CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207589Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 207589 SUPPL # HFD # 540

Trade Name Enstilar

Generic Name (calcipotriene and betamethasone dipropionate) Foam, 0.005%/0.064%

Applicant Name LEO Pharma A/S

Approval Date, If Known October 16, 2015

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)(1)

b) 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:

N/A- Original Application

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

Yes

d) 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#

NDA#

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# 021852	Taclonex (calcipotriene and betamethasone dipropionate) Ointment, 0.005%/0.064%
NDA# 022185	Taclonex (calcipotriene and betamethasone dipropionate) Topical Suspension, 0.005%/0.064%
NDA# 020554	Dovonex (calcipotriene) Cream, 0.005%
NDA# 018741	Diprolene (betamethasone dipropionate) Ointment, 0.05%

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:

1. Study LP0053-1001 A Multicenter, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled, Phase 3 Trial
2. Study LEO 90100-7 A Multicenter, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Phase 2 Trial

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 LP0053-1001 YES ☐ NO ☒

Investigation #2 LEO 90100-7 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:

N/A

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 LP0053-1001 YES ☐ NO ☒

Investigation #2 LEO 90100-7 YES ☐ NO ☒

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

N/A

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"):

1. Study LP0053-1001 A Multicenter, Randomized, Double-Blind, Parallel-Group, Vehicle-Controlled, Phase 3 Trial
2. Study LEO 90100-7 A Multicenter, Double-Blind, Randomized, Parallel-Group, Active-Controlled, Phase 2 Trial

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 # 114063 YES ☒ ! NO ☐
! Explain:

Investigation #2 !
!
IND # 114063 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: Dawn Williams
Title: RPM
Date: October 5, 2015

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

DAWN WILLIAMS
10/16/2015

JILL A LINDSTROM
10/16/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 207589 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Enstilar Established/Proper Name: calcipotriene and betamethasone dipropionate Dosage Form: Foam		Applicant: LEO Pharma A/S Agent for Applicant (if applicable): LEO Pharma Inc.
RPM: Dawn Williams		Division: DDDP

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)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is October 16, 2015	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ 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	☐ Received
❖ 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.

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

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

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager; Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other require actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ 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

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

Comments:

❖ 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
❖ 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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) October 16, 2015 Approval Letter
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☒ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☒ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	August 12, 2015 Proprietary Name Acceptable Letter; August 6, 2015 Proprietary Name Review
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: ☐ None August 6, 2015 DMPP/PLT (DRISK): ☐ None August 20, 2015 OPDP: ☐ None August 26, 2015 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☐ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	March 25, 2015 ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

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

• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC September 2, 2015 If PeRC review not necessary, explain: _____	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ 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, Formal Dispute Resolution Request decisional letters, etc.) *(do not include previous action letters, as these are located elsewhere in package)*	May 28, 2015 Information Request; March 2, 2015 No Filing Issues Identified
❖ 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)	Email dated September 29, 2015 entitled, "Enstilar PI"
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg March 26, 2014
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg June 19, 2013 (CMC Only); May 15, 2013
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None October 16, 2015
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None September 16, 2015
PMR/PMC Development Templates *(indicate total number)*	☐ None 2
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
• Clinical review(s) *(indicate date for each review)*	September 16, 2015; February 6, 2015 Filing Review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ 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 *(indicate date of review/memo)*	Page 21 of September 16, 2015 Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested August 27, 2015 Clinical Inspection Summary; August 25, 2015 VAI Letter; August 19, 2015 VAI Letter
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Statistical Review(s) *(indicate date for each review)*	☐ None September 2, 2015; February 6, 2015 Filing Review
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ No separate review
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None August 20, 2015; February 3, 2015 Filing Review
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None July 7, 2015; February 4, 2015 Filing Review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None October 13, 2015 Addendum to September 1, 2015 Review; September 1, 2015; February 5, 2015 Filing Review
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	Page 3 of February 5, 2015 Filing Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☒ Facilities inspections (*action must be taken prior to the re-evaluation date*) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable Re-evaluation date: ☐ Withhold recommendation ☐ Not applicable

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 *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ 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 *Application Product Names* 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

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/s/

DAWN WILLIAMS
10/19/2015

From: Beitzell, Debra
To: Xu, Nancy; Lindstrom, Jill
Cc: Brodsky, Eric
Subject: RE: Enstilar PI
Date: Tuesday, September 29, 2015 1:22:22 PM

Hi Nancy and Jill,

In general, (b) (4) does not recommend inclusion of negative data pertinent to a W&P because it minimizes the W&P and provides an inconsistent message to the healthcare provider (i.e., negative data are provided, yet the W&P includes clinical recommendations to manage the (b) (4)).

Regarding HPA axis suppression:

Are the negative HPA axis suppression data reflective of the patient population likely to use Enstilar and is the size of study large enough to detect a difference? If not, (b) (4) does not recommend including these data in the labeling. Consider the following options:

- If the negative PD data are **not** considered to be reflective of the indicated patient population and of sufficient size to detect a difference:
  - Remove the negative PD data from (b) (4) and retain the W&P as written.
- If the negative PD data are determined to be reflective of the indicated patient population and of sufficient size to detect a difference:
  - Remove the W&P and include HPA axis suppression as (b) (4) (b) (4)
  - If the team wants to retain the W&P, include the negative data in the W&P and add clarifying information as to why the risk of HPA axis suppression with use of Enstilar still exists (e.g., when used over large areas, with higher doses).

Regarding hypercalcemia/hypercalciuria:

Inclusion of negative PD data pertinent to hypercalcemia/hypercalciuria while including positive data from the Phase 3 trial and having a W&P for these adverse reactions, provides an inconsistent message and may be misleading. (b) (4) recommends that the review team consider whether the Phase 3 trial data are more representative of the true risk of these adverse reactions. If so, (b) (4) recommends removal of the negative PD data.

If you have any questions, or would like to discuss these issues, please let me know.

