CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209305Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 209305 SUPPL # NA HFD # 540

Trade Name Eskata

Generic Name hydrogen peroxide topical solution, 40%

Applicant Name Aclaris Therapeutics, Inc.

Approval Date, If Known December 14, 2017

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES ☒ NO ☐

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

505(b)(2)

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.

NA

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:

NA

c) Did the applicant request exclusivity?

YES ☒ NO ☐

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

5 years

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?

NA

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# 005382 hydrogen peroxide

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#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to

3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

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

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

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

YES ☒ NO ☐

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

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

NA

(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:

NA

(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:

NA

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.")

A-101-SEBK-301 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 1).
YES ☐ NO ☒

A-101-SEBK-302 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 2).
YES ☐ NO ☒

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

NA

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?

A-101-SEBK-301 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 1).
YES ☐ NO ☒

A-101-SEBK-302 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 2).
YES ☐ NO ☒

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

NA

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"):

A-101-SEBK-301 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 1)

A-101-SEBK-302 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 2)

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 A-101-SEBK-301 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 1)

!
!

IND # 117635 YES ☒ ! NO ☐
! Explain:

Investigation #2 A-101-SEBK-302 A randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 Solution 40% in subjects with seborrheic keratosis on the trunk, extremities, and face (Study 2)

!
!
IND # 117635 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? NA

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: Strother D. Dixon
Title: Senior Regulatory Project Manager
Date: February 20, 2018

Name of Division Director signing form: Jill A. Lindstrom, MD, FAAD
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/

STROTHER D DIXON
02/20/2018

JILL A LINDSTROM
02/22/2018

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 209305 BLA # NA	NDA Supplement # NA BLA Supplement # NA	If NDA, Efficacy Supplement Type: NA *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: Eskata Established/Proper Name: hydrogen peroxide, 40% Dosage Form: solution		Applicant: Aclaris Therapeutics, Inc. Agent for Applicant (if applicable): NA
RPM: Strother D. Dixon		Division: Dermatology and Dental Products

NDA Application Type: ☐ 505(b)(1) ☒ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☐ 351(a)

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: December 12, 2017

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 December 24, 2017	☒ 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 _____	☐ 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.

Reference ID: 4195645

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only): Type 2
(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 required 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)* (link)	☒ Included
Documentation of consent/non-consent by officers/employees (link)	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval, 12/14/17
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)*	7/6/17 7/13/17
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☐ None 4/4/17 DMEPA: ☐ None 10/10/17, 11/17/17 and 12/14/17 DMPP/PLT (DRISK): ☐ None 10/6/17 OPDP: ☐ None 10/5/17 SEALD: ☒ None CSS: ☒ None Product Quality ☐ 9/14/17 Other: ☐ DPMH 10/11/17
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	5/5/17 ☐ Not a (b)(2) 12/7/17
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☒ Completed (Do not include)
❖ 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 ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 9/20/17 If PeRC review not necessary, explain: NA	
❖ 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 OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	1 - 5/9/17
❖ 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)	NA
❖ 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 or BPD Type 4 meeting *(indicate date of mtg)*	☐ No mtg 9/28/16
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 5/8/16
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, BPD Type 3, CMC focused milestone meetings) *(indicate dates of mtgs)*	NA
❖ 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
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/27/17
PMR/PMC Development Templates *(indicate total number)*	☒ None
Clinical	

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
• Clinical review(s) *(indicate date for each review)*	11/21/17
• 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)*	Clinical Review, 11/21/17, p. 13 NA
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5] *Division of Cardiovascular and Renal Products*	☐ None 8/31/17
❖ 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)*	NA NA ☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested Letter – 10/16/17 Clinical Inspection Summary – 10/3/17 Letter – 9/28/17
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 10/20/17
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 10/20/17
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☐ None requested

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

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 10/12/17
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 10/12/17
❖ 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[6]	
• 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 10/20/17
❖ 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)*	IQA Review 10/20/17 – p. 51-52
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☒ Acceptable ☐ Withhold recommendation ☐ Not applicable

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

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
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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

/s/

STROTHER D DIXON
12/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209305

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

Aclaris Therapeutics, Inc.
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

ATTENTION: Christopher Powala
Chief Operating Officer

Dear Mr. Powala:

Please refer to your New Drug Application (NDA) dated and received February 24, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydrogen Peroxide Topical Solution, 40%.

We also refer to your correspondence, dated and received April 10, 2017, requesting review of your proposed proprietary name, Eskata.

