicity Assessment Committee ([E]CAC) reviewed your dermal mouse carcinogenicity and oral rat carcinogenicity study reports on June 17, 2014. As requested in your December 20, 2013 submission, a copy of the final report of the (E)CAC regarding (ivermectin) cream, 1% is enclosed.

The recommendations made by the (E)CAC are advisory in nature and should not be interpreted as a measure of the approvability of any application for this product.

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

Sincerely,

{See appended electronic signature page}

Barbara Hill, PhD
Pharmacology Supervisor
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment:
(E)CAC meeting minutes

Executive CAC**Date of Meeting:** June 17, 2014

Committee: Abigail Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Timothy McGovern, Ph.D., OND IO, Alternate Member
Barbara Hill, Ph.D., DDDP, Supervisor
Jianyong Wang, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Jianyong Wang, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 206255
Drug Name: SOOLANTRA (ivermectin) Cream, 1%
Sponsor: Galderma Research and Development, Cranbury, NJ

Background:

Ivermectin is an anti-parasitic agent. The sponsor intends to develop SOOLANTRA (ivermectin) Cream, 1% for the treatment of rosacea. On 12/18/2006 the sponsor submitted two carcinogenicity study protocols (a 2-year dermal mouse carcinogenicity study and a 2-year oral rat carcinogenicity study) to IND 76064. An Exec CAC meeting was conducted on 01/23/2007 and the Committee's recommendations were relayed to the sponsor on 01/25/2007. Subsequently the sponsor conducted the two carcinogenicity studies per CAC's recommendations and the final study reports were submitted to NDA 206255 on 12/20/2013.

Dermal Mouse Carcinogenicity Study:

In a 2-year dermal mouse carcinogenicity study, topical doses of 0 (water control), 0 (vehicle control), 1, 3 and 10 mg/kg/day ivermectin (0.1%, 0.3%, and 1.0% cream applied at 1 ml/kg) were administered to CD-1 mice. The vehicle contains (b) (4), carbomer copolymer type B (b) (4), dimethicone (b) (4), edetate disodium (b) (4), citric acid monohydrate (b) (4), cetyl alcohol (b) (4), stearyl alcohol (b) (4), polyoxyl 20 cetostearyl ether (b) (4), sorbitan monostearate (b) (4), methyl paraben (b) (4), propyl paraben (b) (4), phenoxyethanol (b) (4), propylene glycol (b) (4), oleyl alcohol (b) (4), sodium hydroxide (b) (4) and purified water (b) (4).

Low dose males were necropsied during Week 100 due to declining survival. All other male groups were necropsied during Week 101. All females were necropsied during Weeks 105 and 106. There were no significant differences in the cumulative survival rate among different groups in either gender. Throughout the study, the mean body weight was slightly lower in the high dose male group, compared to the two control groups.

For histopathological examination, a complete list of tissues was examined for water control, vehicle control, and high dose groups. Histology was examined for all tumors in all groups. Non-neoplastic histopathological findings were noted in treated skin and lymphoid organs, including epidermal hyperplasia, amyloidosis, inflammation, ulceration and pustule formation in skin and lymphoid hyperplasia in lymphoid organs. These effects were likely vehicle-related, but a relationship to test article treatment could not be ruled out. There were no significant test article-related neoplastic findings in either sex according to the statistical criteria used by the Executive CAC.

Oral Rat Carcinogenicity Study:

In a 2-year oral rat carcinogenicity study, oral (gavage) doses of 0 (vehicle: 0.5% carboxymethylcellulose), 1, 3 and 9 mg/kg/day ivermectin were administered to Wistar rats.

There were no significant differences in the cumulative survival rate among different groups in females. Mortality rate was higher in high dose males compared to other male groups. Ten high dose females had treatment-related clinical signs during the first two weeks of treatment. Six out of these 10 females were euthanized moribund on Days 6 and 7. The mean body weights of high dose animals were lower in the first few weeks and then gradually recovered to control level. It appeared that the high dose induced significant toxicity during the first few weeks, especially in females, followed by a habituation to the toxicity and recovery. Macroscopically, a higher incidence of hepatic masses and raised areas was noted in high dose males. An increase in liver weight was noted in mid dose and high dose animals.

For histopathological examination, a complete list of tissues was examined for vehicle control and high dose groups. In low dose and mid dose animals, histology was examined for 1) all macroscopic findings, 2) liver in males and 3) spleen, thymus, bone marrow (sternum), lymph nodes (mandibular and mesenteric), pancreas and eyes in males and females. In liver, a dose-related increase in the incidence of periportal to diffuse vacuolation was noted at mid dose and high dose. There were no statistically significant test article-related neoplastic findings in females. A statistically significant increase in the incidence of hepatocellular adenoma was noted in high dose males. There were no statistically significant test article-related neoplastic findings in low dose or mid dose males. The multiples of human exposure for the mid dose and high dose in male rats were 599 and 1766, respectively, when the AUC values obtained in mid dose and high dose males in this study were compared to a mean human AUC value obtained in a maximum clinical use PK trial.

Executive CAC Recommendations and Conclusions:

- 1) Dermal mouse carcinogenicity study:
 - The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
 - The Committee concluded that there were no drug-related neoplasms in the study.

2) Oral rat carcinogenicity study:

- The Committee concurred that the study was acceptable, noting prior Exec CAC concurrence with the protocol.
- The Committee concluded that hepatocellular adenomas in high dose male livers were drug-related and there were no drug-related neoplasms in female rats.

Abigail Jacobs, Ph.D.
Acting Chair, Executive CAC

cc:\

- /Division File, DDDP
- /B. Hill, Supervisor, DDDP
- /J. Wang, P/T reviewer, DDDP
- /P. Philips, Project Manager, DDDP
- /A. Seifried, OND IO

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

/s/

ADELE S SEIFRIED
06/18/2014

ABIGAIL C JACOBS
06/18/2014

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

/s/

BARBARA A HILL
06/23/2014



NDA 206255

INFORMATION REQUEST

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Add an in vitro release test (IVRT) to the drug product release specification as a control for the internal structure (b) (4) of the cream and potential variations in the structure from batch to batch. Your proposed IVRT acceptance criteria (range) for the drug product release specification should be based on data generated from batches manufactured using the Phase 3 manufacturing process and the commercial manufacturing process.
2. Per the SUPAC-SS Guidance, “*The in vitro release rate of a lot of the dosage form prepared by the new/modified process should be compared with the in vitro release rate of a recent lot of comparable age of the dosage form prepared by the pre-change process.*” Therefore, the IVRT study submitted in your NDA to bridge the Phase 3 and commercial drug product manufacturing processes is deficient since the batches tested in the study are not of comparable age. (b) (4)
(b) (4) To prove the process comparability, you can do ONE of the following:
 - a. Submit data indicating that the creams produced by both manufacturing processes do not have a significant change in the drug release characteristics over the proposed expiration dating period.

- b. Submit IVRT bridging studies using Phase 3 and commercial batches of comparable age. Both freshly made and near expired batches should be included in the bridging studies.

Alternatively, if process comparability cannot be adequately established in this review cycle, you may propose to use the Phase 3 manufacturing process for commercial production, and propose any post-Phase 3 manufacturing process changes during the post-approval life-cycle management.

3. Amend the analytical procedures for Description and Packaging in the regulatory specification for drug product to include an instruction for a visual examination of the content and the interior surface of the tube after cutting open the tube.
4. Amend your post approval stability commitment so that it is stated that the data will be submitted to the NDA, and (where it appears) delete the statement “The data will be provided to the Agency upon request”.
5. Amend your post approval stability protocol by adding a test on in vitro drug release and committing to monitor the drug release characteristics until you obtain the Agency’s agreement to waive it through a prior approval supplement.
6. Provide photos of the microscopic appearance test for the vehicle cream, and compare them with representative photos of the pivotal clinical batches.

If you have any questions, call Olga Simakova, Regulatory Project Manager, at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Moo-Jhong Rhee, PhD
Branch Chief, Branch IV
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

MOO JHONG RHEE

05/29/2014

Chief, Branch IV



NDA 206255

CONFIRMATION OF ISSUES DISCUSSED

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) for (ivermectin) cream, 1%.

We refer to the teleconference between representatives of your firm and the Office of New Drug Quality Assessment (ONDQA) and the Office of New Drugs (OND) on May 6, 2014. The purpose of the meeting was to discuss the (b) (4) present in ivermectin cream and in-vitro drug release.

The following attendees from ONDQA and OND, FDA were presented at the meeting.

From ONDQA:

Shulin Ding, PhD, CMC Lead
Raymond Frankewich, PhD, CMC Reviewer
Kelly Kitchens, PhD, Biopharmaceutics Reviewer
Tapash Ghosh, PhD, Biopharmaceutics Team Leader
Olga Simakova, PhD, Regulatory Health Project Manager

From OND:

Jill Lindstrom, MD, Clinical Team Lead, Division of Dermatology and Dental Products
Jane Liedtka, MD, Clinical Reviewer, Division of Dermatology and Dental Products
J. Paul Phillips, MS, Regulatory Health Project Manager, Safety, Division of Dermatology and Dental Products

The following attendees from Galderma were presented at the meeting.

From Sophia, France:

Jean-Pierre Etchegaray, Pharmaceutical Development Expert
Sandrine Segura, Pharmaceutical Development Coordinator
Claire Mallard, Formulation Scientist
Sylvie Cotret, Manufacturing Process Development
Cyril Meunier, Analytical Chemistry

From Princeton, New Jersey, US:

Alison Long, Project Leader

From Montreal, Quebec, Canada:
Phillipe Deaudelin, Regulatory Affairs, Manufacturing and Technical Operations

From Fort Worth, Texas, US:
Oliver Watts, VP Quality and Regulatory Affairs, US
Elaine Clark, Sr. Director US Regulatory Submissions

1. The first point of discussion focused on the presence of (b) (4) in ivermectin cream. The FDA conveyed its concern with the absence of characterization information on (b) (4). Galderma responded that (b) (4).

Galderma further described the photo of the cream stating that the cream contained (b) (4).

When the Agency inquired about the possibility of the association of (b) (4), Galderma responded that they believed, based on the formulation and manufacturing process, (b) (4).

Upon inquiring of the consistency of the cream structure from batch to batch and the impact of the structure on drug release, Galderma responded that every batch of this cream had a similar microscopic appearance.

The FDA expressed a concern regarding assurance of the safety/efficacy of the product from batch to batch in the absence of information showing the impact of the cream structure on drug release.

2. The second point of discussion focused on in vitro release test (IVRT) specifications. Since Galderma has an established IVRT method, the FDA recommended that Galderma propose in vitro release acceptance criteria and include the in vitro release acceptance criteria in the drug product release and stability specifications. Although Galderma did not agree that IVRT specifications are necessary, the FDA explained that IVRT acceptance criteria are established as a quality control parameter, and would ensure that the product quality and drug release are not affected by (b) (4) in the drug product.
3. Galderma inquired if information on (b) (4) needed to be submitted to the NDA, and if the addition of IVRT to drug product specification would be requested through a formal IR letter. The FDA responded that Galderma could submit information for review, and that an IR letter may be expected in a few weeks.

If you have questions please feel free to call me at (240) 402-3814.

Sincerely,

{See appended electronic signature page}

Olga Simakova, PhD
Regulatory Health Project Manager
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

/s/

OLGA SIMAKOVA
05/09/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206255

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Galderma Research and Development, LLC.
14501 North Freeway
Fort Worth, TX 76177

ATTENTION: Elaine Clark
Senior Director, US Regulatory Submissions

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated and received December 20, 2013, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ivermectin Cream, 1%.

We also refer to:

- Our email, dated February 10, 2014, requesting submission of your proprietary name under the NDA
- Your email, dated February 13, 2014, acknowledging the receipt
- Your correspondence, dated and received March 12, 2014, requesting review of your proposed proprietary name, Soolantra

We have completed our review of the proposed proprietary name, Soolantra and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your March 12, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0549. For any other information regarding this application, contact Paul Phillips, Regulatory Project Manager in the Office of New Drugs, at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Kellie A. Taylor, Pharm.D., MPH
Deputy Director
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

/s/

TODD D BRIDGES on behalf of KELLIE A TAYLOR
04/10/2014



NDA 206255

INFORMATION REQUEST

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We are reviewing your application and have the following request for information.

Provide (or identify the location in the NDA of) case narratives for the following subjects with neutropenia:

Trial 40051

5301-2111 (37M)
5140-3006 (34M)
5275-1904 (50M)
5636-4601 (55F)

Trial 18170

8329-014

In addition, provide follow-up information on subject 8110-012 who was discontinued from pivotal trial 18171 secondary to anemia. We would like to know if an alternative cause for the anemia was identified during the work-up by the primary physician.

We request that you submit your response by April 16, 2014.

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

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JILL A LINDSTROM
04/09/2014

Phillips, J. Paul

From: Phillips, J. Paul
Sent: Thursday, March 20, 2014 10:16 AM
To: 'CLARK Elaine'
Cc: Gould, Barbara
Subject: RE: NDA 206255 (ivermectin)

Ms. Clark,

Regarding your questions for clarification of FDA comments in the 74-day letter, below are our responses.

Clarification for Question 1

Regarding the representative sample (2 units): Provide 2 units for each. You may send samples to the attention of the RPM at the following address:

**APPEARS THIS WAY ON
ORIGINAL**

Food & Drug Administration
Attention: J. Paul Phillips
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Clarification for Questions 2 and 3

Regarding microscopic appearance. The intent is to compare microscopic appearance of the product made by two different manufacturing processes throughout the stability study period, and to set specification eventually if warranted. The data should have descriptive and quantitative (if feasible) portions in addition to photos. Descriptive and quantitative portions of the data of the microscopic appearance test should be provided for every time point where the test was conducted and for all three temperatures (25C, 30C and 40C). Changes in microscopic appearance should be noted. Representative photos should be provided as illustrations to augment the descriptive and quantitative portion of the data. All data should be provided in Section 3.2.P.8 Stability.