Thanks,
Debbie

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/s/

NANCY XU
10/16/2015

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207589

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

LEO Pharma A/S
c/o LEO Pharma Inc. (U.S. Agent)
1 Sylvan Way
Parsippany, NJ 07054

ATTENTION: Lori A. Palmer
Senior Director, U.S. Regulatory Affairs

Dear Ms. Palmer:

Please refer to your New Drug Application (NDA) dated and received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Calcipotriene and Betamethasone Dipropionate Foam, 0.005% and 0.064%.

We also refer to your correspondence, dated and received May 29, 2015, requesting review of your proposed proprietary name, Enstilar.

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

If any of the proposed product characteristics as stated in your May 29, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017, (http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Dawn Williams, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DARRELL A JENKINS
08/12/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207589

INFORMATION REQUEST

LEO Pharma A/S
c/o LEO Pharma, Inc.
Attention: Lori Palmer
Director, US Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Palmer:

Please refer to your New Drug Application (NDA) dated and received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enstilar (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064%.

We are reviewing the nonclinical and clinical pharmacology sections of your submission and have the following comments and information requests. We request a prompt written response by June 12, 2015, in order to continue our evaluation of your NDA.

1. Under NDA 207589 your proposed acceptance criteria for organic impurities associated with calcipotriene in LEO 90100, [redacted] (b) (4) [redacted] (b) (4) %), any unspecified impurity [redacted] (b) (4) %) and total impurities (≤ [redacted] (b) (4) %), are much higher than those specified under NDA 021852. The results of batch analyses submitted to NDA 207589 (3.2.P.5.4) appear to suggest that the levels of impurities observed in batches of LEO 90100 do not exceed the specification limits for impurities set in NDA 021852. In general, acceptance criteria for impurities are expected to reflect consideration of the minimum levels that are consistent with legitimate manufacturing and marketing concerns, as well as the applicable guidances and regulations. Explain why the proposed acceptance criteria for organic impurities associated with calcipotriene in the drug product of NDA 207589 cannot be set at levels similar to NDA 021852.

2. Regarding qualification of impurities, the portion of NDA 207589 entitled [redacted] (b) (4) [redacted] (b) (4). LEO 90100 [redacted] (b) (4) foam, Toxicological Qualification of Impurities [redacted] (b) (4) and [redacted] (b) (4) LEO Pharma A/S, Preclinical Development. September 16, 2014", states that several lots of calcipotriene used in nonclinical studies contained relatively high

concentrations of [redacted] or [redacted]. For example, that document includes statements such as (with editing):

"No repeated dose toxicity study has been performed with [redacted]. However, [redacted] was included in batches for toxicological testing of [redacted] in concentrations up to [redacted] % for repeated oral (10) and dermal (11) toxicity…in rats."

The certificates of analysis (COAs) of the test materials associated with some of the studies that were referenced by [redacted] do not appear to support those claims (i.e., for some of the nonclinical studies mentioned, the COAs that could be located do not appear to indicate the presence of specific impurities within the test material). Please verify which repeated-dose toxicity studies conducted with calcipotriene involved test materials that contained substantial quantities of relevant specific impurities, and submit adequate documentation to confirm the levels of those impurities that were present in those test materials.

3. The recommended design for the vasoconstrictor assay for the purpose of determining the topical corticosteroid potency is to conduct single point visual assessment of vasoconstriction at 2 hours, following 16 hour application of the test formulation under non-occlusive conditions. [redacted]

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

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, MD
Cross Discipline Team Leader
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

GORDANA DIGLISIC
05/28/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207589

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

LEO Pharma A/S
c/o LEO Pharm Inc.
Attention: Lori Palmer
Director, US Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Palmer:

Please refer to your New Drug Application (NDA) dated and received December 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Enstilar® (calcipotriene and betamethasone dipropionate) foam, 0.005%/0.064%.

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.

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 8, 2015.

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

1. Your application describes a product that is intended for multiple uses. According to USP <51>, multi-use products must either contain an antimicrobial preservative, or demonstrate that they are self-preserving. Provide a summary of antimicrobial effectiveness studies performed with the drug product. This summary should include a

description of test methods and results. You are encouraged to consult USP <51> for suggested test methods.

2. It is unclear from your application whether you plan to perform microbial limits testing on the (b) (4), prior to formulation of the final drug product. Clarify whether this testing will be performed.

3. You describe microbial limits testing performed on the (b) (4) as well as the final drug product, using methods described in USP <61> and USP <62>. Describe the results of method verification studies performed using the (b) (4) and the drug product.

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 by March 30, 2015:

1. We recommend that you develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for your drug product to be used systemically at release and during stability testing as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data to support your proposed acceptance criteria.

2. Along with the proposed in vitro release specification, include the IVRT method development and validation report. The IVRT method development report should contain, but not be 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

3. The IVRT method validation report should contain, but is not limited to the following validation components:

    a. Linearity and Range

    b. Accuracy/Precision and Reproducibility

    c. Mass Balance

    d. Sensitivity and Specificity

    e. Selectivity

    f. Robustness

    g. Membrane Inertness

    h. Receptor Solution Solubility/Stability

4. The IVRT method's sensitivity, specificity, selectivity and robustness need to be evaluated 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.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.

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), patient PI, and Instructions for Use. 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), patient PI, and Instructions for Use, 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.

Pediatric studies conducted under the terms of section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) may also qualify for pediatric exclusivity under the terms of section 505A of the Act. If you wish to qualify for pediatric exclusivity please consult the Division of Dermatology and Dental Products. Please note that satisfaction of the requirements in section 505B of the Act alone may not qualify you for pediatric exclusivity under 505A of the Act.

We reference the partial waiver granted on December 3, 2013, for the pediatric study requirement for this application for pediatric patients 0 to 11 years 11 months.

We reference the partial deferral granted on December 3, 2013, for the pediatric study requirement for this application for pediatric patients 12 years to 16 years 11 months.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

KENDALL A MARCUS
03/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114063

MEETING MINUTES

LEO Pharma A/S
c/o LEO Pharma, Inc.
Attention: Lori Palmer
Director, US Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Palmer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (calcipotriene and betamethasone dipropionate) topical foam, 0.005%/0.064%.