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

If any of the proposed product characteristics as stated in your April 10, 2017, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

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 Tri Bui Nguyen, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-3726. For any other information regarding this application, contact Strother D. Dixon, Regulatory Project Manager, in the Office of New Drugs at (301) 796-1015.

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

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

/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
07/06/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 209305

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Aclaris Therapeutics, Inc.
Attention: Christopher Powala
Chief Operating Officer
101 Lindenwood Drive
Malvern, PA 19355

Dear Mr. Powala:

Please refer to your New Drug Application (NDA) dated and received February 24, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for hydrogen peroxide solution, 40%.

We also refer to your amendments dated March 6, 10, and April 12, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is December 24, 2017.

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 November 9, 2017.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

We request that you submit the following information by May 16, 2017:

1. In the bioanalytical validation report (RPT [redacted] (b) (4)) for glutathione (GSH) and glutathione disulfide (GSSG) in human blood, you stated that the GSH derivative, GSH-NEM, was separated into two peaks in the chromatograph with retention times of approximately 2.4 (left peak) and 2.6 (right peak) minutes. The peak at ~2.4 minutes (left peak) was used for the quantitation of GSH-NEM. However, the right peak was integrated instead in chromatogram of GSH-NEM shown in bioanalytical analysis report for Study A-101-SEBK-205 (RPT 16243). Clarify this discrepancy and provide a rationale/justification. If re-analysis of your data is needed, we recommend that you submit updated reports as soon as possible for review of your application to continue in a timely manner.
2. Formal QT/QTc study waiver request.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments or questions:

1. In the Highlights (HL) section of the label, increase the left margin to 1/2 inch.
2. In the HL section, the revised date is below the half page portion of the page. Decrease the font or decrease the top header to ensure the entire HL section is one-half page or less.
3. In the HL section of the label, add a numerical identifier to cross-reference the supporting information in the Full Prescribing Information (FPI) for the statement "The safety of more than 4 ESKATA treatments has not been determined."
4. The study number in the subsection14.2 title is 301 in the Table of Content (TOC) and 302 in the FPI. Provide the correct study number.
5. The cross-references in Section 2 of the FPI should refer to the section, followed by a numerical identifier, be in italics and enclosed within brackets.
6. In the title for the Subsection 6.1 of the FPI, the "s" is missing from “Trials”.
7. The label should include section 8.3 Females and Males of Reproductive Potential, if applicable. See the draft guidance industry, *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products- Content and Format.*
8. To the beginning of the Patient Counseling Information section of the FPI, add the cross-reference "Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use)."
9. You place the instructions for the patients on the use of ESKATA in section 16 How Supplied/Storage and Handling. You should create a separate “Instructions for Use” document. Refer to the Patient Counseling Information section of guidance for industry *Labeling for Human Prescription Drug and Biological Products —Content and Format*.
10. The Patient Information is a subsection under section 17 (Patient Counseling Information). Provide language for Section 17 and create delineation between Section 17 and the Patient Information labeling.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by May 23, 2017. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in 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), Medication Guide, and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager, at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

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

/s/

JILL A LINDSTROM
05/09/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117635

MEETING MINUTES

Aclaris Therapeutics, Inc.
Attention: Christopher Powala
Chief Operating Officer
101 Lindenwood Drive
Suite 400
Malvern, PA 19355

Dear Mr. Powala:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hydrogen peroxide topical solution, 40%.

We also refer to the meeting between representatives of your firm and the FDA on May 6, 2015. The purpose of the meeting was to discuss the development program for hydrogen peroxide topical solution, 40%.

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 Strother D. Dixon, Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 2
Meeting Date and Time:	May 6, 2015; 8:30 AM
Meeting Location:	FDA White Oak, Building 22
Application Number:	IND 117635
Product Name:	hydrogen peroxide topical solution, 40%
Proposed Indication:	For the treatment of seborrheic keratosis lesions in adult patients
Sponsor Name:	Aclaris Therapeutics, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Acting Deputy Director, DDDP
Milena Lolic, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Kumar Mainigi, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
Yichun Sun, PhD, Acting Quality Assessment Lead, Branch V, DNDQAII
Roy Blay, PhD, Reviewer, DGCAB
CDR Mary E. Brooks, RN, BSN, MS, USPHS, USPHS, Senior Regulatory Review Officer / Nurse Consultant, GHDB
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES
Christopher Powala, Chief Operating Officer, Aclaris Therapeutics
Neal Walker, DO, President & CEO, Aclaris Therapeutics
Stuart Shanler, MD, Chief Science Officer, Aclaris Therapeutics
Brian Beger, VP, Clinical Operations, Aclaris Therapeutics
(b) (4), Preclinical Consultant
(b) (4)