Of note, if you did some special investigational studies in R&D to understand microscopic appearance data, the special study results can be provided in Section 3.2.P.2 Pharmaceutical Development.

Clarification for Question 7

We requested testing for sensitivity, specificity, selectivity and robustness performed with altered product lots that contain around 50% and 150% of the label claim for the following reasons:

- Sensitivity – ensure the method consistently identifies higher or lower release rates with increased or decreased loading drug concentrations
- Specificity – ensure the method identifies proportional changes in drug release as a function of loading drug concentration
- Selectivity – ensure the method identifies the drug release from higher and lower loading drug concentrations as inequivalent to that from the reference product (per SUPAC-SS statistical criteria for equivalence)

Regards,

Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov

From: CLARK Elaine [mailto:Elaine.CLARK@galderma.com]
Sent: Monday, March 10, 2014 10:06 PM
To: Phillips, J. Paul
Subject: RE: NDA 206255 (ivermectin)

Hello Paul,

It was good to catch you by phone today! As discussed, I have a few follow-up questions from my team regarding the attached request for information contained within our Day 74 Filing Communication. We are actively working on fulfilling the request and some of these questions are logistical in nature. The last one regarding Question 7 may require further discussion, and we would be available for a telephone conversation with CMC review staff if that is helpful or necessary. The others are fairly straightforward:

Question 1 regarding the representative sample (2 units) requested for each to-be-marketed packaging configuration and each non-child-resistant configuration: there are a number of different packaging configurations/sizes/suppliers described in the NDA. Would FDA like 2 units of each, or 2 units of a "representative" selection? We do have all of the following available and can send some or all of these. I also presume these are to be sent to your address/attention directly and not through the document control room, but could you please verify where we should make shipment once u have made your selection?

- (b) (4) 30 gram, 45 gram, and 60 gram child-resistant
- (b) (4) 30 gram child-resistant (intended size/supplier for commercial launch)
- (b) (4) 30 gram, 45 gram, and 60 gram non-child-resistant (clinical supply example)
- (b) (4) 30 gram non-child-resistant
- (b) (4) 2 gram and 5 gram non-child-resistant sample sizes (b) (4)

Questions 2 and 3 regarding the microscopic appearance test photos: there are a multitude of photos we can provide and we would like guidance as to the extent of photos requested. I have provided a table below to illustrate—for each formal and supportive stability study, we would propose to submit the photos taken at 25°C and 30°C (long term) at the last timepoint available. Would this be appropriate or does FDA have a different expectation?

Could you also please advise how we should submit the photos—are these to be provided electronically to the eCTD via the Gateway? And if so, we would like to know where within the eCTD structure to include them and if there are any specific file requirements? Alternatively, should these be provided on disk? And if so, how/to whom/where to submit to capture formal response to the information request?

Stability study number	Time point proposed	Lot number	Number of photos
BD.O5.PSP.0140	6m	100334, 100335, 100336, 100338, 100339, 100337, 100340	14

1.BD.O5.PSP.0141	6m	100322, 100323, 100324, 100328, 100329, 100330, 100331, 100332, 100333	18
1.BD.O5.PSP.0053	36m	067095, 067224/066993, 067096, 067100, 067101, 067102	12
1.BD.O5.PSP.0066	36m	067097, 067098, 067099, 067103, 067104, 067105	12
1.BD.O5.PSP.0113	24m	083720	2
1.BD.O5.PSP.0126	18m	090846, 090847, 090843, 090842, 090845, 090844, 090840, 090841	16

Question 7 regarding the IVRT method and request to perform with altered product lots containing 50% and 150% of the label claim of API vs. the reference: our Pharmaceutical Development team is uncertain of the objective of this test and would like clarification to understand FDA expectations for the resultant data this experiment would generate.

As I mentioned earlier over the phone, our team understands the intent of the other IVRT questions; namely that the response to Question 5 would address validation of the IVRT system, and the response to Question 6 would address validation of the analytical method to quantify the concentration of API in the (b) (4) but they are unsure what additional information is expected to be obtained by the test requested in Question 7 assessing formulations containing +/- 50% of API over the reference? If you could respond in email that would be great, but if this is not clear and a telephone conversation would help, please let me know. Many thanks and I hope to hear from you soon.

Best regards,
Elaine

Elaine M. Clark

Sr. Director, US Regulatory Submissions
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (817) 720-1040
mobile (b) (6)
e-mail Elaine.clark@galderma.com

From: CLARK Elaine
Sent: Tuesday, March 04, 2014 9:20 AM
To: 'Phillips, J. Paul'
Cc: Gould, Barbara
Subject: RE: NDA 206255 (ivermectin)

Good morning Paul,
Thank you for the courtesy copy of the Filing Communication—I will distribute internally to our project team so we can begin to address the issues as directed. We will have the reformatted labeling submitted on or before March 24, 2014 as requested. I will return to you if there are any questions regarding the other issues once the Galderma team has had a chance to review the Day 74 letter.
Best regards,

Elaine

Elaine M. Clark

Director, US Regulatory Submissions
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (817) 720-1040
mobile (b) (6)
e-mail Elaine.clark@galderma.com

From: Phillips, J. Paul [<mailto:Paul.Phillips@fda.hhs.gov>]
Sent: Tuesday, March 04, 2014 7:21 AM
To: CLARK Elaine
Cc: Gould, Barbara
Subject: NDA 206255 (ivermectin)

Ms. Clark,

Please see the attached courtesy copy of a filing communication for NDA 206255 (ivermectin). A hard copy will also be mailed to you.

Regards,

J. Paul Phillips, MS
Regulatory Health Project Manager, Safety

Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food & Drug Administration
W.O. Bldg. 22, Room 5234
10903 New Hampshire Ave.
Silver Spring, MD 20993

Telephone: (301) 796-3935
Fax: (301) 796-9895
e-mail: Paul.Phillips@fda.hhs.gov



NDA 206255

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) dated and received December 20, 2013, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (ivermectin) cream, 1%.

We also refer to your amendments dated January, 8 2014, February 7 and 17, 2014.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 20, 2014.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 10, 2014. We are not currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues:

Chemistry, Manufacturing and Controls

- Equivalence of the proposed commercial manufacturing process to the Phase 3 manufacturing process

- Method development and validation of in-vitro release testing (IVRT)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Chemistry, Manufacturing and Controls

1. Provide a representative sample (2 units) for each to-be-marketed packaging configuration, and each non-child-resistant configuration studied in the supporting stability studies.
2. Provide 6 months of stability data (long term and accelerated) for the registration stability batches including microscopic appearance data. Provide photos from the microscopic appearance test.
3. Provide microscopic appearance data for all supporting registration stability batches, including the photos.
4. Clarify which manufacturing process (Phase 3 or commercial process) was used in the manufacture of European clinical supplies.
5. Provide the in-vitro release testing (IVRT) method development and validation reports. 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
6. 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 & Dose Depletion
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability

7. The IVRT method's sensitivity, specificity, selectivity and robustness need 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.
8. 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					

Clinical/Pharmacology

1. Submit incurred sample reanalysis reports for all clinical trials where pharmacokinetics was assessed.
2. Provide information on the activity of metabolites M1 and M2.

Labeling

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.
Comment: Margins need to be adjusted to ½ inch on all sides.
2. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *White space needs to be deleted between the HL heading and limitation statement. White space needs to be deleted between the product title and US approval date. White space needs to be added between each major heading.*

3. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment: *Adverse Reactions statement needs to have a reference inserted.*

4. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment: *The statement identifying the established pharmacologic class needs to be inserted.*

5. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The revision date needs to be right justified.*

We request that you resubmit labeling that addresses these issues by March 24, 2014. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

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

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

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

/s/

SUSAN J WALKER
02/28/2014

Thomas, Teena

From: CLARK Elaine <Elaine.CLARK@galderma.com>
Sent: Thursday, February 13, 2014 4:43 PM
To: Thomas, Teena
Cc: Anderson, Janet; Makela, Cristina; Phillips, J. Paul
Subject: RE: NDA 206255 Ivermectin

Hello Teena,

Thank you for your reminder—we are working on the proprietary name request and plan to submit to the NDA very soon; I will send you an email with the planned date of submission once I have ascertained this internally.

Best regards,

Elaine

Elaine M. Clark

Sr. Director, US Regulatory Submissions
Galderma Laboratories, L.P.
14501 North Freeway
Fort Worth, TX 76177
phone (817) 961-5492
fax (682) 831-6915
mobile (b) (6)
e-mail Elaine.clark@galderma.com

From: Thomas, Teena [<mailto:Teena.Thomas@fda.hhs.gov>]
Sent: Monday, February 10, 2014 1:53 PM
To: CLARK Elaine
Cc: Anderson, Janet; Makela, Cristina; Thomas, Teena
Subject: NDA 206255 Ivermectin

Hi Elaine,

The Division of Dermatology and dental Products(DDDP) is reviewing your NDA 206255 for Ivermectin and came to know that you haven't submitted a proprietary name for this NDA. If you plan to submit the proprietary name for the NDA please submit as soon as possible. Please note that the Proprietary name "Soolantra" was conditionally accepted under the IND and you still need to submit a proprietary name under the NDA.

Submit a new request for a proprietary name review that includes all required information as detailed in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Please feel free to contact me if you have any questions.

Thank you,

Teena

Teena Thomas, Pharm.D, CGP
Safety Regulatory Project Manager

FDA, CDER
Office of Surveillance and Epidemiology
Bldg.22, Room 3461
10903 New Hampshire Ave.
Silver Spring, Maryland 20993-0002

Tel: 301.796.0549

E-mail : teena.thomas@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/

TEENA THOMAS
02/14/2014



NDA 206255

INFORMATION REQUEST

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

Dear Ms. Clark:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) cream, 1%.

We are reviewing the Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request that you submit your written response to the NDA by February 17, 2014.

1. We request that you submit all relevant establishment information involved in the manufacture of avermectin. Please provide for each site: establishment name, address, local contact (name, phone number, fax number, email), function(s) performed at each site (i.e., manufacturing, release testing, and/or stability testing), and relevant DMF numbers. This is because we do not consider avermectin as an appropriate starting material for ivermectin.
2. We request that you provide a statement of readiness for inspection for each establishment applicable to your NDA, including those relevant to the manufacture of avermectin.

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

Sincerely,

{See appended electronic signature page}

Jill Lindstrom, MD
Clinical Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

JILL A LINDSTROM
02/13/2014



NDA 206255

NDA ACKNOWLEDGMENT

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

Dear Ms. Clark:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: (ivermectin) Cream, 1%

Date of Application: December 20, 2013

Date of Receipt: December 20, 2013

Our Reference Number: NDA 206255

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2014, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatology and Dental Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-3935

Sincerely,

{See appended electronic signature page}

J. Paul Phillips, MS
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

J P PHILLIPS
01/14/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076064

MEETING MINUTES

Galderma Laboratories, L.P.
Attention: Elaine M. Clark
Sr. Director, U.S. Regulatory Submissions
14501 North Freeway
Fort 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 (ivermectin) Cream, 1%.

We also refer to the meeting between representatives of your firm and the FDA on June 12, 2013. The purpose of the meeting was to discuss the content and format of the proposed 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 Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy 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 Date and Time: June 12, 2013; 9:00 a.m.
Meeting Location: FDA WO 22/room 1315

Application Number: IND 076064
Product Name: (ivermectin) Cream, 1%
Proposed Indication: Topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older

Sponsor Name: Galderma

Meeting Chair: Stanka Kukich, M.D.
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

Stanka Kukich, M.D., Deputy Director, DDDP
Gordana Diglisic, M.D., Clinical Team Leader, DDDP
Melinda McCord, M.D., Clinical Reviewer, DDDP
Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jianyong Wang, Ph.D., Pharmacology Reviewer, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Raymond Frankewich, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III
Matthew Guerra, Ph.D., Biostatistics Reviewer, DB III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Roy Blay, Ph.D., Reviewer, DGCPC
Douglas Warfield, Operations Research Analyst, OBI
J. Paul Phillips, MS, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Elaine Clark, Senior Director, US Regulatory Submissions
Jean-Paul Chappuis, Project Leader
Michael Graeber, MD, US Development and Site Director
Jean Jacovella, MD, Medical Advisor
Jesse Kooker, Head of Global Data Management and Programming
Jeanne Marceau-Suissa, MD, Medical Advisor

Martine Ortega, Regulatory Affairs Project Group Manager
Michel Poncet, Senior Statistical Expert
Caroline Robo, Regulatory Affairs Project Manager
Bernard Ruty, Preclinical Development Manager
Sandrine Segura, Pharmaceutical Development Project Coordinator

Purpose of the Meeting:

The purpose of the meeting is to discuss the content and format of the proposed NDA. It should be noted that the Phase 3 clinical trials are ongoing at this time.