We also refer to the teleconference between representatives of your firm and the FDA on March 26, 2014. The purpose of the meeting was to discuss the content and format of your proposed NDA submission.

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 Dawn Williams, Regulatory Project Manager, at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA Meeting

Meeting Date and Time: March 26, 2014; 8:30 am

Application Number: IND 114063
Product Name: (calcipotriene and betamethasone dipropionate) topical foam, 0.005%/0.064%
Proposed Indication: Treatment of psoriasis (b) (4)
Sponsor Name: LEO Pharma A/S

Meeting Chair: Gordana Diglisic, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES
Amy Egan, MD, MPH, Acting Deputy Director, ODE III
Stanka Kukich, MD, Deputy Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Norman See, PhD, Pharmacology Reviewer, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matt Guerra, PhD, Biostatistics Reviewer, DB III
Roy Blay, PhD, Good Clinical Practice Assessment Branch, OSI

SPONSOR ATTENDEES
Lori Palmer, Director, US Regulatory Submissions
Malene Kjær Müller, MSc, Senior Director, US Regulatory Affairs
Thomas Helboe, MSc, PhD, Asset Director, Project Management
Martin Oleson, MD, PhD, Principal Medical Advisor, Medical Department
Monika Rosén, PhD, Senior Medical Writer, Medical Documentation
Lisbet Wreghitt, MSc, Clinical Focus Team Leader, Clinical Project Management
Claus Bay, MSc, Head, Biostatistics and Data Management
Charlotte Devantier Jensen, MSc, PhD, Pharmacovigilance Scientist, Global Pharmacovigilance
Lene Thomsen, MSc, Senior Scientific Advisor, Pharmaceutical Product Development

Susanne Lagerlund, MSc, Regulatory Asset Lead, Regulatory Affairs
Hanne Arentsen, MSc, Regulatory Project Manager, Regulatory Affairs

MEETING OBJECTIVES:
To discuss the content and format of the proposed NDA submission for LEO 90100

Regulatory Correspondence History

We have had the following meeting/teleconferences with you:
- June 19, 2013 End of Phase 2 CMC
- May 15, 2013 End of Phase 2 Final Responses
- March 7, 2012 Pre-IND

We have sent the following correspondences:
- December 3, 2013 Advice
- September 5, 2013 Advice
- August 30, 2013 Advice
- December 14, 2012 Advice
- June 1, 2012 Study May Proceed

Regulatory

Question 1:
Does the FDA agree that the enclosed TOC provides a complete list of documentation required in order to file, and support a substantial review of, the proposed application?

Response:
From a technical standpoint (not content related) yes, the proposed format for the planned NDA is acceptable. See additional comments below:

- 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 reviewers.

- For m1.6.3 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.

- When sponsor submits word documents, the leaf title should include "word", so reviewers could quickly identify the word version of the document.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.

- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs). Case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form" Please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf

Question 2:
LEO intends to cross refer to previous NDA submissions (in both paper and eCTD formats) within a planned eCTD NDA submission. Does the Agency agree with the proposal?

Response:
Yes. Your approach appears reasonable. However, we would prefer that you submit all cross referenced data in an electronic format at the time of NDA submission.

Sponsors' options of cross referencing information submitted to another application would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc,.,) of the referenced document along with a hypertext link to the location of the information, when possible.

2. To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind,). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference" and application number (e.g. Cross Ref to nda123456). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

Meeting Discussion:
The sponsor plans to convert Module 3 of reference NDA 21852 to eCTD format, and to provide hyperlinks in the proposed new NDA at the time of NDA submission. However, if eCTD conversion is not accomplished, then we strongly encourage you to provide those documents requested in the "CMC Additional Comments" section in the proposed new NDA.

Prior to using cross application linking in an application, it is recommended that sponsor submit an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

Chemistry, Manufacturing and Controls (CMC)

Question 3:
Does the Agency agree with the proposal regarding provisions of drug substance documentation for the LEO 90100 NDA?

Response:
Yes, it is acceptable. For ease of the review, provide the drug substance specification in the NDA for this product.

Question 4:
Does the Agency agree with the proposal to cross refer to Taclonex® Ointment NDA for information regarding the pharmaceutical development and manufacture of the (b) (4) control of excipients of the (b) (4), and description and validation of analytical procedures for control of the (b) (4) of LEO 90100?

Response:
Yes, it is acceptable.

Question 5:
Can the Agency confirm the number of samples required for dosage form evaluation?

Response:
Provide three units for each proposed fill size.

Additional Comments
Although you may cross reference to NDA 021852 for CMC information of the (b) (4) (b) (4), the following information will need to be provided in the NDA submission:

- Establishments including the establishments involved in the manufacture and testing of the [redacted].
- Formulation composition table for the [redacted] and the proposed to-be-marketed foam formulation.
- Composition of all clinical formulations and a table correlating formulation, drug substance batch number, and drug product batch number with study numbers (clinical, toxicology, and stability).
- Specification tables for drug substances.
- Specification tables for the [redacted], and the proposed foam.
- Flow chart for the entire manufacturing process (including [redacted] of the proposed foam, and a summary of all in-process controls (including [redacted]) and their acceptance criteria.
- Batch analysis, in-process test results, manufacturing deviations, and Out-Of-Specification investigation reports (if there are any) for the most recent 10 batches of the [redacted]
- Proposed batch size, hold time and storage conditions for the [redacted]
- Master Batch Record and Executed Batch Record for the proposed foam product, including both [redacted] operation
- Method validation package for the proposed foam including method procedures and validation reports
- A claim of categorical exclusion from the preparation of Environmental Assessment on the basis of 5 year combined production forecast for all relevant NDAs and supplements

Clinical/Biostatistics

Question 6:
Does the FDA agree with the proposed plan for pooling of efficacy and safety data?

Response:
Yes. Your approach appears reasonable.