Purpose of the Meeting:
To discuss the development plan for hydrogen peroxide topical solution, 40%

Regulatory Correspondence History

We have had the following teleconferences with you:
- February 25, 2015 – Type C/Guidance
- April 24, 2013 – Type B/Pre-IND

We have sent the following correspondences:
- March 4, 2015 – Advice
- November 6, 2014 – Advice
- October 30, 2013 – Study May Proceed
- September 26, 2013 – Information Request

Regulatory

Question 1:
Does the Division agree that the NDA should be filed pursuant to Section 505(b)(2) of the FD&C Act?

Response:
Yes, if you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference, then your marketing application will be a 505(b)(2) New Drug Application (NDA). Refer to the 505(b)(2) REGULATORY PATHWAY section below for further information about submitting a 505(b)(2) NDA.

Question 2:
Can the Division comment on the draft product label in light of the design of the Phase 3 program?

Response:
Labeling for a drug product, including the indication and restrictions thereof, is data driven. Thus, we are unable to provide any comments regarding the labeling at this time. Labeling recommendations will be provided following the NDA review.

Question 3:
Can the Division comment on the Sponsor's assessment that hydrogen peroxide would be subject to 5 years of market exclusivity?

Response:
The Agency does not make exclusivity determinations pursuant to sections 505(c)(3)(E) and (j)(5)(F) of the Federal Food, Drug, and Cosmetic Act, and 21 CFR 314.108, until approval of an NDA. As described in 21 CFR 314.50(j), an applicant should include in its NDA a description of the exclusivity to which the applicant believes it is entitled. FDA will consider the applicant's assertions regarding exclusivity after approval of the application.

Question 4:
Can the Division comment on the Sponsor's plan to identify and submit for review, the potential trade names?

Response:
You may submit the proposed proprietary name at any time after the completion of Phase 2 trials. The information on submitting the requests for proprietary name review can be found at http:/www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf.

Chemistry, Manufacturing and Controls (CMC)

Question 5:
Does the Division have any comment on the chemistry, manufacturing, and controls development plan leading to the NDA filing?

Response:
It is reasonable to provide CMC information for the drug substance through a referred drug master file (DMF). The adequateness of the DMF will be determined during NDA review.

A test for uniformity of dosage units according to USP <905> should be added to the drug product specification. Compatibility of the (b) (4) package components with the drug product solution should be evaluated. CDRH will provide comments on your drug product package (device) and its specification if it is deemed to be a device.

The CMC information recommended for NDA submission can be found in ICH guideline M4Q(R1) *The Common Technical Document for the Registration of Pharmaceuticals for Human Use- Quality Overall Summary of Module 2 Module 3: Quality* (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4_R1_Quality/M4Q_R1_.pdf).

A final determination regarding whether your applicator is a device will not be made until submission of a sample for review. If your product is a device, the following information is necessary to begin the combination product device constituent review. Limited information was provided in the briefing packet. CDRH expects the sponsor at this stage in the IND to have to a device /system requirement document which provide documentation and performance testing that follows the correlates to the device design specifications. The following questions below will most likely result in additional information questions due the limited information provided in the packet.

The briefing package provided limited information on the device constituent parts of the combination product. As part of future IND submissions, please provide at least the following elements to support the safety and performance of the device constituent part:

1. Full description information for the system including schematics and material listings.
    a. Schematics of all individual device components

   b. Materials list for each components
   c. Raw material source supplier
2. Product labeling and instructions for use which describe the process of using the device to deliver the medication.
3. Final finished device biocompatibility performance testing as defined by ISO 10993.
4. A listing of design requirements specifications for the system
5. Performance testing which demonstrates satisfaction of design requirements; specific performance testing for this combination product will likely include, but may not be limited to:
   a. Device sterilization
   b. Device stability after preconditioning activities such as aging
   c. Testing which assesses forces required to activate and express contents
   d. Testing which assesses dispensing accuracy
   e. Testing which ensures the device will not leak contents
   f. Testing which ensures the system will retain any glass particles from the ampoule
   g. Ease of expression
   h. Applicator drip testing
      i. Glass shard testing a. Outer tube puncture testing
      ii. (b) (4) glass fragment testing

Provide a sample applicator for the meeting.