Regulatory Correspondence History

We have had the following meetings or tcons with you:

- 03/18/2008: End-of-Phase 2 meeting
- 02/09/2009: Post-SPA meeting
- 08/10/2011: Pre-Phase 3 meeting
- 11/26/2012: Tcon regarding Phase 3 protocol

We have sent the following correspondences:

- 01/25/2007: Executive Carcinogenicity Assessment Committee recommendations
- 01/30/2007: Adv letter
- 01/15/2008: Adv letter
- 05/27/2008: Adv letter
- 09/26/2008: Adv/IR letter
- 10/22/2008: SPA agreement letter
- 12/30/2008: Adv letter
- 04/28/2010: IR letter
- 05/20/2010: IR letter
- 03/22/2011: IR letter
- 04/20/2011: Adv/IR letter
- 08/17/2011: IR letter
- 12/28/2011: Adv/IR letter
- 04/16/2012: Adv letter

General/Regulatory

Question 1:

Although the majority of the nonclinical pharmacology and toxicology studies performed in support of the proposed NDA are proprietary studies conducted by or for the Applicant, the Applicant will rely on published literature to describe the peri- and post-natal developmental toxicity of ivermectin. As advised by the Agency during the End-of-Phase 2 meeting held 18 March 2008, reliance upon literature will require a 505(b)(2) NDA submission as opposed to a 505(b)(1) NDA. As the Applicant will rely on literature alone to describe the peri- and postnatal

developmental toxicity of ivermectin, and does not intend to rely on previous Agency findings of safety for a specific reference listed drug, no comparative bioavailability data will be provided.

A summary of the published literature that will support the 505(b)(2) NDA for Ivermectin 1% Cream is provided in Section 10.2.1.

Does the Agency agree with submission of the proposed NDA as a 505(b)(2) application with reliance upon published literature as described?

Response:

Your proposal appears acceptable from a Pharmacology/Toxicology perspective. Submit the full literature reference for the peri- and post-natal developmental toxicity studies with the NDA.

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

You should identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature.

Be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an ANDA that cites the duplicate product as the reference listed drug.

You should provide a scientific rationale that justifies reliance on the published literature for approval of your product.

Question 2:

A summary of the development program conducted in support of an NDA for Ivermectin 1% Cream is provided in Section 10.1 of this briefing package. A proposed Target Product Profile (TPP) summarizing the desired labeling resulting from this development program is also provided in Appendix 1.

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

Response:

Your development program appears to support the proposed NDA submission.

Question 3:

A draft Table of Contents for the proposed NDA is presented in Appendix 2 of this briefing package.

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

Response:

The proposed format and content appear to be acceptable. With regard to the proposed content refer to the responses to Q 4, Q 5, Q 6, Q 9, Q 11, Q 12, Q 14, Q 15, Q 16 and Q 17.

With regard to the proposed format see additional comments below.

- FDA FORM 3674 should reside under m1.2 cover letter section with a clear leaf title.
- Providing a linked reviewer's aid/ reviewer's guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application can be helpful to the reviewers.
- 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.

- For archival purposes, you should also submit a pdf file of any labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- Providing Table of Contents in 2.1, 3.1, 4.1 and 5.1, is not necessary in the eCTD structure. Provide a reviewer's aid instead.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.
- Providing one 3.2.S and 3.2.P Manufacturing section with attribute of "ALL" and differentiating documents by leaf title is acceptable. Additionally, indicating the substance/product at the beginning of leaf title helps sorting abilities when sorting by substance or product.
- Do not provide placeholders for sections that will not be submitted (e.g. 4.2.1.2 Secondary Pharmacodynamics, N/A). Placeholders are only required when submitting ANDAs
- If a study supports multiple eCTD heading elements in m4, provide the study under one heading element and then use a single page cross reference document from the other heading element with a link to indicate that the study is provided under another heading element. This helps the reviewer only review the study once and also makes them aware that a single study supports multiple sections of the eCTD, within module 4.
- Regarding use of the m5-3-7 heading element, FDA doesn't 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.
- Regarding Module 3 of the Table of Contents (Quality), we have the following comments:
 1. Our preference is that the drug substance information from these two suppliers (b) (4) be combined in one drug substance section rather than two separate sections. A comparison and discussion should be provided regarding the differences and whether or not they would be expected to affect the drug product.
 2. We recommend a single, harmonized drug substance specification as the regulatory specification be included in Section S.4.1.
 3. Parts 3.2.A.1 (Facilities and Equipment (biotech only)) and 3.2.A.3 (Novel Excipients) should be included in the TOC. If there is no information to put in these sections, they may be left blank.
 4. The drug product Master Batch Records including filling/capping operation must be included in Section 3.2.R.P.
 5. A table correlating formulations with batch numbers and study numbers (clinical, toxicology, and stability) should be included in Module 3.

Meeting Discussion:

The sponsor will submit in the pharmaceutical development section of the NDA, information regarding drug substance from two suppliers and discuss any differences that may affect the drug product.

Question 4:

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

Does the Agency agree?

Response:

No. As outlined in the guidance for industry *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, it states “[y]ou should provide each literature reference as an individual PDF file.”

Question 5:

The proposed indication for Ivermectin 1% Cream is for topical treatment of inflammatory lesions of rosacea in adults 18 years of age and older. Based on the scarcity of reported cases of rosacea in the pediatric population (Chamaillard 2008), the Applicant takes the position that development of Ivermectin 1% Cream in the treatment of pediatric rosacea is unfeasible. The necessary studies would be highly impractical because the number of patients less than 18 years of age is small. In addition, most of the limited cases which do present can be successfully managed with currently existing products. A position paper detailing these issues was prepared by five dermatologists considered to be experts in the field of pediatric dermatology and is provided in Appendix 3. A summary of the key findings from the position paper is provided in Section 10.2.2.

Consequently, the Applicant proposes to request a waiver from the requirement to perform clinical studies in the pediatric population, pursuant to section 505B(a)(4)(A)(i) of the Pediatric Research Equity Act. The pediatric waiver request will be provided to the Agency in Section 1.9 of the proposed NDA.

Does the Agency agree?

Response:

Your proposal appears reasonable. Submit your request and justification in the NDA submission. Requests for waiver and/or deferral of studies required under the Pediatric Research Equity Act (PREA) will be considered at the time of submission. For additional information refer to the information under “PREA Requirements” following the Administrative Comments at the end of this document.

Question 6:

Provided that no safety signals or serious risks are detected after completion of the Phase 3 studies, the Applicant considers that postmarketing safety surveillance of Ivermectin 1% Cream can be accomplished according to 21 CFR 314.80 and does not believe a formal REMS program will be required.

A summary of safety data obtained to date is provided in Section 10.2.3.

Does the Agency agree?

Response:

At this time we are not aware of any serious safety signal that would necessitate a REMS.

Question 7:

Given that Ivermectin 1% Cream is intended for use in patients 18 years of age and older, the Applicant has developed the product in a container closure system comprising a tube with a screw cap. The Applicant considers that the proposed container closure system, together with labeling statements recommending to keep the product out of reach of children, will be acceptable.

However, in 2012, the Applicant became aware that the manufacturer of a topical ivermectin product approved for the treatment of head lice infestations in patients 6 months of age and older (Sklice) was required to evaluate options for a child resistant container closure system for their product, as a postmarketing commitment. In consideration of this postmarketing commitment for Sklice, the Applicant has explored options for implementing a child resistant container closure system for Ivermectin 1% Cream and will initiate a stability program to evaluate the drug product in its current tube fitted with a child resistant cap.

A summary of the safety profile for Ivermectin 1% Cream is provided in Section 10.2.3. A summary of the proposed non-child resistant container closure system and an alternative child resistant container closure system is provided in Section 10.3.2.5.

Does the Agency agree that the current non- child resistant container closure system, together with appropriate labeling statements, is acceptable for the approval and marketing of Ivermectin 1% Cream?

Response:

The current non- child resistant container closure system is acceptable for filing but the adequacy of the data supporting NDA approval will be determined in the NDA review.

We acknowledge your rationale for proposing a non-child resistant container closure system. However, the unintended ingestion of a 60 gram tube of ivermectin cream, 1% (600 mg) is a potentially lethal dose. Due to the theoretical concern regarding medication errors involving the ingestion of your product, we recommend that you consider the child-resistant closure.

Question 8:

Alternatively, should child resistant packaging be required, does the Agency agree that 3 months of stability data at the time of NDA submission for drug product in a child resistant container closure system, together with 36 months of stability data in the current non-child

resistant container closure system, are sufficient to support approval of a child resistant container closure system?

Response:

The information proposed would be sufficient for NDA filing, provided that the results of an in-use stability study (including package integrity and weight loss) with the child-resistant container/closure system will also be provided in the initial submission of the NDA, and the fabrication material of the child-resistant closure is the same as the non-child-resistant closure.

Chemistry, Manufacturing and Controls (CMC)

Question 9:

Section 10.3.2.3 describes the proposed shelf-life specification of the drug product. The Applicant considers that the impurities in the drug product have been adequately qualified in the chronic dermal carcinogenicity studies in mice (see Section 10.4).

A summary of the impurities likely to be present in Ivermectin 1% Cream and the justification for specifications of each is provided in Section 10.3.2.4.

Does the Agency concur with the proposed specifications?

Response:

The adequacy of qualification of impurities contained in the drug product will be determined during the NDA review. Provide the impurity profile (including impurities and degradation products) comparison for the lots of ivermectin cream used in pivotal toxicology studies and Phase 3 clinical trials, and the to-be-marketed drug product.

The determination for the acceptability of your proposed impurity specifications can not be made now with the limited information provided in the briefing package. The determination can be made only after the review of the complete clinical, toxicology, and CMC information submitted to the NDA.

At the time of the NDA submission address the following:

1. You have designated (b) (4) in the proposed formulation. (b) (4) is a clinical claim which can not be substantiated by physiochemical data alone. We recommend that you designate the function of (b) (4) in the formulation based on its physicochemical characteristics.
2. The method validation reports for assay and related substances of drug substance and drug product should include peak purity analysis for each peak of interest to demonstrate method specificity.

3. You state on page 59 of the briefing package that (b) (4) in the proposed formulation. Provide data/information in the NDA to support your statement.
4. Weight loss and package integrity data should be included in the registration and in-use stability reports.
5. The test of content uniformity should be included in the drug product specification in accordance to USP<3> Topical and Transdermal Drug products – Product Quality Tests. The visual examination portion of the test can be folded into the test on description with appropriate acceptance criterion such as white to pale yellow, homogeneous cream with no observable phase separation.
6. Description of filling/capping operation with in-process controls should be provided in the NDA. The description should include the number or percentage of units typically tested per batch for each in-process test.
7. Clarification regarding whether the tubes are blind-end and whether a DMF will be referenced for each container/closure component should be provided in the NDA submission.

Meeting Discussion:

The sponsor will propose a function for (b) (4) based on physical chemical property and will provide a rationale in the NDA.

Pharmacology/Toxicology

We have the following comments.

1. Add a section in the NDA for prenatal and postnatal development, including maternal function (Section 4.2.3.5.3).
2. You should submit appropriate SAS datasets with the final carcinogenicity study reports to the NDA. The carcinogenicity study reports should be submitted in conformance to the electronic format specified in the guidance document “Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications”, which can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>. The tumor dataset should be submitted in the format (table) described in Appendix 1 of an associated document, “Study Data Specifications”, which can be found at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>. Any data without 100% conformity will be returned for resubmission. Draft guidance for the statistical analysis

of chronic rodent carcinogenicity studies is available at
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf>.

3. Your proposed (b) (4) for the drug labeling is not acceptable for this topical drug product. This section should be deleted.

Clinical Pharmacology

There were no questions for Clinical Pharmacology in this meeting package. At the time of the NDA submission provide the following:

- Clarify if there were changes in the formulation of Ivermectin Cream, 1% during development. If there were changes, provide a tabular summary of all clinical trials and associated formulations used and specify how the different formulations were adequately bridged.
- Provide all bioanalytical method validation reports and bioanalysis reports for all trials where pharmacokinetic (PK) assessment was performed.
- Ensure that you have sufficient long-term storage stability data to support the duration of sample storage for all PK samples. Provide a table of all clinical trials with PK assessment and the duration from first enrollment or first PK sample collection to last sample analysis for each trial.
- Provide raw PK data and calculated PK parameters values in SAS transport format (.xpt).

Clinical/Biostatistics

Question 10:

The Applicant refers to previous Agency communications on pivotal Phase 3 studies with regards to the absence of re-randomization of subjects entering Part B of the pivotal studies and its potential impact on maintenance of the blind in Part A.

A summary of measures that were used to protect the blind of the two pivotal Phase 3 studies are provided in Section 10.5.1. Detailed descriptions of the specific statistical analyses used to support the absence of bias in the efficacy outcome are presented in an Integrated Statistical Analysis Plan for Efficacy, which is provided in Appendix 7.

Does the Agency agree that the additional statistical analyses are appropriate to support the absence of bias in the efficacy outcome?

Response:

The validity of comparisons in well-designed clinical trials depends on proper randomization and blinding. The lack of randomization and blinding can result in bias, which cannot be accounted for through alternative statistical methodology. The Agency commented during the Pre-Phase 3 meeting (8/10/2011) and reiterated in an advice letter (4/16/2012) the need for re-randomization at Week 12 to maintain blinding and minimize bias. While you "froze" the Week 12 IGA and

lesion count data points within 5 days of entry and now propose to carry out various additional analyses; however, such approaches do not alleviate the concern regarding bias in efficacy assessments and reporting of adverse events.

Question 11:

In accordance with the *Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (April 2009)*, the Applicant proposes to provide the Agency with Sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while remaining within the suggested size limitations for Module 2 (i.e., maximum 400 pages for Section 2.7 Clinical Summaries).

The Applicant will provide ISE and ISS appendices (tables, figures, and datasets) in Section 5.3.5.3 Reports of Analyses of Data from More than One Study.