Efficacy data intended to establish an efficacy claim should be presented for each trial separately to check the consistency and replication of treatment effect across trials. For the integrated summary of efficacy (ISE), you may pool the efficacy data. In your submission, you should

include discussions regarding the strength of evidence across all trials, including discussion of any difference in outcomes across trials.

With regard to the safety data, you should also provide an analysis of the following:

- A separate analysis of the data from each of the Phase 2 trials (LEO 90100-7 and LEO 90100-35) and the Phase 3 trial (LP0053-1001)
- Pooled data from vehicle controlled trials with LEO 90100 (LP0053-1001 and 2 arms of LEO 90100-35)

Meeting Discussion:
The sponsor agreed to provide a safety data analysis (including local safety and laboratory data) from the vehicle controlled trials.

Question 7:
Does the FDA agree with the strategy for the statistical analysis of primary and secondary efficacy endpoints for the ISE?

Response:
Your proposed strategy for the statistical analysis of primary and secondary efficacy endpoints for the ISE appears to be reasonable.

Question 8:
Given the differences in the design of the local safety and tolerability assessment between the Phase 2 trials and the Phase 3 trial, and the inconsistency in assessing and reporting in the Phase 2 trials, does the FDA agree that pooling of local safety and tolerability data from the two Phase 2 trials and the Phase 3 trial is not meaningful?

Response:
Yes. Your approach appears reasonable.

Question 9:
Does the FDA agree with this proposal regarding submission of data tabulation datasets, data definition files and annotated case report forms?

Response:
Yes. Your approach appears reasonable. For ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml files.

In addition, you should provide the following:

- Subject narratives for all serious adverse events (AEs), all severe AEs and AEs resulting in discontinuation from the trials with Case report forms (CRFs). A study's CRFs should be placed in a CRF folder under the applicable study 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

- CRFs should be referenced under the study in which it belongs and tagged as "casereport-forms" in that study's stf.xml file.

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

- Line listings for all safety data.

- Frequency tables for sensitivity safety study results. Define and justify the threshold for calling a score positive (or negative) for sensitization.

- The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials**.**

Question 10:
Does the FDA agree with this proposal regarding analysis datasets?

Response:
Your proposal to submit analysis datasets based on CDISC/Adam standards, Analysis Data version 2.1, is acceptable. Your proposal to submit the SAS code used to generate the Multiple Imputation (MI) datasets is acceptable. In addition, submit the SAS code used to analyze the primary and secondary endpoints using these imputed datasets.

In addition to analysis datasets for the Phase 3 trial LP0053-1001 and the Phase 2 trial (LEO 90100-7), you should submit analysis datasets for the Phase 2 trial (LEO 90100- 35).

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.

Question 11a:

Does the FDA agree to the proposed plan for establishing a "bridge" for LEO 90100 to safety data for the two approved calcipotriene/BDP products?

Response:
To establish a "bridge" for LEO 90100 to safety data for the two approved calcipotriene/BDP products, you propose to include the following:

- Direct comparison of safety data for LEO 90100 and Taclonex ® ointment from Phase 2 trial LEO 90100-35
- Comparative vasoconstriction data (LP0053-69)
- Systemic exposure data from the Maximum Use Systemic Exposure trial (LEO 90100-30) compared with historical data from similar trials with Taclonex® Ointment (MCB 0201 FR and MBL 0404 FR) and Taclonex® Topical Suspension (LEO 80185-G24).
- Adverse event data from short term trials with LEO 90100 (LP0053-1001, LEO 90100-7, and LEO 90100-35), Taclonex® Ointment (MCB 0003 INT, MCB 0002 INT, MCB 0001 INT, MCB 0201 FR, and MCB 9905 INT) and Taclonex® Topical Suspension (LEO 80185-G23, MBL 0202 INT, and LEO 80185-G21)
- Comparative safety data from long-term clinical trials with Taclonex® Ointment (MCB 0102 INT) and Taclonex® Topical Suspension (MBL 0502 US and MBL 0407 INT)

Your approach appears reasonable but we have the following additional comments:

1. We note that you plan to provide cross trial comparative data on the systemic exposure in terms of effects on HPA axis, calcium metabolism and pharmacokinetics under maximum use conditions obtained in trial LEO 90100-30 and those obtained with Taclonex® Ointment and Taclonex® Topical Suspension, by displaying them side-by-side. We recommend you to include information on trial design which includes information on number of subjects, age range, amount of formulation used, body surface area applied, disease severity and analytical methods used in a tabular format. A discussion of similarity and differences in the cortisol and calcium bioanalytical methods used across the trials being compared should be provided.

2. We notice you have conducted a multi-point vasoconstriction assessment. Such an approach will not be acceptable for providing any comparison between different dosage forms. In your NDA, submit single point visual assessment data at 2 hours following 16 hours of study medication application to clearly identify the potency class of LEO 90100 foam.

Meeting Discussion:
The sponsor indicated that the vasoconstrictor trial was conducted with drug application for 6 hours and they plan to include the 2 hour post treatment duration data point based on post hoc analysis. The Agency stated that the typical trial design is to apply the drug for 16 hours, but we will review the sponsor's trial results in the NDA.

3. Submit in the NDA bioanalytical method validation reports, bioanalysis reports, including quality control results, and long term storage stability for active moieties, metabolites, cortisol and calcium assessment in the maximal use PK trial (LEO 90100-30).

Question 11b:
Provided that the outcome of the bridging analyses supports the conclusion that the currently available long term safety data for Taclonex® Ointment and Taclonex® Topical Suspension can be extrapolated to provide sufficient information on the long term safety of LEO 90100 aerosol foam, does the Agency agree that a long term safety study will not be required as a Post Marketing Requirement?

Response:
Yes.

Question 12:
Based on the above, LEO does not intend to submit a REMS for LEO 90100. Does the Agency agree?

Response:
At this time the Division is not aware of any serious safety issue that would necessitate a REMS.

Question 13:
Does the FDA agree to the proposed presentation of the efficacy results from the pivotal trials in the TPP?

Response:
It appears reasonable.

Question 14:
Does the FDA agree with the process for generating the table of adverse drug reaction frequencies for the USPI, including the grouping of similar preferred terms and exclusion of clearly unrelated AEs?