Meeting Discussion:
A brief presentation of the delivery device was provided by the sponsor. The sponsor was advised to present information regarding general device performance, including the amount of force required to crush the ampoules, flow rates, leak testing and device disposal. The device sample provided was the final finish design.

The sponsor stated that this device had not been used in their Phase 2 trials. The sponsor will provide device performance data prior to the initiation of Phase 3 trials.

The Agency requested the sponsor add identification test for hydrogen peroxide to the drug product specification.

Pharmacology/Toxicology

Question 6:
Does the Agency agree that the above toxicology and non-clinical safety assessment studies are adequate to support the NDA?

Response:
In principle we agree. However, you should request for waiver(s) or technical inability to conduct any particular study in writing under the current IND.

Clinical/Biostatistics

Introductory Comments:
For establishing the efficacy and safety of your product, you proposed to conduct the following clinical trials:

- Protocol A-101-SEBK-301 for randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of A-101 solution 40% in subjects with 1-3 seborrheic keratosis on the trunk and extremities

- Protocol A-101-SEBK-302 for randomized, double-blind, vehicle-controlled, parallel group study of the safety and effectiveness of a-101 solution 40% in subjects with 1-2 seborrheic keratosis on the face

- A-101-SEBK-303 an open-label study of the safety of A-101 solution 40% in subjects with 4 seborrheic keratosis on the trunk, extremities and face

In your trials, you plan to treat 1-3 SK lesions and 1-2 SK lesions in Studies 301 and 302, respectively. The Division considers that the proposed number of SK lesions to be relatively low for establishing efficacy for the indication you are seeking. Furthermore, your study power and analysis will be mainly driven by the response rate for subjects with only 1 treated SK lesion since you expect the efficacy results for this group to be much higher than those with 2 or 3 treated SK lesions. In addition, your proposed trial design may raise concern about randomization as well as blinding.

As an alternative design, you may consider designing your clinical trials to enroll subjects with a minimum of 4 SK lesions that can be on the trunk, extremities and/or the face. Each of these SK lesions should meet a minimum level of severity to justify their treatment. The primary endpoint should be assessed at the subject level where success is defined as complete clearance of all 4 treated SK lesions at the selected time-point. A less stringent success criterion (i.e., three out of four treated SK lesions) can be considered as a secondary endpoint to support the findings of the primary endpoint. For the integrity of the clinical trials, the Division recommends that the efficacy evaluations be carried out by an independent assessor to ensure blinding. Furthermore, full details about the randomization should be provided to ensure that your trials are well-designed and conducted.

Each of the clinical trials may enroll subjects with SK lesions on the trunk, extremities and/or the face that meet the SK lesion inclusion criteria. Randomization can be stratified to ensure a minimum number of subjects (or number SK lesions per subject) having SK lesions on the face. The Division considers such a trial design has flexibility because it allows for enrolling subjects with SK lesions on the trunk, extremities and/or the face instead of being restricted to one anatomical location. Furthermore, such trial design would enable establishing the efficacy in

each region after establishing efficacy in the overall population (trunk, extremities, and the face) provided that the trials are sufficiently powered and the Type I error rate is controlled. In addition, this trial design would enable checking consistency of findings for each anatomical location across the two trials and provide replication of study findings.

Meeting Discussion:
The sponsor agreed with the Division recommendation that clinical trials would enroll subjects with at least 4 SK lesions on the trunk, extremities and/or the face that meet the SK lesion inclusion criteria. Additionally, the sponsor agreed with the Division recommended primary endpoint of success defined as complete clearance of all 4 treated SK lesions at the selected time-point. The sponsor proposed to use percentage of lesions cleared as the secondary endpoint in lieu of the Division proposed endpoint of using the three out of the four lesions treated. The Division will consider the sponsor proposal upon receiving the sponsor full protocols for their Phase 3 trials.

Question 7:
Does the Agency agree with the design of the Phase 3 protocols to support the indication of A-101 as a treatment to remove seborrheic keratosis lesions in adult patients?

Response:
As discussed at the February 25, 2015 guidance meeting, we anticipate that the treatment of benign skin lesions such as seborrheic keratoses with a medication such as the one you propose will differ substantially from the surgical treatment options currently used by providers, which are not typically reimbursed by most insurance carriers. It is likely that an approved drug product for this indication would allow treatment of multiple SK lesions, and we recommend that clinical trials be conducted under the predicted conditions of use. See response to question 6.