Draft Tables of Contents for Sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety have been provided in Sections 10.5.2 and 10.5.3 of this briefing package, respectively, to demonstrate the planned analyses to be presented in the proposed NDA.

Based on the draft Tables of Contents provided for Sections 2.7.3 and 2.7.4, does the Agency agree that separate ISE and ISS narratives are not required in the proposed NDA?

Response:

Your proposal to submit Sections 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety that are sufficiently detailed to also serve as the full narrative portions of the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS), respectively, while remaining within the suggested size limitations for Module 2 (i.e., maximum 400 pages for Section 2.7 Clinical Summaries) is acceptable.

Question 12:

Integrated Statistical Analysis Plans for Efficacy and Safety are provided in Appendix 7 and Appendix 8, respectively.

These documents describe studies from the ivermectin clinical program that provide direct evidence for the efficacy and safety of Ivermectin 1% Cream, and propose strategies for pooling relevant studies to assess the safety of Ivermectin 1% Cream in the proposed indication. A summary of the pooling strategies for Clinical Summaries of Efficacy and Safety is provided in Section 10.5.4.

Does the Agency agree with the proposed statistical analysis plans for the summaries of clinical efficacy and safety?

Response:

While pooling for the Clinical Summary of Efficacy is generally done for completed Phase 3 trials, refer to the response to Question 10.

Your approach to the Summary of Clinical Safety appears reasonable.

At the time of the NDA submission provide the following:

- Pooled safety data for trials with the same dose and dosing regimen.
- Line listings for all safety data.
- Subject narratives for all deaths, all serious adverse events (SAEs), all severe adverse events, all adverse events (AEs) involving neutrophil counts outside the normal range, and adverse events (AEs) resulting in discontinuation from the trials.

Meeting Discussion:

The sponsor proposed to submit subject narratives and case report forms (CRF) for severe events of special interest in certain system organ class. In addition the sponsor proposed to submit narratives for events of low neutrophil count below 1.5 Giga/L.

- Subject narratives for all pregnancies including outcomes
- Summary Table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Reported by $\geq 1\%$ of subjects for individual trials and pooled data sets
- Summary Table of Treatment-Emergent Treatment-Related Adverse Events (Adverse Reactions) by System Organ Class and Preferred Term Reported by $\geq 1\%$ of subjects for individual trials and pooled data sets.

For labeling, the Adverse Reactions section must include a listing of all such reactions that occurred at or above a specified rate that is appropriate to the drug's safety database. Adverse reactions do not include all adverse events observed during the use of a drug, only those for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event. See guidance for industry *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.

- Table of Vital Signs Outside the Reference Range
- In addition to line listings and shift tables for all laboratory values, provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.
- Define and justify the threshold for calling a score positive (or negative) for sensitization/irritation.
- Add “inadequate response” and “worsening disease” to the list of reasons for discontinuation.
- Include the demographic category of Hispanic/Latino for all pooled groups.
- Submit the following items with the final study report for the thorough QT study (TQT):
 - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol

- d. Electronic or hard copy of the Investigator's Brochure
- e. Annotated CRF
- f. A data definition file which describes the contents of the electronic data sets
- g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
- h. Make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
- i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
- j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure
 - vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table (see Attachment 1)

Question 13:

On 7 March 2013, the Applicant submitted an amendment to the IND (SN 0057) describing sensitivity analyses to be performed to determine the impact from study dropouts/safety discontinuations on specific safety data from the Phase 3 pivotal studies.

A summary of the sensitivity analyses submitted in SN 0057 is provided in Section 10.5.5.

Does the Agency agree with the proposed analyses?

Response:

See response to Question 10.

Question 14:

In accordance with 21 CFR 314.50(f) and ICH M4E (R1), the Applicant proposes to include the following subject Case Report Forms (CRFs) in the proposed NDA:

- Subjects who died.
- Subjects who had other serious adverse events.
- Subjects who prematurely discontinued from studies due to an adverse event, whether or not the event was considered related to the study drug.

In addition, CRFs included in Section 16.3 of clinical study reports will also be provided in the proposed NDA.

Does the Agency agree?

Response:

Your approach appears reasonable.

In addition, you should submit Case Report Forms (CRFs) for all subjects who reported severe AEs, pregnancies, neutrophil cell counts (NCC) outside the normal range and clinically significant changes in laboratory values or vital signs.

CRFs should be placed in a CRF folder under the applicable trial with a file tag of "case-report-forms." Also provide the following:

Electronic links for:

- a. all serious AEs
- b. all severe AEs
- c. all patients discontinued regardless of reason
- d. all deaths
- e. all pregnancies
- f. all AEs in subjects with NCC outside the normal range

CRFs that are not submitted should be readily available upon request.

Question 15:

All efficacy and safety data from the 2 pivotal Phase 3 studies conducted in North America (studies 18170 and 18171) will be submitted in the initial NDA submission.

The initial NDA submission will also include available results from an on-going foreign (non-US), investigator-blinded Phase 3 supportive clinical study (study 40173), comparing Ivermectin 1% Cream QD versus metronidazole 0.75% cream BID for 16 weeks (Part A), followed by an extension period without application of study medication until relapse (Part B). A report with efficacy and safety results from Part A will be finalized and included with the initial NDA, as well as the relevant safety data from Part B (defined as related SAEs, AESIs as defined in the protocol, and cases of NCC <1.5 G/L) through a cut-off date corresponding to the Part A completion (April 2013).

In addition, for NCC values <1.5 G/L, an IDMC assessment of hematological laboratory tests for the 3 Phase 3 studies will be included in the initial NDA up to the cut-off date of August 2013 (corresponding to the Last Subject Out of the last pivotal Phase 3 study). The full safety data for Part B of study 40173 (until completion) will be submitted in the 4-month safety update.

The protocol for Phase 3 study 40173 is provided in Appendix 9. A summary of the study design for 40173 is provided in Section 10.5.6.

Does the Agency agree with the data proposed to be included in the initial NDA submission?

Response:

Your approach appears reasonable.

See the additional information requests in Attachment 2 under the heading “Clinical Investigator Site Information”.

Question 16:

Does the Agency agree with the inclusion of the full safety data for Part B of study 40173 (until completion) within the 4-month safety update?

Response:

Your approach appears reasonable.

In addition, if your topical formulation of ivermectin is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120 day safety update for the Phase 3 trials.

Meeting Discussion:

The Agency agreed that the sponsor will not need to submit the Bioresearch Monitoring (BIMO) data sets for study 40173.

Question 17:

The Applicant intends to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) implementation guide, version 3.1.2, amendment 1, with the accompanying Define.xml. A summary of the proposed dataset submission plan is provided in Section 10.5.7.

Does the Agency agree with the proposed dataset submission plan?

Response:

Your proposal to submit study datasets in accordance with the current Study Data Tabulation Model (SDTM) implementation guide, version 3.1.2, and to submit analysis datasets in ADaM format for those studies that confirm the efficacy at the current formulation is acceptable.

For the analysis datasets, we have the following general 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.

- You plan to use the Multiple Imputation (MI) method as a sensitivity analysis for imputation of missing data, which involves generating multiple datasets. Instead of submitting the multiple imputed datasets, please provide the code including seed number used to implement MI. In addition, statistical programs for any non-standard analyses should also be submitted.

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).

At the time of NDA submission:

- a. Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
- b. Clarify whether the UV/visible spectra for the drug product was obtained with the final to-be-marketed formulation. If not, provide your rationale/discussion regarding why a new spectra with the final to-be-marketed formulation will not be needed.
- c. Provide your rationale/discussion regarding why the Repeat Insult Patch Test (RIPT) with the final to-be-marketed formulation will not be needed.
- d. Provide your rationale/discussion regarding the acceptability of your foreign data. The acceptance of the foreign clinical data depends on its ability to be extrapolated to the US population. Refer to Guidance for Industry, E5-Ethnic factors in the Acceptability of Foreign Clinical Data, September 2006.

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 or NDA might identify additional comments or information requests.
2. 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 21 CFR 54 and 21CFR 314.50(k).
3. You should provide the Agency with SAS transport files in electronic form. The sponsor might refer to the Analysis Data model (ADaM) Examples in Commonly Used Statistical Analysis Methods for guidance:
http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. The FDA prefers that the sponsor arrange a test submission, prior to

actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.

4. 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 a Pediatric Study Plan (PSP) within 60 days of an End-of-Phase 2 (EOP2) meeting held on or after November 6, 2012. If an EOP2 meeting occurred prior to November 6, 2012 or an EOP2 meeting will not occur, then:

- if your marketing application is expected to be submitted prior to January 5, 2014, you may either submit a PSP 210 days prior to submitting your application or you may submit a pediatric plan with your application as was required under the Food and Drug Administration Amendments Act (FDAAA).
- if your marketing application is expected to be submitted on or after January 5, 2014, the PSP should be submitted as early as possible and at a time agreed upon by you and FDA. We strongly encourage you to submit a PSP prior to the initiation of Phase 3 studies. In any case, the PSP must be submitted no later than 210 days prior to the submission of your application.

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. For additional guidance on submission of the PSP, including a PSP Template, please refer to:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov.

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57. In particular, please note the following formatting requirements:

- Each summarized statement in the Highlights (HL) must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- The section headings and subheadings (including title of the Boxed Warning) in the Table of Contents must match the headings and subheadings in the FPI.
- The preferred presentation for cross-references in the in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, "[see *Warnings and Precautions (5.2)*]".

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

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.				

Attachment 1

Highlights of Clinical Pharmacology Table

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	• Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	• Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	• Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	

Attachment 2

CLINICAL INVESTIGATOR SITE INFORMATION

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 (see 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).

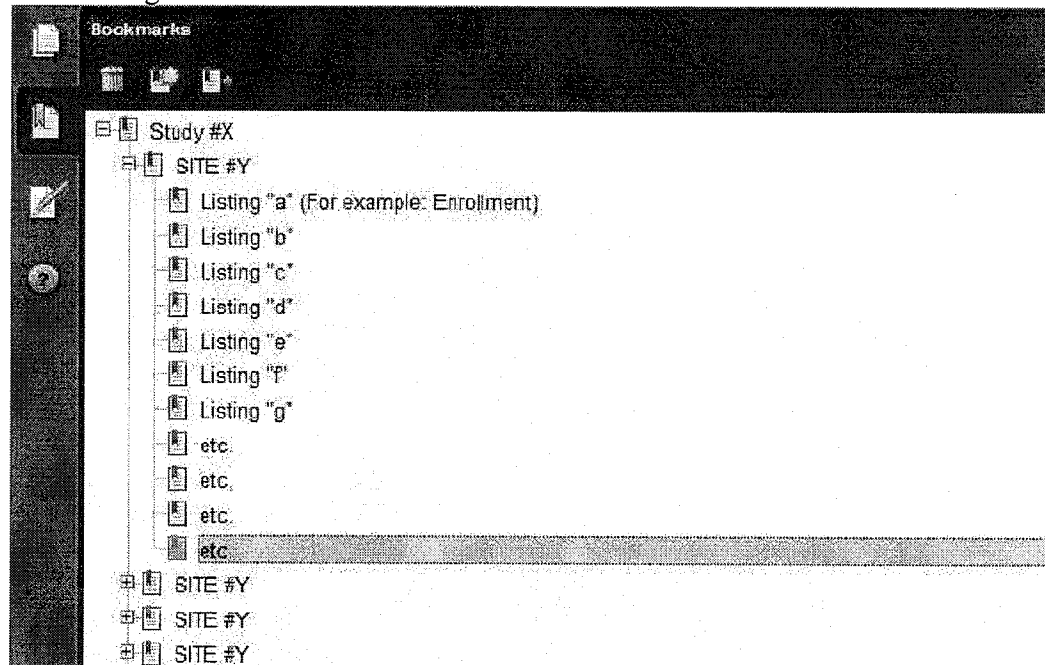
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. 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.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

- a. 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
 - b. 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.
 - c. 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.
4. 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).
 5. 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

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. 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
 - b. Subject listing for treatment assignment (randomization)
 - c. 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
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. 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.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. 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.

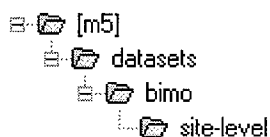
I. Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. 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

- B. 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/

STANKA KUKICH
06/21/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 076064

MEETING MINUTES

Galderma Research and Development, Inc.
Attention: Allen E. Fields, DrPH
Director Regulatory Submissions
5 Cedar Brook Drive, Suite #1
Cranbury, NJ 08512

Dear Dr. Fields:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (ivermectin) Cream, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on August 10, 2011. The purpose of the meeting was to discuss the development program for (ivermectin) Cream, 1%.

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 Paul Phillips, Regulatory Project Manager at (301) 796-3935.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy 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-Phase 3

Meeting Date and Time: August 10, 2011; 9:00 a.m. (ET)
Meeting Location: Teleconference

Application Number: IND 076064
Product Name: (ivermectin) Cream, 1%
Proposed Indication: Topical treatment of inflammatory lesions of papulopustular rosacea

Sponsor/Applicant Name: Galderma Research and Development, Inc.