Response:
Your approach appears reasonable.

Additional Comments

- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. 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).

- Trial LEO 90100-30, trial LP0053-69, trial LP0053-66, and trial LEO 90100-01 were conducted outside of the United States. In your NDA submission, provide a discussion of applicability of this data to the United States population.

- Provide the instructions for use of your drug product by subjects enrolled in your Phase 3 and Phase 2 trials.

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. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements of Prescribing Information website including the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, regulations, related guidance documents, a sample tool illustrating the format for Highlights and Contents , and the Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances. We encourage you to use the SRPI checklist as a quality assurance tool before you submit your proposed PI.

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.				

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

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

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

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

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

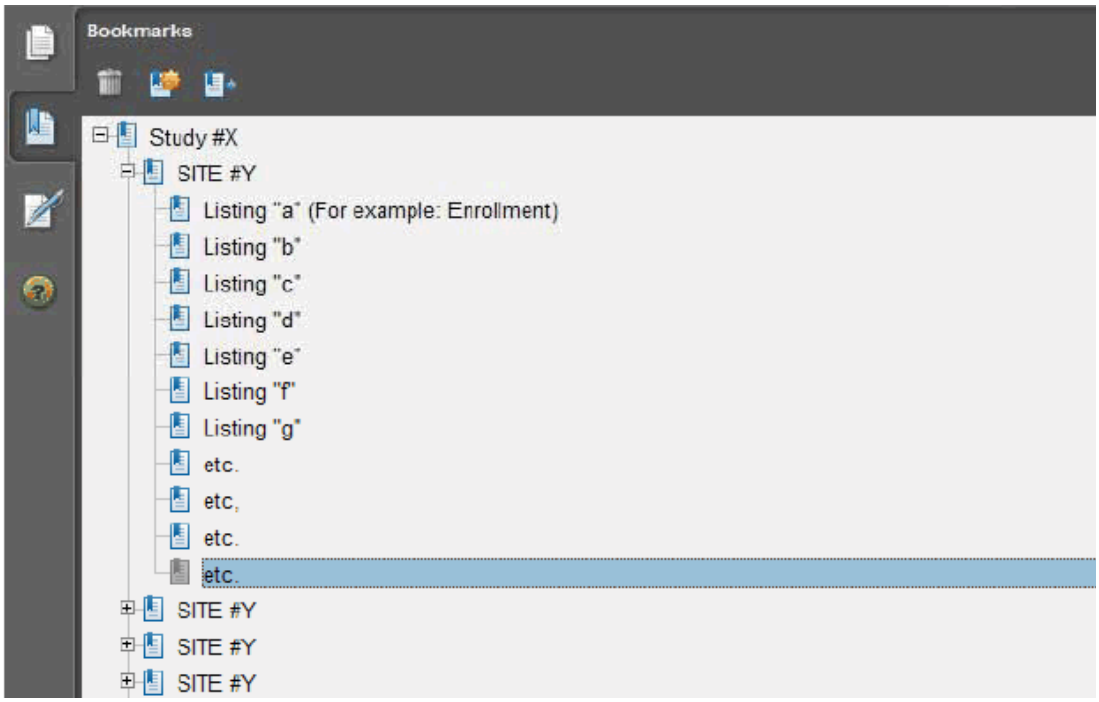
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, 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. Attachment 1

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	STF File Tag	Used For	Allowable File Formats

Item[1]			
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.

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

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

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

/s/

GORDANA DIGLISIC
04/01/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114063

MEETING MINUTES

LEO Pharma A/S
Attention: Lori A. Palmer
Regulatory Lead, Corporate Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Palmer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%.

We also refer to the meeting between representatives of your firm and the FDA on June 19, 2013. The purpose of the meeting was to discuss Chemistry, Manufacturing and Controls questions for end of phase 2.

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 Cathy Tran-Zwanetz, (301) 796-3877.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	End of Phase 2 CMC meeting
Meeting Date and Time:	June 19, 2013 at 9:30 AM
Meeting Location:	FDA White Oak, Building 22, Room 1309
Application Number:	IND 114063
Product Name:	(calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%
Indication:	Topical treatment of plaque psoriasis in adults 18 years of age and older
Sponsor Name:	LEO Pharma, Inc.
Meeting Chair:	Moo-Jhong Rhee, Ph.D.
Meeting Recorder:	Cathy Tran-Zwanetz

FDA ATTENDEES

Office of New Drug Quality Assessment
Moo-Jhong Rhee, Ph.D., Branch Chief
Shulin Ding, Ph.D., CMC Lead
Zhengfang Ge, Ph.D., ONDQA Reviewer
Cathy Tran-Zwanetz, Regulatory Project Manager

Division of Dermatology and Dental Products
Gordana Diglisic, M.D., Clinical Team Leader
Melinda McCord, M.D., Clinical Reviewer
Barbara Gould, Chief Project Manager

SPONSOR ATTENDEES

Malene Mueller, M.Sc.(Pharm), Director, Regulatory Affairs
Thomas Helboe, M.Sc. (Pharm), Ph.D., Director, Project Manager
Lori A. Palmer, Global Regulatory Lead, Regulatory Affairs
Karen Wibe Enevoldsen, M. Sc. (Pharm), Ph.D., Head of Section, Pharmaceutical Product Development

Pernille Birch Vestergaard, M.Sc. (Pharm), R&D Scientist, Pharmaceutical Product Development

Flemming Simonsen, DVM, DABT, Toxicologist, Preclinical Development
Susanne Lagerland, M.Sc. (Chem Eng.), Head of Section, Regulatory Affairs

1.0 BACKGROUND

The objective of this meeting is for the sponsor to obtain feedback on their late development program for commercial manufacture for (calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%. The preliminary meeting comments were sent Friday, June 14, 2013. Sponsor sent samples prior to meeting.

Regulatory Correspondence History

We have had the following meetings with you:

- May 29, 2013 End of Phase 2 Meeting
- March 7, 2012 Pre-IND Meeting

We have sent the following correspondences:

- December 14, 2012 Advice
- June 1, 2012 Study May Proceed

2. DISCUSSION

Question 1a:

Does the Agency concur that the intended commercial batch size [redacted (b) (4)] can vary up to a limit corresponding to the commercial batch size of the [redacted (b) (4)]?

Response:

Yes, we agree, provided that there are no changes in the equipment, process, and in-process controls for the [redacted (b) (4)].

DISCUSSION:

Sponsor agreed, no discussion needed.

Question 1b:

Does the Agency concur with the proposal that the batch size for the primary stability batches may be less than [redacted (b) (4)], however not less than [redacted (b) (4)]?

Response:

Yes, we agree with your proposal regarding the batch size of primary stability batches, provided that you agree on the following:

1) The manufacturing process (including the [redacted (b) (4)]) of the primary stability batches will be representative of the commercial scale manufacturing process.
2) The batch size of the bulk [redacted (b) (4)]) for the primary stability batches will be no smaller than [redacted (b) (4)] of the commercial scale.

DISCUSSION:
No discussion needed.

Question 2a:

(b) (4)

Response:

(b) (4)

DISCUSSION:
No discussion needed.

Question 2b:

(b) (4)

Response:
No, we do not agree. See response to Question (b) (4)

DISCUSSION:
No discussion needed.

Question 2c:
Does the Agency concur that it will be appropriate to file any post-approval supplement for a [redacted] (b) (4) site under Category IV- Manufacturing Sites of "*Guidance for Industry, Changes to an Approved NDA or ANDA*" rather than under the "*Guidance for Industry, Nonsterile Semisolid Dosage Forms, Scale-Up and Postapproval Changes: CMC; In Vitro Release Testing and In Vivo Bioequivalence Documentation*", where an in-vitro release test could be required to demonstrate product sameness?

Response:
We recommend that you follow SUPAC-SS for the information included in the submission to support a site change (including [redacted] (b) (4)) because the proposed product is a semi-solid and Guidance for Industry, Changes to an Approved NDA or ANDA does not provide the Agency's recommendation regarding the information that should be provided to support a site change. We agree that In Vitro Release Testing (IVRT) and In Vivo Bioequivalence are not needed to support a [redacted] (b) (4) for this product.

DISCUSSION:
No discussion needed.

Question 3a:
Given that the administered foam exhibits an inherent highly variable viscosity, does the Agency concur with the proposal that viscosity can be excluded from the commercial specification for LEO 90100?

Response:
Yes, we agree.

DISCUSSION:
No discussion needed.

Question 3b:
Provided that the quality of the administered foam and the physical performance of the drug product are sustained, does the Agency concur with the proposal that a [redacted] (b) (4) [redacted] (b) (4) is acceptable for the sample [redacted] (b) (4) size of LEO 90100?

Response:

We recommend that you conform to the standard prescribed by USP<601>. We noted that you estimated the leakage rates for the (b) (4) 60 g package sizes using the data from (b) (4) package size. We recommend that you measure the actual leakage rate for each fill size for batch release and stability studies.

DISCUSSION:
No discussion needed.

Question 4a:
Does the Agency concur with labeling the strength of LEO 90100 to correspond with the amount of actives in the (b) (4) and the weight to correspond with the amount of (b) (4) (b) (4)?

Response:
Yes, we agree, provided that the residual propellants in the foam deposited on the skin are not significant enough to change the strength of the active ingredients. Provide information regarding the level of residual propellants in the foam deposited on the skin.

DISCUSSION:

The Sponsor verbally provided preliminary data regarding residual propellants in the discharged foam. The Sponsor also stated that this information can be found in the IND submission module 2.4 page 9 and module 4.3. The Sponsor will provide more data in the NDA.

The Sponsor inquired how much residues would be considered to be significant by the FDA. FDA agreed to review the information and provide a response.

FDA acknowledged that the preliminary numbers provided verbally are within the acceptable assay range of ±10% of label claim.

Question 4b:
Does the Agency concur that the test for minimum fill is performed at (b) (4) and that standardized overfill, not to exceed an overage of (b) (4)% of the total labeled weight, can be utilized to ensure compliance with Minimum Fill <755>?

Response:
Yes, you may test the minimum fill weight at (b) (4). However, you will need to include weight loss in the registration stability protocol for the primary stability batches. A (b) (4)% overfill is acceptable.

DISCUSSION:
The Sponsor agreed, no discussion needed.

Question 5:
Does the Agency concur with the intended storage orientation described in Table 10-4 for the primary batches in the ICH stability study?

Response:
No, we disagree. Observations made in the earlier stability studies may not be reproducible in the registration stability batches due to various reasons such as differences in scale, process, site, etc. Therefore, it is important to repeat the same investigation in the registration stability studies in order to make conclusive determination. We highly recommend that you conduct full testing for both upright and inverted orientations in the ICH stability studies which will become registration stability studies.

We did not find data regarding leakage and drug delivery (rate ad amount) in the referenced tables (Table 11-11 and 11-12); therefore, we can not assess the impact of storage orientations on leakage and drug delivery.

DISCUSSION:
In the NDA, Sponsor agreed to do full testing for the registration stability batches for both orientations. The Agency agreed that the Sponsor can submit a proposal for partial testing on the worst case orientation for the post approval stability protocol in the NDA. The sponsor indicated (b) (4) (b) (4)

Question 6:
Does the Agency concur that demonstration of compliance with USP<381> is not relevant for LEO90100 and that the conduction of extractable and leachable studies as described above will provide the information necessary to demonstrate appropriate control of the leachable profile?

Response:
We agree that many tests prescribed by USP<381> (including those tests listed on the top of page 30 of the briefing package) are not applicable to your product.

Your selection of solvents for the extractable/leachable testing is acceptable, and the proposed extractables/leachables study appears to be reasonable with one exception. We recommend that you evaluate extractables/leachables on individual formulation-contacting packaging components (including (b) (4) in addition to conducting the evaluation in the can as proposed. We are concerned that a (b) (4) can may not give those formulation-contacting components an adequate exposure to the formulation.