Meeting Chair: Stanka Kukich, MD
Meeting Recorder: Paul Phillips

FDA ATTENDEES

Stanka Kukich, M.D., Deputy Director, DDDP
Gordana Diglisic, M.D., Clinical Team Leader, DDDP
Melinda McCord, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jerry Wang, Ph.D., Pharmacology Reviewer, DDDP
Kathleen Fritsch, Ph.D., Biostatistics Reviewer, DB III
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Raymond Frankewich, Ph.D., Product Quality Reviewer, DNDQA II, Branch IV
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Allen Fields, Regulatory Submissions Director
Jean-Paul Chappuis, Development Project Leader
Michael Graeber, North American Development and Site Director
Jean Jacovella, Medical Advisor
Didier Leclercq, Global Development Director
Julie Lepin, Regulatory Affairs Project Group Manager
Michel Poncet, Biometrics Manager

Bernard Ruty, Preclinical Development Manager
Nathalie Wagner, Clinical Pharmacokinetics Specialist
Philip Brown, Senior VP, Medical & Regulatory Affairs

1.0 BACKGROUND

We have had the following meetings with the sponsor:

- 03/18/2008: End-of-Phase 2 Meeting (Type B)
- 02/09/2009: Post-SPA Meeting (Type A)

We have sent the following correspondences:

- 01/25/2007: Executive Carcinogenicity Assessment Committee Report for Carcinogenicity Special Protocol Agreement Letter
- 01/30/2007: Advice/Information Request Letter
- 01/15/2008: Advice/Information Request Letter
- 05/27/2008: Advice/Information Request Letter
- 09/26/2008: Advice/Information Request Letter
- 10/22/2008: Special Protocol Agreement Letter
- 12/30/2008: Advice/Information Request Letter
- 04/28/2010: Advice/Information Request Letter
- 05/20/2010: Advice/Information Request Letter
- 03/22/2011: Advice/Information Request Letter
- 04/20/2011: Advice/Information Request Letter

2.0 DISCUSSION

2.1 Chemistry, Manufacturing and Controls (CMC)

The briefing package contained very little CMC information, and no CMC questions were submitted for this meeting. We have the following comments after reviewing the CMC information provided to-date to the IND:

1. We recommend that the USP method be the regulatory method for the drug substance because USP monograph on ivermectin has a tighter control over the related substances than EP. If you prefer the EP method, a strong justification with validation data of the EP method must be provided at time of NDA submission.
2. Indicate whether Phase 3 formulation is the same as that was used in Phase 2 studies, and whether you are anticipating any formulation changes in the future.
3. Include an evaluation of weight loss, package integrity (such as formulation interaction with the container), and inverted or side-way tube orientation in the registration stability protocol.

4. Include tests for phase separation and particle formation (such as precipitation of the active ingredient) in the registration stability protocol using visual and microscopic examination.
5. You have designated [REDACTED] (b) (4) respectively, in the proposed formulation. [REDACTED] (b) (4) are clinical claims which require supporting data. Since this supporting data is not provided in the IND, clarify the physiochemical function of the excipients. We recommend that you designate the function of each inactive ingredient based on its physicochemical characteristics.

2.2. Pharmacology/Toxicology/Clinical Pharmacology/Biopharmaceutics

Question 1:

The sponsor is seeking confirmation from the Agency on the appropriateness of the nonclinical and clinical pharmacokinetic and metabolism data package to support an NDA submission. In particular, considering that (1) the relative bioavailability of the topical formulation is much less than the oral immediate-release formulation, (2) the plasma pharmacokinetic (PK) profile of CD5024 was predictable in subjects with PPR under clinical maximal use conditions, and (3) the individual metabolites' specific contribution to the overall toxicity of CD5024 has been established in compliance with the FDA guidance on Safety Testing of Drug Metabolites, **the Sponsor seeks agreement that no further drug-drug interactions studies (*in vitro* and *in vivo*) are required to support an NDA submission.**

Response:

From a pharmacology/toxicology perspective, the submitted nonclinical PK/TK studies are considered acceptable to support an NDA submission.

From the clinical pharmacology and biopharmaceutics perspective, the additional information included in this briefing package to address the Agency's concern on the metabolic fate of CD5024 and the safety of its metabolites appears reasonable to support the filing of an NDA. However, adequacy of the data is a review issue.

Specifically, the following information was provided:

- The calculation of the relative bioavailability of CD5024 topical formulation in rosacea subjects (Study RD.03.SPR.40064) compared to that of the currently marketed oral immediate release tablet (Study RD.03.SPR.18120) where both parent compound and major metabolites were quantified using the same analytical method
- The result of the metabolism investigations conducted in human plasma samples from the maximal use PK study with CD 5024 1 % cream in subjects with rosacea (Study RD.03.SPR.40064)
- The evaluation of the overall safety of the major metabolites observed in humans.

In addition, we acknowledge the tabulated list of non-clinical and clinical studies that have been conducted to support the metabolism of CD5024 provided on page 44 of the briefing package.

We also acknowledge the limited PK samples for up to 12 weeks that have been obtained from Study RD.03.SPR.40027 (Dose-finding), RD.03.SPR.40051 (Long-term safety) and RD.03.SPR.40106 (Phase 2 safety study) and limited PK sampling over a 56 week period that will also be collected in your proposed Phase 3 study RD.03.SPR.18170 (Page 41 of the briefing package).

2.3. Clinical/ Biostatistics

Question 2:

Concurrence is sought that the clinical development plan, in particular the Phase 3 clinical program of two pivotal Phase 3 studies including a long term safety phase to demonstrate efficacy and safety of CD5024 1% cream in papulo-pustular rosacea (PPR) subjects, is adequate to support a New Drug Application (NDA).

Response:

The proposed Phase 3 protocol (RD.03.SPR.18170) "*A Phase 3 randomized, double-blind, 12 week vehicle-controlled, parallel-group study assessing the efficacy and safety of CD5024 1% cream versus vehicle in subjects with papulopustular rosacea, followed by a 40-week investigator-blinded extension comparing the long-term safety of CD5024 1% cream versus azelaic acid 15% gel*" consists of 3 parts: Part A, B and C.

Part A is conducted as a multicenter, double-blinded, vehicle-controlled trial (s) in which subjects are randomized 2:1 to treatment with CD5024 1% cream versus vehicle cream applied once daily for 12 weeks. The objective of the first part is "to assess the efficacy and the safety of CD5024 cream to treat inflammatory lesions of moderate to severe rosacea".

With regard to Part A of the Phase 3 protocol(s) the following agreements were documented in the 10/22/2008 SPA Agreement letter:

- Study Population:

The population to be studied is acceptable. This population is specified as having an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe) on a 5 point scale, the presence of at least 15 and not more than 70 inflammatory lesions (papules and pustules) on the face, and no more than two nodules on the face.

- Endpoints:

- The following co-primary endpoints are acceptable:
 1. Success Rate, based on IGA score, will be defined as the percentage of subjects who achieve '0 = Clear' or '1 = Almost Clear' on IGA (0 to 4 scale) at Week 12
 2. Absolute change in inflammatory lesion counts from Baseline to Week 12
- The following secondary endpoints are acceptable:

1. Absolute change together with percent change in inflammatory lesion count
 2. Time to onset of efficacy analysis (nested analysis of co-primary endpoints for successively earlier timepoints)
- It is agreed that no claim (b) (4) will be possible based on the proposed study design. (SPA dated October 22, 2008)

Meeting Discussion:

The sponsor requested that the reference to the absolute change together with percent change for the secondary endpoint be corrected to be consistent with previous discussion with the Agency following the SPA letter. Based on the February 9, 2009 Guidance Meeting the secondary endpoint should be percent change in inflammatory lesion count.

Part B is a 40-week extension period comparing treatment with CD5024 1% cream or azelaic acid 15% gel. During this investigator-blinded, active-controlled part of the trial, subjects treated with CD5024 1% cream once daily in Part A of the study will continue on this treatment and subjects treated with vehicle cream will switch to azelaic acid 15% gel twice daily. The objective of the second part of the study is "to assess the long-term safety of CD5024 cream" with focus on the adverse event of neutropenia.

We acknowledge your rationale for selecting an active control in the long-term safety extension trial. The design of the clinical trials can significantly influence the ability to make causality judgments about the relationship between the drug and the adverse events. A vehicle-controlled trial allows the adverse event rate in the drug-treated group to be compared directly with the background event rate in the patient population being studied.

A trial with active control will not allow direct assessment of the background event rate in population studied. However, if you use an active comparator in Part B of Protocol RD.03.SPR.18170, you might consider randomizing subjects to either CD5024 cream or azelaic acid 15% gel rather than assigning all subjects randomized to CD5024 cream in Part A to continue with CD5024 cream in Part B and assigning all subjects randomized to vehicle in Part A to begin treatment with azelaic acid in Part B. Using re-randomization will prevent unblinding of the Part A treatment assignment. The randomization ratios could be unbalanced so that more subjects would be randomized to the CD5024/CD5024 arm than the CD5024/azelaic acid arm. Alternatively you might consider randomizing subjects from the vehicle arm in Part A to either CD5024 cream or azelaic acid 15% gel. In any case, the size of the comparator arm should be sufficiently large to make adequate comparisons.

The adequacy of the long term safety data is a review issue. You are referred to the Guideline for Industry: *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions*.

Meeting Discussion:

The Agency clarified that the above recommendations were designed to help minimize bias, maintain blinding, and ensure adequate number of subjects.

Part C is a safety follow-up without treatment. During the last 4 weeks of the 56 week trial, all treatments are discontinued and safety data is collected at the “end of study visit”.

Safety monitoring:

In addition to the proposed safety monitoring, the protocol RD.03.SPR.18170 (all parts) should be modified to include:

- monthly urine pregnancy testing when on treatment
- active assessment for local cutaneous reaction (e.g. stinging/burning, dryness and itching at each visit; using appropriate scales)
- lesion counts (at each visit)

Meeting Discussion:

The sponsor agreed to modify the safety monitoring to include monthly urine pregnancy testing and active assessment for local cutaneous reactions. However, the sponsor proposed not to include lesion count assessment as a safety monitoring for Part B since disease severity will be monitored by IGA assessment. The Agency responded that the proposal was acceptable.

Additional comments:

Your plan is to conduct Phase 3 trials in 50 sites in Europe and North America. You are reminded that the acceptance of the foreign clinical data depends on its ability to be extrapolated to the US population. You are referred to the *Guidance for Industry E5-Ethnic Factors in the Acceptability of Foreign Clinical Data*. To reduce the potential impact of small centers on the analysis, you are encouraged to reduce the number of centers in the study so that an adequate number of subjects per center are enrolled.

Submit Phase 3 protocol(s) RD.03.SPR.18170 to the IND which are consistent with the SPA agreement (dated October 22, 2008) and incorporate current recommendations.

Meeting Discussion:

The sponsor acknowledged Agency recommendations and agreed to submit a revised protocol to the IND which is consistent with the SPA agreement.

2.4. 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. 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).

3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

3.0 PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

4.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/

STANKA KUKICH
08/19/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 76,064

Galderma Research and Development, Inc.
Attention: Allen E. Field, DrPH
Director of Regulatory Submissions
14501 N. Freeway
Fort Worth, Texas 76177

Dear Dr. Fields:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ivermectin Cream, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on February 9, 2009. The purpose of the meeting was to clarify any issues regarding the SPA response dated October 22, 2008.

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

If you have any questions, call Kelisha Turner, Regulatory Project Manager at (301) 796-0766.

Sincerely,

{See appended electronic signature page}

Stanka Kukich, M.D.
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

MEETING DATE: February 9, 2009
TIME: 3:30pm – 4:00pm
LOCATION: Teleconference
APPLICATION: IND 76,064
DRUG NAME: Ivermectin Cream, 1%
TYPE OF MEETING: Guidance Meeting – Type A

MEETING CHAIR: Stanka Kukich, M.D., Deputy Director

MEETING RECORDER: Kelisha Turner, B.S., Regulatory Project Manager

FDA ATTENDEES:

Stanka Kukich, M.D., Deputy Director, DDDP
Jill Lindstrom, M.D., Team Leader, Clinical, Dermatology, DDDP
Patricia Brown, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jianyong Wang, Ph.D., Pharmacology Reviewer, DDDP
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DBIII
Mat Soukup, Ph.D., Biostatistician, DBIII
Abimbola Adebowale, Ph.D., Pharmacokinetics Reviewer, DCPIII
Margo Owens, Team Leader, Project Management Staff, DDDP
Kelisha Turner, B.S., Regulatory Project Manager, DDDP

EXTERNAL CONSTITUENT ATTENDEES:

Martine Bouclier - Nonclinical Support Manager
Jean-Paul Chappuis - Project Lead
Maryse Corroller - Regulatory Affairs Project Manager
Michael Graeber - Head of Global Clinical Development
Denis Gross - Global Regulatory Affairs Director
Didier Leclercq - Global Development Director
Manuela Leone - Global Head of Clinical Dvt & Dvt Operations
Yin Liu - Head of US Biometrics
Christian Loesche - Senior Medical Expert
Michel Poncet - Biometrics Manager
Bernard Ruty - Head of Nonclinical Development
Nathalie Wagner - Clinical Pharmacokinetics Specialist
Allen Fields - Director of Regulatory Submissions

MEETING OBJECTIVES:

To clarify issues regarding the SPA response dated October 22, 2008.

DISCUSSION POINTS:

Question 1:

In the Special Protocol Assessment of study protocol **RD.06.SPR.18116**, the Division agreed with the two co-primary endpoints proposed by the Sponsor: (1) "Success rate based on Investigator's Global Assessment (IGA) score" and (2) "Absolute Change in inflammatory lesion counts from baseline to Week 12". In addition, the Division proposed to include the following secondary endpoints: (a) "Absolute change together with percent change in inflammatory lesion count"; this was not proposed in the original protocol submitted by the Sponsor, since the "Absolute change" endpoint is already included in the co-primary endpoints, and (b) "Time to onset of efficacy analysis".