DISCUSSION:
Sponsor agreed to perform the extractables studies on individual formulation-contacting components. Depending on the finding, leachable studies can be done in the can with the container closure system and that data will be provided. Justification will be provided in the NDA if the leachable studies are not done.

FDA commented that the risk of extractables/leachables would need to be re-assessed if changes (e.g. supplier change) occurred in one or multiple formlation-contacting packaging components after the completion of extractables/leachables studies. The sponsor inquired of the information needed to support a packaging component change. FDA responded that the Sponsor could propose a plan to qualify new vendors/ parts for the container closure system in the NDA.

Question 7:
Does the Agency concur that referring to the indirect food regulation (21 CFR 177) is appropriate, and that no further information on the construction materials of the (b) (4) (b) (4) will be provided in neither the NDA nor in any cross-referenced Type III Drug Master File?

Response:
Although reference to the indirect food regulation will be helpful, the results of the extractables/leachables studies will be critical in the determination of the safety of formulation-contacting packaging components (such as (b) (4)) and the necessity in knowing the chemical composition of the construction materials.

You will also need to provide the following information in the NDA or reference to a DMF for (b) (4) as well as other formulation-contacting packaging components:

- Name and address of the supplier,
- Supplier's technical sheet and certificate of analysis
- The certificate of analysis issued by the manufacturer of the aerosol container/closure system to release the part for the assembly of the aerosol container/closure system.
- NDA applicant's in-coming specification for the release of the aerosol container/closure system for drug product manufacture. The specification must include proper tests to ensure the aerosol container/closure system has all the correct components.

DISCUSSION:
No discussion needed.

Question 8a:
Based on the fact that the use of DME as a propellant in LEO 90100 is not considered to be a safety concern, does the Agency concur that it is not necessary to update the CTD sections for DME in IND 114063 to support the Phase 3 program?

Response:

We concur.

DISCUSSION:
No discussion needed.

Question 8b:
Likewise does the Agency concur that it is also sufficient to provide the same CTD sections for DME with the same level of information in the planned NDA?

Response:
It is sufficient for NDA filing. The adequacy of the information to support NDA approval will be determined in the NDA review.

DISCUSSION:
No discussion needed.

Additional Comment

Conduct an in-use stability study. Include weight loss and package integrity in the in-use stability study protocol.

DISCUSSION:
FDA clarified that the test on package integrity could be a visual examination of the container closure system,both exterior and interior.

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.

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

/s/

CATHERINE A TRAN-ZWANETZ
07/18/2013

MOO JHONG RHEE
07/18/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114063

MEETING MINUTES

LEO Pharma, Inc.
Attention: Lori Palmer
Regulatory Lead, Corporate Regulatory Affairs
1 Sylvan Way
Parsippany, NJ 07054

Dear Ms. Palmer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%.

We also refer to the meeting scheduled on May 15, 2013 between representatives of your firm and the FDA. The purpose of the meeting was to discuss your proposed late development program. Your premeeting briefing package (April 5, 2013) provides background and questions for discussion.

We acknowledge the email on May 15, 2013, notifying us that after receipt and review of the premeeting communication consisting of Agency responses to your questions, you have determined that the responses to your questions are sufficient and additional discussion is not necessary.

This letter and the enclosed final responses represent the official record.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure – Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FINAL RESPONSES

IND: 114064

Product: (calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%

Regulatory Path: 505(b)(1)

Sponsor: LEO Pharma, Inc.

Indication: Topical treatment of plaque psoriasis in adults 18 years of age and older

Type of Meeting: End of Phase 2 Meeting

Meeting Date: May 15, 2013; 10:30 am

Introductory Comment:

This material includes the Agency's final responses to the questions submitted for your meeting scheduled for May 15, 2013, at 10:30 in Room 1415, Building 22 of the White Oak Campus between LEO Pharma and the Division of Dermatology and Dental Products. This material was shared to promote a collaborative and successful discussion at the meeting. After receipt of the preliminary responses, you had two options:

- If these answers and comments were clear to you and you determined that further discussions were not required, you had the option of canceling the meeting.

- If you determined that discussion was needed for only some of the original questions, you had the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to telecon).

You conveyed to Dawn Williams via email on May 15, 2013 that the responses to your questions were sufficient and additional discussion was not necessary. As such, the below responses represent our final responses to your questions.

MEETING OBJECTIVES:
The objective of this meeting is to obtain feedback on your late development program for (calcipotriene and betamethasone dipropionate) Aerosol Foam, 0.005%/0.064%.

Regulatory Correspondence History

We have had the following teleconference with you:

- March 7, 2012 Pre-IND Meeting

We have sent the following correspondences:

- December 14, 2012 Advice
- June 1, 2012 Study May Proceed

Pharmacology/Toxicology

Question 1:
Does the Agency agree that additional nonclinical studies on DME are not required to be included in the future marketing application for LEO 90100?

Response:
Yes.

Clinical Pharmacology/Biopharmaceutics/Clinical/Biostatistics

Question 2a:
Does the Agency agree that the proposed clinical development program contains the required components to support the review of an application seeking approval of LEO 90100 for the topical treatment of plaque psoriasis in patients 18 years and older?

Response:
Your proposal to rely on long term safety data from Taclonex® Ointment and Taclonex® Topical Suspension is reasonable. However, you should provide in the IND a discussion regarding how you intend to establish a "bridge" between your proposed product (LEO 90100 Aerosol Foam) and Taclonex® Ointment /Taclonex® Topical Suspension to demonstrate that reliance is appropriate.

In addition, you will need to address the pro-arrhythmic potential of your product as per ICH Guidance for Industry E14 Clinical evaluation of QT/QTc Interval Prolongation and Pro-arrhythmic Potential for Non-Anti-arrhythmic Drugs.

Question 2b:
In particular, does the Agency agree that an adequate and well-controlled phase 2 trial demonstrating the combination principle, together with one phase 3 trial comparing LEO 90100 with its vehicle, form an acceptable basis for the purpose of an NDA, considering the large body of evidence consistently showing superiority of the calcipotriene/BDP combination over the monocomponents in the treatment of plaque psoriasis?

Response:
Yes.

Question 3:

Considering the number of subjects included in clinical trials with LEO 90100 and the extensive number of patients who have received topical calcipotriene/BDP combination in other formulations, does the Agency agree that the safety database can be considered adequate to define the safety profile of LEO 90100?

Response:
The proposed safety database appears to be acceptable. Regarding the long term safety, see response to Q 2a.

Question 4:
Does the Agency agree with the Sponsor's primary endpoint and the appropriateness of the suggested scale for the IGA?

Response:
Yes. The proposed primary efficacy endpoint of the proportion of subjects who achieve 'treatment success' ('clear' or 'almost clear' for subjects with at least moderate disease at baseline, 'clear' for subjects with mild disease at baseline) according to the IGA at Week 4 and the 5-point Investigator's Global Assessment of Disease Severity (IGA) are acceptable.

You proposed to analyze the primary endpoint using the Zelen's exact test; however, as the Zelen's exact test is used for testing the homogeneity of the odds ratio across strata, it is not clear how you would use it for establishing efficacy. We recommend the primary endpoint be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by the factor(s) used to stratify the randomization. You might use the Zelen's exact test as a sensitivity analysis to the Breslow-Day test for testing homogeneity across strata.

In addition to 2 secondary endpoints you plan to evaluate 41 tertiary endpoints. The Agency considers the analysis of tertiary endpoints to be exploratory.

The following are additional comments regarding your submitted Phase 3 protocol:

- In the meeting background package (page 41), you stated that randomization will be stratified by investigational site; however, you stated in the protocol (Appendix 3) that randomization will be stratified by only baseline disease severity (IGA=2 or IGA≥3). Therefore, it is not clear how you plan to conduct the randomization. It should be noted that the statistical analysis should follow the randomization. We recommend that the randomization be stratified by site. In addition, with an average site enrollment of about 13 subjects per site, there is potential for cells with zero frequency. Therefore, we recommend you reduce the number of sites and enroll more subjects per site.

- You proposed to use LOCF as the primary imputation method for handling missing data. As the scientific justification for using LOCF is weak, you should provide an adequate rationale for using LOCF or propose a more scientifically sound method (e.g. multiple imputation). In addition, you should prespecify several sensitivity analyses that utilize

alternate assumptions to those in the primary imputation method, to ensure that the results are not driven by the method of handling missing data.

Question 5:
Does the Agency agree with the proposed discontinuation criteria for individual subjects in the pivotal phase 3 trial?

Response:
Regarding the local safety evaluation, the proposed discontinuation criteria are acceptable. However, subjects who discontinue treatment due to an adverse event should not be withdrawn from the trial but should continue to be evaluated until the adverse event resolves or the etiology is identified and the adverse event stabilizes.

Question 6:
Does the Agency agree to the proposed plan for evaluation of markers of (b) (4) in the phase 3 trial?

Response:
You propose to evaluate the effect of your drug product on (b) (4) with baseline vitamin D levels, albumin-corrected serum calcium levels and urinary calcium: creatinine ratios (from spot urine samples) at Visit 1 and Visit 4. However, in the absence of complete data from the maximal use systemic safety trial (LEO 90100-30) which included a comprehensive assessment of the effects of your drug product on calcium metabolism, you may consider modifying your laboratory assessment to include the evaluation of PTH, alkaline phosphatase and phosphate in the Phase 3 trial.

Question 7:
Does the Agency agree that the proposed assessment is designed appropriately to evaluate local safety and tolerability?

Response:
Your proposal to assess application site reactions for edema, erythema, dryness and erosion on perilesional skin using a 4-point scale is acceptable. However, the assessment of local safety and tolerability should not be limited to the target lesion.

Question 8:
Assuming that no new safety signals emerge from the conduct of the proposed and ongoing clinical trials with LEO 90100, does the Agency agree that no additional long term safety trials beyond those already conducted for the approved calcipotriene plus BDP fixed combination products will be required?

Response:
Refer to the response to Question 2a.

Question 9:

Does the Agency agree that, in view of these findings, the conduct of a vasoconstrictor trial would not provide accurate and conclusive information on the vasoconstrictive properties of LEO 90100, and also agree with the LEO proposal not to conduct this trial?

Response:
Vasoconstrictor (VCA) trial is not required. However, to better characterize the new formulation we recommend you to consider conducting the VCA trial. The trial could be conducted by dispensing sufficient amount of the foam formulation into a dish, waiting an adequate period of time for the propellants to evaporate and using the drug containing residue in your VCA trial. You should ensure that the amount of residue that you use is comparable to the amounts of other active comparator formulations that you would use in the trial.

We also note that your proposed comparators for the VCA trial (shown below) will be inadequate for you to clearly identify the potency class of your foam formulation.

(b) (4)

We recommend that you ensure adequate bracketing for this trial.

Question 10:
Does the Agency agree with the proposed approach for reporting frequencies of adverse reactions in the clinical program?

Response:
Yes.

Additional comments:
We note that a maximal use PK trial (LEO 90100-30) is ongoing in Canada. Based on the limited summary that you have provided we have the following comments:

1. We note that you have obtained serial PK samples at Week 4 for up to 7 hours post-application. The purpose of the maximal use PK trial is to assess complete PK profile under maximal use conditions. If significant systemic drug exposure is observed, then the adequacy of PK sampling for up to only 7 hours might be an issue.

2. You should ensure that the population studied in the maximal use PK trial is representative of the United States population and at the upper end of disease severity for the proposed indication.

3. You should record the amount of formulation used in the maximal use PK trial.

4. Both Phase 2 Trial LEO 90100-7 and Trial LEO 90100-35 were conducted at the same study sites. Clarify whether any subjects participated in more than one Phase 2 trial.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. 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. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

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.

DATA STANDARDS FOR STUDIES

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

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/s/

SUSAN J WALKER
05/29/2013