It was agreed by the Agency that no claim will be made on (b) (4) based on the study design. In relation to this statement in the SPA letter, the Sponsor would like to clarify that (b) (4) (b) (4)

The Sponsor is seeking clarification from the Agency that the "Absolute change in inflammatory lesion counts" should be included as a co-primary endpoint only and that the proposed secondary endpoint should actually read "percent change in inflammatory lesion count". Thus, claims based on percent change and time to onset, (b) (4) may appear in the clinical section of the labeling. Does the Agency Agree?

Response:

The Agency reiterates its comments from the SPA review of Protocol SPR.18116 that success on the IGA score (defined as 'clear or almost clear' which is also at least a two grade improvement) and absolute change in inflammatory lesion counts are considered the co-primary endpoints. The percent change in inflammatory lesions is considered supportive. A determination of effectiveness will rest on analysis of the co-primary endpoints. The Agency is in agreement that no claim (b) (4) can be made based on the present study design. Whether other endpoints are included in labeling will be a review issue.

Meeting Discussion:

The Agency confirmed that absolute change in inflammatory lesion counts is considered a component of the co-primary endpoint and percent change as a secondary endpoint.

Question 2:

In the Special Protocol Assessment of study protocol **RD.06.SPR.18116**, the Division indicated that the need for contraceptive use by females of childbearing potential will be determined based on results of the maximal use systemic exposure study to be conducted prior to Phase 3 trials.

The Sponsor would like to determine with the Division the conditions for contraceptive use by females of childbearing potential in the pivotal Phase 3 program. It is the Sponsor's opinion that such conditions are supported by (1) and (2):

By a non-clinical teratogenic threshold level:

During the End of Phase 2 meeting, held on 18 March 2008 for this project, the Division considered the finding of carpal flexure noted in the rabbit oral embryo-fetal development study (**RD.03.SRE.12460**) in the 4.5mg/kg/day group as a malformation and significant. As a follow-up, the Sponsor requested a Type C meeting (IND 76,064 SN # 0006) addressing in particular this issue. The meeting was denied but, in agreement with the Division, the issue was subsequently addressed in the IND through the submission of a briefing package (IND 76,064 SN # 0009); this briefing package included a position paper with complementary arguments to support the opinion that carpal flexure which is observed in the absence of osseous malformations, is a reversible deformation and not a teratogenic finding. Consequently, the Sponsor considers that a systemic exposure to ivermectin corresponding to the oral dose of 4.5mg/kg/day (i.e. an AUC value of 12 556 ng.h/mL) in the rabbit embryo-fetal development study will not cause any serious adverse effects in fetal development.

By the results of the maximal use systemic exposure investigations:

Per the Division's recommendations during the End of Phase 2 meeting, the Sponsor submitted an analysis of PK data of the most exposed patients from the Phase 2 study **RD.03.SRE.40027**, in the briefing document for the Type C meeting (IND 76,064, SN#0009).

The highest pre-dose ivermectin plasma concentration observed in this study was 6.127ng/mL from which a mean AUC_{0-24H} value of 131 ng.h/mL could be extrapolated.

In addition, the Sponsor conducted a repeat-dose pharmacokinetic study under maximal use conditions in patients with severe papulo-pustular rosacea (IGA=4, on a 0-4 scale, and with 27 to 88 inflammatory lesions), study **RD.03.SPR.40064**. After 28 days of once daily, controlled applications, the most exposed patient had a maximal plasma concentration of CD5024 (C_{max}) of 3.94 ng/mL and an AUC_{0-24H} of 75.16 ng.h/mL.

Considering the systemic exposure at the oral dose of 4.5 mg/kg/day in the rabbit embryo-fetal development study the following safety ratios can be calculated:

- From extrapolated highest plasma AUC data in study **RD.03.SRE.40027**, a safety ratio greater than 96.
- From actual highest plasma AUC data in study **RD.03.SRE.40064**, a safety ratio greater than 167.

It is the Sponsor's opinion that these PK data, compared with systemic exposure at the oral dose of 4.5mg/kg/day in the rabbit embryo-fetal development study provide a safety margin which is sufficiently high, thus supporting no requirement of mandatory contraception."

This Type A meeting briefing package contains the PK assessment based on the systemic parent compound analytical data. Complementary, supportive data on possible metabolite(s) systemic levels will be submitted to the Division as a supplemental package.

Response:

Without actual data that clearly demonstrate the reversal of the carpal flexure finding noted in the rabbit embryo/fetal development study, this finding is considered a malformation and significant. Such information will be included in the label for the drug product if the product is approved for marketing.

The multiple of human exposure for possible teratogenic effects based on the NOAEL identified in the rabbit study (i.e., 1.5 mg/kg/day; Day 20 AUC_{0-24 hr} = 2766 ng.hr/ml) is 36 X the highest AUC_{0-24 hr} value obtained in the Maximal Use Systemic Exposure clinical pharmacokinetic study (i.e., 75.16 ng.hr/ml). Therefore, it appears reasonably safe to allow enrollment of female subjects of childbearing potential without requiring mandatory use of contraception.

Meeting Discussion:

The sponsor stated that there was no need for additional clarification.

Question 3:

The Sponsor would like to inform the Agency that study protocol **RD.06.SPR.18116** will be submitted under Clinical Trial Application (CTA) regulation in several European Countries with the objective to open European sites to enroll approximately 200 patients in these sites. The foreign clinical sites will not be open under the IND 76,064 but will comply with 21.CFR.312.120 "Foreign clinical studies not conducted under an IND". The study will be conducted in the foreign sites under a separate protocol. This protocol should be identical to the protocol submitted under the IND 76,064. Of note, some local requirements will be managed through local amendments. This may apply to the need for contraceptive use by females of childbearing potential which may be required or not, depending on the position of each national Competent Authority of the concerned European member states. At completion of the multinational study, the Sponsor's intend to submit pooled data from U.S. and foreign sites in the future application for marketing approval.

Does the Agency concur with the Sponsor's proposal to pool data from foreign and U.S. sites for this study? Should the Sponsor's data pooling plan be submitted to the Agency prior to the MAA dossier submission?

Response:

In your SPA (stamp date 09/08/2008) you stated, ``This clinical protocol [Protocol SPR.18116] that is being submitted for Special Protocol Assessment is one of two pivotal efficacy trials of identical design to support approval of Ivermectin 1% Cream for the indication of topical treatment of inflammatory lesions of papulopustular rosacea." Comments conveyed in the SPA letter were intended to be applied to each of the planned identically designed Phase 3 trials. As such, these two trials should individually stand alone in order to establish the efficacy of Ivermectin 1% Cream.

Meeting Discussion:

The sponsor explained their proposal to pool data from European sites not under the IND with data from U.S. sites under the IND. The Agency clarified that all sites in the trial need to be under the same protocol. Pooling should not be used to establish efficacy. No agreements were made regarding the sponsor's proposal. The Agency reminded the sponsor that in the SPA response [October 22, 2008], the Agency provided comments based on your proposal to conduct two trials with identical protocols. In response, the sponsor indicated they will conduct two independent well controlled studies with similar protocols.

Linked Applications

Sponsor Name

Drug Name / Subject

IND 76064

GALDERMA RESEARCH AND DEVELOPMENT CD5024

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

/s/

STANKA KUKICH

02/19/2009



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 76,064

Galderma Research and Development, Inc.
Attention: Allen E. Fields, M.S./DrPH, M.Ed.
Director of Regulatory Submissions
14501 N. Freeway
Fort worth, Texas 76117

Dear Mr. Fields:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ivermectin Cream, 1%.

We also refer to your September 8, 2008, request for a special Clinical protocol assessment, received September 8, 2008. The protocol is titled, "A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Study to Demonstrate the Efficacy and Safety of CD5024 1% Cream in Subjects with Papulopustular Rosacea over 12 Weeks Treatment".

The following documents our agreements concerning the protocol:

Clinical

Study Population: The population to be studied is acceptable. This population is specified as having an Investigator Global Assessment (IGA) score rated 3 (moderate) or 4 (severe) on a 5 point scale, the presence of at least 15 and not more than 70 inflammatory lesions (papules and pustules) on the face, and no more than two nodules on the face.

Endpoints:

- The following co-primary endpoints are acceptable:
 1. Success Rate, based on IGA score, will be defined as the percentage of subjects who achieve '0 = Clear' or '1 = Almost Clear' on IGA (0 to 4 scale) at Week 12
 2. Absolute change in inflammatory lesion counts from Baseline to Week 12
- The following secondary endpoints are acceptable:
 - a) Absolute change together with percent change in inflammatory lesion count
 - b) Time to onset of efficacy analysis (nested analysis of co-primary endpoints for successively earlier timepoints)
- It is agreed that no claim for (b) (4) will be possible based on the proposed study design.

Biostatistics

Sample Size Calculation: Based upon the sponsor's assumed estimates of treatment effect

sample size calculations have been verified.

Analysis Populations: The use of the ITT population as the primary analysis population and the PP as supportive is acceptable.

Testing Approach: CMH stratified by analysis center to assess the percent of subjects with Week 12 IGA scores of 'Clear' or 'Almost Clear' is acceptable. The use of ANCOVA to test the change in inflammatory lesion counts including baseline inflammatory count as the covariate and terms for treatment and analysis center is acceptable. Efficacy will be established if *both* of these co-primary endpoints are significant at the two-sided $\alpha = 0.05$ significant level.

Missing Data: The use of LOCF as primary and the proposed sensitivities analyses using alternate imputation strategies are acceptable.

Multiplicity Adjustment: The proposed serial gatekeeping approach to control the Type I error for testing the co-primary endpoints at earlier time points if and only if both co-primary endpoints at later time points are significant at the two-sided $\alpha = 0.05$ level is acceptable.

The following documents our disagreements concerning the protocol:

Safety monitoring: The sponsor should include additional laboratory monitoring, at Baseline and at Week 12 or Early Termination visits, consisting of liver function testing and complete blood count with differential and platelets. Although laboratory testing was performed in Phase 2, the sample sizes involved may not allow detection of rarer events.

In view of the fact that ivermectin is a potential human teratogen, urine pregnancy testing should be performed at the Week 3, 6, and 9 visits as well as at Baseline and at Week 12 or Early Termination visits.

The need for contraceptive use by females of childbearing potential will be determined based on results of the Maximal Use Systemic Exposure Study to be conducted prior to Phase 3 trials. The urine pregnancy test should have a sensitivity of at least 25mIU/L.

In addition, we have the following comment (which does not affect the above agreements):

Investigator credentials including IRB information should be submitted prior to initiation of the study.

If you have any questions, call Emelia Annum, Regulatory Project Manager, at (301) 796-2223.

Sincerely,

{See appended electronic signature page}
Susan J. Walker, M.D., FAAD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Linked Applications

Sponsor Name

Drug Name

IND 76064

GALDERMA RESEARCH
AND DEVELOPMENT

CD5024

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

/s/

EMELIA K ANNUM

10/22/2008

STANKA KUKICH on behalf of SUSAN J WALKER

10/22/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 76,064

Galderma Laboratories, L.P.
Attention: Allen E. Fields, M.ED, M.S.
Director of Regulatory Submissions
14501 N. Freeway
Fort Worth, TX 76177

Dear Mr. Fields:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Ivermectin 1% Cream for the treatment of topical treatment of inflammatory lesions of papulopustular rosacea.

We also refer to the meeting between representatives of your firm and the FDA on March 18, 2008. The purpose of the meeting was to evaluate the drug development program to date and discuss the Phase 3 plan and protocols for Ivermectin 1% Cream for the topical treatment of inflammatory lesions of papulopustular rosacea

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tamika White, Regulatory Project Manager, at (301) 796-0310.

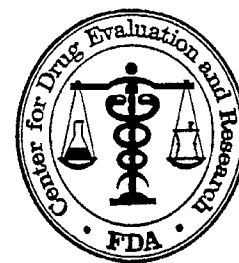
Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES



Meeting Date: March 18, 2008 **Time:** 9:30 A.M.

Location: WO 22, Room 1313 **Meeting ID:** 23409

Topic: IND 76,064 for Ivermectin 1% Cream for the topical treatment of inflammatory lesions of papulopustular rosacea

Subject: End of Phase 2 Meeting

Sponsor: Galderma Laboratories, L.P.

Meeting Chair: Susan J. Walker, M.D./Division Director, DDDP, HFD-540

Meeting Recorder: Tamika White/Regulatory Project Manager, DDDP, HFD-540

FDA Attendees:

Susan J. Walker, M.D./Division Director, DDDP, HFD-540
Jill Lindstrom, M.D./Team Leader, Clinical, Dermatology, DDDP, HFD-540
Patricia Brown, M.D./Clinical Reviewer, DDDP, HFD-540
Barbara Hill, Ph.D./Acting Supervisor, Pharmacology, DDDP, HFD-540
Shulin Ding, Ph.D./Pharmaceutical Assessment Lead, ONDQA
Christopher Hough, Ph.D./CMC Reviewer, ONDQA
Lydia Velazquez, Pharm.D./Team Leader, Clinical Pharmacology, DPEIII
Abi Adebowlé, Ph.D./Pharmacokinetics Reviewer, DPEIII, HFD-880
Clara Kim, Ph.D./Reviewer, Division of Biometrics III, HFD-725
Tamika White/Regulatory Project Manager, DDDP, HFD-540

Sponsor Attendees:

Sandrine Segura, M.Sc./Pharmaceutical Development Project Team Representative
Bernard Rutý, Pharm.D., Ph.D./Head of Preclinical Development
Nathalie Wagner, M.Sc./Clinical Pharmacokineticist
Michael Graeber, M.D./Head of U.S. Development
Christian Loesche, M.D./Head of EU Clinical Development
Michel Poncet, M.Sc./Head of Global Biometrics
Yin Liu, Ph.D./Head of U.S. Biometrics
Didier Leclercq/Director of Full Development
Jean-Paul Chappuis, Ph.D./Global Project Leader
Denis Gross, Pharm.D., Ph.D./Head of Regulatory Affairs Project Group
Allen Fields, M.ED, M.S./Director of Regulatory Submissions Galderma R&D

Purpose:

To evaluate the drug development program to date and discuss the Phase 3 plan and protocols for Ivermectin 1% Cream for the topical treatment of inflammatory lesions of papulopustular rosacea.

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Concurrence is sought that all excipients of the formulation of CD5024 1% Cream that will be used in the Phase 3 program are qualified for use at the proposed levels in topical drug products in the US, in particular polyoxyl 20 cetostearyl ether (also known as cetareth 20), dimethicone ^{(b) (4)} and phenoxyethanol.

Response:

The Agency agrees.

Question 2:

Concurrence is sought that the dosage form is a cream, according to the CDER definition for topical dosage form (Revision June 21st, 2006).

Response:

There is not enough information for the Agency to comment on the dosage form at this time. You should submit a representative sample of the drug product from a batch made at the designated commercial manufacturing site for our review as soon as possible if not submitted at the meeting.

Meeting Discussion

The sponsor submitted drug product samples for the proposed Phase 3 trials for review to determine whether the Agency concurs with the dosage form.

Question 3:

Concurrence is sought that limits of impurities in the drug product set out in the specification are appropriate for Phase 3 studies and for future commercial batches.

Response:

The specification for the drug product impurities is adequate for Phase 3 studies. Whether it is adequate for NDA approval is a review issue.

Question 4:

In consideration of (1) the current knowledge on the stability profile of the drug product and (2) the ongoing and planned stability programs on both pilot batches manufactured at the subcontractor site and representative batches manufactured at the commercial site, concurrence is sought that this information package will be suitable as a prerequisite to the Phase 3 program.

Response:

We concur.

Pharmacology/Toxicology

Question 1:

Considering that:

- the drug substance CD5024 and the drug product CD5024 1% Cream do not absorb light in the 290 to 800 nm range of wavelengths,
- CD5024 was not photogenotoxic in vitro,

- topical CD5024 1% Cream was not phototoxic in a guinea pig model although equivocal results were obtained in a photosensitization assay in the same species, and
- topical CD5024 1% Cream did not induce any skin adverse effect when administered along with simulated sunlight in a 13-week dose-range finding photocarcinogenicity study in the hairless mouse,

Concurrence is sought that there is no need to perform a photo(co)carcinogenicity study on CD5024 1% Cream.

Response:

No, we do not agree. Since the drug product will be used chronically on sun-exposed skin, data from a study to determine the photo co-carcinogenic potential associated with ivermectin cream should be included with an NDA submission (refer to the “Guidance for Industry – Photosafety testing” guidance document).

Question 2:

CD5024 was reported to be excreted in milk in several animal and human studies. In addition, published pre- and post-natal studies in the rat have demonstrated very high sensitivity of pups from lactating females receiving CD5024 orally due to their immature blood brain barrier. Thus, breastfeeding will be part of the exclusion criteria of the Phase 3 program and the use of CD5024 1% Cream will be therefore contraindicated during lactation in the future labeling. Under these conditions, it is the Sponsor's view that performing a pre- and post-natal development study with CD5024 in rats is unnecessary. The Sponsor requests the Agency's position in this respect.

Response:

No, we do not agree. A peri- and post-natal development study should be conducted with ivermectin according to ICH guidelines set forth in the ICH-S5A and ICH-S5B guidance documents. The recommended timing for conduct of this nonclinical reproductive and developmental toxicology study is outlined in the ICH M3 guidance document. However, it might be possible to provide adequate literature data to address this issue. You should submit appropriate literature references to address the peri- and post-natal development effects of ivermectin to the IND for review. If you decide to rely on literature data to address the need for a peri- and post-natal development study, then the NDA would be a 505(b)(2) NDA submission and not a 505(b)(1) NDA submission.

It is noted that you are currently conducting an oral rodent fertility study with ivermectin. The adequacy of this study will be determined after review of the study report.

Meeting Discussion

The sponsor stated that they will submit data to address peri- and post-natal developmental toxicity to the IND.

The Agency reiterated that relying on literature would make the application a 505(b)(2).

Question 3:

Concurrence is sought that (1) the current nonclinical safety data package on CD5024 1% Cream supports the initiation of a clinical Phase 3 program and (2), the complete nonclinical safety data package proposed by the Sponsor will be adequate for the sake of a New Drug Application.

Response:

No, we do not agree. A few deficiencies were identified after review of the original IND submission. In addition, refer to the response provided for question 1.

The vehicle related effects noted in the in vivo cardiovascular and pulmonary safety pharmacology study and the possible interaction of anesthesia and ivermectin make it impossible to determine the effects of ivermectin on cardiac and/or pulmonary parameters in the study that was included in the original IND submission. The pulmonary and cardiovascular safety pharmacology studies should be repeated in unanesthetized animals and use a vehicle that does not cause pulmonary and/or cardiovascular effects. In addition, you should conduct an in vitro study to evaluate the potential for delayed ventricular repolarization (QT interval prolongation) associated with ivermectin (refer to ICH-S7A and ICH-S7B guidance documents). These study reports should be submitted to the IND for evaluation prior to initiation of Phase 3 clinical studies.

It is noted that conduct of an in vitro hERG assay is ongoing to support Phase 3 clinical studies. This study should be submitted to the IND as soon as possible. You make reference to an ongoing study being conducted in conscious dogs with ivermectin that evaluates cardiovascular parameters and a 9 month dog study conducted with ivermectin that evaluated cardiovascular parameters in the briefing package. The study reports for these studies should be submitted to the IND for evaluation.

The Division considers the finding of carpal flexure noted in the oral rabbit embryofetal development study conducted with ivermectin as a malformation. The statement provided by the conducting contract lab that this carpal flexure should not be considered a malformation since no underlying skeletal alterations could be identified and that they believe this would correct itself during development needs to be supported by submission of actual data to support this statement. Therefore, the increased litter proportion of carpal flexure in the high dose group of the oral rabbit embryofetal development study conducted with ivermectin is considered a malformation and significant.

The preclinical signals observed raise concern about risks for women of childbearing potential who would be enrolled in Phase 3 trials. Data from a PK study conducted under "maximal use conditions" are needed, prior to initiation of Phase 3 trials, to inform about the risks for women of childbearing potential. Also see clinical pharmacology/ biopharmaceutics comments below.

It is noted that a 6 month oral rat toxicology study with ivermectin and a 9 month dermal minipig toxicology study with ivermectin cream are currently ongoing based on the information provided in the briefing document. Study reports for both these studies should be included with the NDA submission. The adequacy of these studies will be determined after review of the study reports.

It is noted that a dermal mouse carcinogenicity study and an oral rat carcinogenicity study are currently ongoing based on the information provided in the briefing document. Study reports for both these studies should be included with the NDA submission. The adequacy of these studies will be determined after review of the study reports.

Meeting Discussion

The sponsor stated that they consider carpal flexure as a variation and not a malformation. They will submit data from the contract lab to support their position.

The Agency indicated that these data impact Phase 3 trials and the issue needs to be resolved prior to initiation of Phase 3.

Clinical Pharmacology/Biopharmaceutics

Question 1:

The Sponsor demonstrated that the pharmacokinetic behavior of CD5024 observed upon topical application of CD5024 1% Cream is similar in healthy volunteers and in patients with rosacea. This behavior is consistent with a slow release of CD5024 from the skin and the absence of CD5024 accumulation in a deeper body compartment. The plasma steady-state is reached after 4 weeks of topical administration with no evidence of plasma accumulation over a 12-week topical treatment. Therefore, the Sponsor seeks agreement that no further pharmacokinetic studies are required to support the pharmacokinetic profile of CD5024 1% Cream applied once daily in patients.

Response:

No, we do not agree. We have the following comments

We acknowledge the information you have provided on the pharmacokinetic studies conducted in healthy volunteers and trough concentrations in patients with rosacea, however, we are unable to determine whether this information adequately addresses the pharmacokinetic differences between healthy volunteers and rosacea patients with the upper level of disease severity.

In addition, it is not clear whether the formulations used in the pharmacokinetic studies are the same as the to-be-marketed formulation.

Please note that for topical drug products, the pharmacokinetic (i.e. of parent and active metabolite) study should be conducted with the to-be-marketed formulation under “maximal use conditions” (i.e. maximal body surface area, maximal frequency of use, and maximal dose) in the patients with rosacea towards the upper level of severity, that is consistent with your clinical trials and the proposed labeling of your drug product.

Generally, it is preferable to conduct the maximal use PK study prior to conducting the Phase 3 clinical trials because this information can be helpful in guiding the design of the trials. In your particular development program, obtainment of such PK data prior to Phase 3 will be essential, as information regarding systemic exposure will help determine whether women of child bearing potential will need to use contraception during the pivotal trials.

Meeting Discussion

The Agency requested data to support the sponsor’s claim that there is no significant difference between the to-be-marketed formulation and the formulation used in the PK studies.

The Agency reiterated that the study design (e.g. the severity of disease) should be consistent with the proposed clinical studies.

Question 2:

Considering (1) results of in vitro metabolism and drug interaction studies carried out with CD5024 and (2), plasma concentrations found after topical application of CD5024 1% Cream in healthy volunteers and in patients, it is concluded that chronic topical application of CD5024 1% Cream has no

potential to cause clinically significant drug-drug interactions, even using conservative assumptions. Therefore the Sponsor deems that it is unnecessary to perform further metabolism or drug-drug interaction studies. Does the Agency concur with this proposal?

Response:

No, we do not concur with this proposal. We have the following comments:

Based on the summary of the findings of your in vitro metabolism studies provided in the briefing package, you indicated that the in vitro studies identified CYP3A4 as the major pathway responsible for the metabolism of your drug. In addition, your drug demonstrated inhibition of CYP3A4. The results also suggested that under the experimental in vitro conditions, your drug is converted to a metabolite that is a more potent inhibitor of CYP3A4 than the parent drug. However, it appears that the metabolite may not be well characterized (potency, contribution to efficacy and/or safety). Therefore, there are some unresolved issues with regards to the metabolic fate of the metabolite since you stated that it is a potent inhibitor of CYP3A4.

We recommend that you resolve the issues (e.g. its metabolic fate) involving the metabolite that was identified as being a more potent inhibitor of CYP3A4 than the parent drug. In addition, you may need to investigate this metabolite further (e.g. by conducting in vitro metabolic drug interactions).

One venue you may wish to explore is conducting a relative bioavailability study between the oral immediate-release tablet and the topical formulation in severe disease patients. If the bioavailability of the topical formulation (applied to severe rosacea patients) is much less than the oral immediate-release formulation, some of your pharmacokinetic obligations may be resolved depending on the findings.

Meeting Discussion

The Agency requested that the sponsor submit the information summarized during the meeting to the IND for review.

Clinical

Question 1:

The Sponsor proposes a waiver to conduct an additional standard Repeated Insult Patch Test (RIPT) since the drug product is almost identical to the tested product with the exception of a slightly greater concentration of parabens.

Response:

You state that, "...no major signs of irritancy or sensitization were identified with formulation No.0575.755 applied under maximized conditions in over 200 subjects." The higher concentration of total parabens in formulation 575.754 would likely result in a higher rate of sensitization. How would you propose to address this in labeling? Submit your request for waiver, along with rationale, to the IND.

Meeting Discussion

The sponsor stated that they do not intend to include the results of the RIPT study in labeling and plan to submit a request for a waiver, along with rationale.

Question 2:

The Sponsor seeks concurrence that the dose-response relationship of CD5024 and the suitability of the dose regimen have been properly demonstrated in the Phase 2 dose-ranging study. On the basis of these results, the Sponsor proposes to continue the development of CD5024 1% Cream with the Phase 3 program addressed in the following questions.

Response:

Dose should be investigated for safety and efficacy across a range of doses, bracketing response. Your choice of the 1% cream used QD appears to be appropriate.

Question 3:

The Phase 3 program will include two adequate and well-controlled efficacy and safety trials of identical design. Concurrence is sought on the suitability of the proposed study design for the claimed indication. In particular, the Sponsor seeks concurrence that the proposed study population, inclusion/exclusion criteria, and efficacy co-primary endpoints will support the indication of topical treatment of inflammatory lesions of papulopustular rosacea.

Response:

The population proposed in Phase 3 (subjects with an IGA score of 3 or 4, with 15 to 70 inflammatory lesions, and with no more than two nodules) is acceptable. The population studied will be reflected in labeling.

The design involves demonstration of superiority of CD5024 1% cream over vehicle over a 12 week treatment period.

The proposed co-primary endpoints are:

- Success rate based on IGA score, defined as the percentage of subjects who achieve at least a 2-grade improvement, from Baseline to Week 12 (ITT-LOCF)
- Percentage change in inflammatory lesions from baseline to week 12 (ITT-LOCF)

Success should be defined as those who are clear or almost clear on the IGA; this will represent a 2 grade improvement for all subjects and is inherently clinically meaningful. On the IGA scale, "0" should represent true absence of disease, without erythema. The clinical significance of your definition of success, subjects who achieve a 2-grade improvement from baseline, has not been established.

The Division recommends using absolute change in lesion count as a co-primary endpoint instead of percent change. The reason for this recommendation is that the absolute change is expected to have less extreme outliers compared to the percent change and the distribution of the absolute change is expected to be closer to meeting the normality assumptions.

The proposed secondary endpoint is:

-  (b) (4)

Additional comments:

Washout periods should be sufficient to ensure that prior treatments will not impact baseline disease assessment. Two weeks is not sufficient for corticosteroids or immunomodulators, which can cause drug induced rosacea, recovery from which takes longer than two weeks. Two weeks may also be insufficient for topical antibiotics, anti-rosacea drugs, and retinoids. Safety monitoring should include active assessment for local cutaneous reactions, such as but not limited to, burning, scaling, and itching.

Meeting Discussion

The sponsor agreed that zero on the IGA scale will not include erythema.

The sponsor discussed how lesion counts will be analyzed. The sponsor will submit this information to the IND for review.

Addendum

Please submit the information above with the final Phase 3 protocol.

Question 4:

The Phase 3 program will include a one-year open label long-term safety study. Concurrence is sought on the suitability of the proposed study design according to the recommendations of ICH E1A guideline.

Response:

Planned safety monitoring includes physical examination, vital signs, laboratory work (hematology and chemistry), and recording of adverse events. Urine pregnancy testing will be performed at screening, baseline, and end of study.

Safety monitoring should also include active assessment for local cutaneous reactions.

If the long term safety study involves continuous dosing or has very short rest periods between dosing intervals, then sufficient nonclinical chronic toxicology studies would need to be completed and submitted for evaluation to the IND prior to initiation of the long term safety study.

Meeting Discussion

The sponsor stated that they will submit the long term nonclinical data prior to chronic dosing in clinical studies.

Question 5:

The Sponsor seeks concurrence that the proposed overall clinical development program, and in particular the type of studies and number of subjects exposed, will be appropriate to support the filing

of a New Drug Application for CD5024 1% Cream in the topical treatment of inflammatory lesions of papulopustular rosacea.

Response:

You propose to establish safety and efficacy in two, randomized, vehicle-controlled studies. Long term safety will be examined in a 52 week, open-label study.

Please address the following:

1) Cardiac safety monitoring:

In the absence of a thorough QT/QTc study demonstrating no effect on cardiac repolarization (or a definitive PK study demonstrating no systemic exposure under maximum use conditions in diseased subjects), ECG monitoring should be performed to ensure subject safety, at a minimum at baseline, when drug concentration has reached steady state, and at end of treatment.

2) Topical safety studies:

It appears that you have no plan to complete a photoallergenicity study. Photoallergenicity should be studied in not less than 50 evaluable subjects.

If there is no absorption in the UVB, UVA, or visible light spectrum, you may request a waiver for the photoallergenicity study.

3) Teratogenic risk:

The preclinical signals observed raise concern about risks for women of childbearing potential who would be enrolled in Phase 3 trials. Data from a PK study conducted under “maximal use conditions” are needed to determine the teratogenic risk for women of childbearing potential.

Meeting Discussion

The sponsor proposed conducting ECG monitoring on a subset of patients.

The Agency responded that in the absence of demonstration of lack of effect of their product on cardiac repolarization, ECG monitoring of all subjects would be needed.

Biostatistics

These questions pertain to the Phase 3 vehicle-controlled efficacy/safety trials:

Question 1:

Concurrence is sought that the sample size justification is adequate.

Response:

Your sample size calculation, based on your assumptions – success rates on IGA and treatment effect on absolute change in lesion counts – appears to be adequate.

Question 2:

Concurrence is sought that the planned methods for the co-primary endpoints and the associated per-protocol and sensitivity analyses to assess robustness are adequate.

Response:

- Imputation of all missing Investigator's Global Assessment (IGA) observation is expected to be very similar to that of last observation carried forward (LOCF). We recommend that you propose another sensitivity analysis, such as imputing all missing values in the IGA as "successes".
- The protocol should include a specific sensitivity analysis in case the center by treatment interaction is significant, to ensure that efficacy results are not driven by extreme centers. For example, evaluate efficacy after deleting extreme centers.

Question 3:

Concurrence is sought regarding multiplicity and Type I Error Control.

Response:

We agree with your justification of not needing multiplicity adjustment.

Question 4:

Concurrence is sought regarding the handling of small centers.

Response:

Your proposed method of handling small centers seems to be appropriate.

Additional 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. You are 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. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
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.

6. In response to a final rule published February 11, 1998, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data “by gender, age, and racial subgroups” in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this demographic analysis.
7. 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.
8. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
9. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

Minutes Preparer: _____
Tamika White/Regulatory Project Manager, DDDP, HFD-540

Chair Concurrence: _____
Susan J. Walker, M.D./Division Director, DDDP, HFD-540

Linked Applications

Sponsor Name

Drug Name

IND 76064

GALDERMA RESEARCH AND DEVELOPMENT CD5024

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

/s/

SUSAN J WALKER

03/26/2008



Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs

FACSIMILE TRANSMITTAL SHEET

DATE: January 25, 2007

To: Clarisse Stone, Ph, RAC	From: Adele Seifried
Company: Galderma R&D Inc.	OND IO
Fax number: (609) 409-7704	Fax number: 301-796-9855
Phone number: (609) 860-8218	Phone number: 301-796-0535

Subject: Response to Carcinogenicity Special Protocol Assessment Request - Final CAC Report - IND 76,064

Total no. of pages including cover: 7

Comments:

Document to be mailed: ☐ YES ☒ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0535. Thank you.

Executive CAC**Date of Meeting:** January 23, 2007

Committee: David Jacobson-Kram, Ph.D., OND IO, Chair
Joseph Contrera, Ph.D., OPS, Member
Bayo Laniyonu, Ph.D., DMIHP, Alternate Member
Paul Brown, Ph.D., DDDP, Pharm Tox Supervisor
Barbara Hill, Ph.D., DDDP, Presenting Reviewer

Author of Draft: Barbara Hill

The following information reflects a brief summary of the Committee discussion and its recommendations.

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassay, as this does not affect the sponsor's ability to initiate the bioassay. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following section E of the 'Guidance for Industry, Providing Regulatory Submission in Electronic Format, New Drug Application.'

IND# 76,064

Drug Name: Ivermectin cream

Sponsor: Galderma Research & Development Inc, Cranbury, NJ

Background:

Ivermectin is a semisynthetic, anti-parasitic agent derived from avermectins, a class of broad-spectrum anti-parasitic agents. The sponsor has proposed to develop ivermectin cream, 1% for the treatment of papular pustular rosacea. An oral rat carcinogenicity study protocol and a dermal mouse study protocol, along with supporting studies, were submitted to the IND with a request for Special Protocol Assessment.

Oral (Gavage) Rat Carcinogenicity Study Protocol and Dose Selection:

Species/strain: Rats/Wistar

Number/sex/dose: 72/sex/dose for main study animals
9/sex/dose for toxicokinetic animals

Duration: 104 weeks

Route: Oral (gavage)

Dose volume: 2.5 ml/kg/day

Doses proposed: 0 (vehicle control), 0.1, 1, 9 mg/kg/day ivermectin

Vehicle: 0.5% methylcellulose

Dosing procedure: Test article will be administered daily, seven days/week for 104 weeks.

Justification for Dose Selection:

Dose selection proposed by the sponsor was based on the results of a three month oral (gavage) rat dose range finding study. Oral (gavage) doses of 0, 1, 3, 9 and 12 mg/kg/day ivermectin (dose volume = 2.5 ml/kg/day) were administered to Wistar rats for 90 days. The vehicle used in this study was 0.5% carboxymethylcellulose.

Treatment related mortality was noted in the mid-high and high dose groups during the first two weeks of treatment. Two mid-high dose females, four high dose males and seven high dose females were sacrificed moribund due to severe clinical signs, body weight loss and decreased food consumption.

Treatment related effects on clinical chemistry parameters (increased glucose, cholesterol and ALP levels and decreased triglyceride levels) were noted in the mid-high and high dose groups compared to the control group at the end of the treatment period. A dose dependent decrease in seminal vesicle weight was noted in mid-low, mid-high and high dose males (decrease of 19% to 30%) compared to control males. Increased liver weights (increase of 8 to 15%) were noted in mid-high and high dose animals compared to control animals. Treatment related histopathological effects in the seminal vesicles (decreased secretion) and prostate (decreased secretion) were noted in mid-low, mid-high and high dose males. A treatment related minimal to slight apoptosis was noted in mid-low, mid-high and high dose animals.

The NOAEL was identified as 1 mg/kg/day ivermectin in rats after oral administration for 3 months, under the conditions of this study.

The sponsor stated that the 9 mg/kg/day ivermectin dose should be considered as the maximum tolerated dose (MTD) since treatment related mortality associated with severe clinical signs occurred during the first two weeks of dosing, involving 12.5% of the female rats receiving 9 mg/kg/day and 25% of males and 44% of females receiving 12 mg/kg/day. After two weeks of dosing, stained or soiled fur was the only persistent clinical sign of toxicity in animals treated at 9 and 12 mg/kg/day. Based on the results of the 3 month oral rat toxicology study conducted with ivermectin, it appears that the initial two week period is the time period of most concern for mortality. Rats appear to develop a tolerance after the initial 2 week treatment period.

The sponsor has proposed to increase the number of animals per group in the oral rat carcinogenicity study to 72/sex/dose to counterbalance the early mortality noted in the 3 month oral rat toxicology study. This proposal appears acceptable since the surviving female rats appeared to recover completely with continued dosing at the 9 mg/kg/day dose in the 90 day oral rat toxicology study. Therefore use of 9 mg/kg/day ivermectin as the high dose group with an increase in the number of rats per group to 72/sex/group in the oral rat carcinogenicity study appears acceptable.

Dermal Mouse Carcinogenicity Study Protocol and Dose Selection:

Species/strain: CD-1 mice
Number/sex/dose: 65/sex/dose for main study animals
18/sex/dose for low, mid and high dose toxicokinetic animals; 6/sex/group for water and vehicle control groups

Duration: 104 weeks
Route: Topical
Dose volume: 1 ml/kg/day
Doses proposed: 0 (water control), 0 (vehicle control), 0.3 (0.03%), 3 (0.3%) and 10 (1%) mg/kg/day ivermectin cream

Vehicle: Clinical vehicle

Dosing procedure: Test article will be administered topically (unoccluded), seven days/week for 104 weeks.

Justification for Dose Selection:

Dose selection proposed by the sponsor was based on the results of a three month dermal mouse dose range finding study. Dermal doses of 0, 1, 3 and 10 mg/kg/day (0, 0.1%, 0.3% and 1% ivermectin cream; dose volume = 1 ml/kg/day) were administered to CD-1 mice for 90 days. The vehicle used in this study was the clinical vehicle.

No treatment related toxicity was noted in this study. The NOAEL was identified as 10 mg/kg/day (1% ivermectin cream; dose volume = 1 ml/kg/day) in mice after topical administration for 3 months, the highest dose evaluated in this study.

The results of the 3 month dermal mouse toxicology study conducted with ivermectin cream indicated that 1% ivermectin cream (the maximum feasible concentration) at a dose volume of 1 ml/kg/day should be tolerated as the high dose group in a dermal mouse carcinogenicity study. The sponsor stated that the 1% ivermectin cream at a dose volume of 1 ml/kg/day is the MTD since a previously conducted dermal mouse dose range finding study demonstrated that severe systemic toxicity (including mortality) was noted with topical administration of the 1% ivermectin cream at a dose volume of 2 ml/kg/day. It appears that topical administration of the 1% ivermectin cream at a dose volume of 2 ml/kg/day would not be tolerated as the high dose group in a dermal mouse carcinogenicity study. Therefore, use of the 1% ivermectin cream at a dose volume of 1 ml/kg/day as the high dose group in the dermal mouse carcinogenicity study appears acceptable.

Executive CAC Recommendations and Conclusions:

Oral (Gavage) Rat Carcinogenicity Study Protocol

- 1) The Committee proposed the following doses for the oral rat carcinogenicity study: 0 (vehicle control), 1, 3 and 9 mg/kg/day ivermectin based on MTD (mortality and severe clinical signs).
- 2) The Committee noted that the planned hematology and toxicokinetic evaluation is not necessary for this study.
- 3) The sponsor should notify the agency if there is excessive mortality prior to changing dosing or terminating any animals.
- 4) If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:
 - (a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups
 - (b) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
 - (c) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
 - (d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

Dermal Mouse Carcinogenicity Study Protocol

- 1) The Committee proposed the following doses for the dermal mouse carcinogenicity study: 0 (untreated control), 0 (vehicle control), 1 (0.1%), 3 (0.3%) and 10 (1%) mg/kg/day ivermectin cream (dose volume = 1 ml/kg/day) based on MTD (mortality).
- 2) The Committee noted that the planned hematology and toxicokinetic evaluation is not necessary for this study.
- 3) The sponsor should notify the agency if there is excessive mortality prior to changing dosing or terminating any animals.
- 4) If the sponsor plans histological evaluation of tissues from only control and high dose treatment groups, they will also need to conduct histopathologic examination of other dose groups under any of the following circumstances:
 - (e) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the dose groups

- (f) for an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, they will also need to look at the next lower dose group
- (g) for an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g., hemangiosarcoma, lymphoma etc.; see McConnell et al, JNCI 76:283, 1986) they should look at all relevant tissues for that dose level and the next lower dose level,
- (h) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\

- /Division File, DDDP
- /P. Brown/Supervisor, DDDP
- /B. Hill/Reviewer, DDDP
- /V. Lutwak/Project Manager, DDDP
- /A. Seifried, OND IO

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

/s/

David Jacobson-Kram
1/25/2007 01:55:46 PM