The multicenter, randomized, double-blind, vehicle-controlled, parallel arms study design is appropriate for pivotal trials. Although the open label study under protocol 303 will be somewhat limited due to the lack of a control arm, it may be useful for collection of additional safety data.

You propose to limit distribution of your product to dermatologists and restrict use to office based use. As previously noted, it is not clear that other medical specialists, such as internists or family practitioners, would not be able to diagnose and successfully treat seborrheic keratoses. Preliminary review of the Phase 2 safety data did not identify a specific serious risk that might need to be listed in the prescribing information.

Provide a rationale and your plan to limit distribution to dermatologists for in office use.

Meeting Discussion:
The sponsor clarified their intent to limit use to in office practice.

Question 8:
Does the Agency have any comment on the validated PLA scale?

Response:
Submit all the supporting documentation for PLA validation along with Phase 3 protocols to the IND. The comments on the utility of the PLA scale for efficacy assessment will be provided following the review of the Phase 3 protocols.

Lesion clearance is the recommended efficacy outcome. Since the categories are differentiated by lesion thickness, clarify how investigators and prescribers might accurately determine lesion thickness to a certainty of less than 1 mm.

Question 9:
Does the Division agree with the proposed statistical methodology to assess efficacy to support approval?

Response:
Refer to the introductory clinical comments above. The following are general comments regarding the statistical methodology specified in the submitted Phase 3 protocols:

- For interpretation of study findings, the protocols should include a plan to investigate the treatment-by-center interaction and propose a sensitivity analysis to address center outliers if present. To appropriately investigate the center-to-center variability, your Phase 3 trials should be designed to have a reasonable number of subjects per treatment arm per center (e.g., 8 subjects). The investigation should be done on the original data; however, an appropriate pooling algorithm should be pre-specified for handling small centers if the actual enrollment is too small in some centers, as small centers could result in computational/convergence issues in the analysis.

- In addition to the primary analysis population (i.e., the intent-to-treat (ITT) population), we recommend including a per-protocol (PP) population as a supportive analysis population. The key criteria used to define the PP population should be pre-specified in the protocols.

- You have proposed to impute missing data as non-responders as the primary imputation method. In addition, you have proposed to impute missing data using the last observation carried forward (LOCF) approach as a sensitivity analysis for the handling of missing data. We recommend that the protocols pre-specify sensitivity analyses that utilize alternate assumptions to those in the primary imputation method (e.g., multiple imputation) to ensure that the results are not driven by the method of handling missing data.

Question 10:
Does the Division agree with the proposed clinical endpoint for determining primary efficacy in the Phase 3 protocols?

Response:
The primary efficacy analysis is proposed as a responder analysis comparing the two treatment groups based on the proportion of subjects for whom all target lesions are judged to be Clear (PLA=0) at Visit 8 (Day 106).

Complete clearance of all treated lesions is an acceptable primary endpoint.

Question 11:
Does the Agency agree with our assessment that no human dermal safety studies are needed?

Response:
Cumulative irritation studies may be waived in cases where the product formulation has already been shown to be significantly irritating in early Phase clinical studies and will be identified as such in proposed labeling. Likewise, if no component of the drug product absorbs light corresponding to wavelengths of 290 to 700 nm (UVB, UVA, and visible), then Phototoxicity and Photoallergenicity studies may be waived. It appears that your product fulfills the above mentioned exclusions for the human dermal safety studies.

However, you have not provided a rationale for waiving sensitization testing. The duration of exposure to your product is sufficient to cause a significant irritancy; therefore, allergic contact dermatitis may be a possibility as well. Provide a rationale for not conducting sensitivity study. We recommend that you conduct a sensitization dermal safety study or incorporate in your Phase 3 protocol a condition under which you may re-test a subject with potential allergic contact dermatitis.

Question 12:
Does the Division have any comment on the Sponsor's plan to request a pediatric waiver?

Response:
In accordance with FDASIA, you must submit the PSP within 60 days of the EOP2 meeting. See discussion under PREA Requirements below. Your rationale and supporting documentation including SK incidence and prevalence data should accompany any waiver request.

Question 13:
Does the Agency have any comment on the draft protocol?

Response:
In protocol A-101-SEBK-205, you propose to separate the baseline endogenous pharmacokinetic (PK) sampling day and the post dose sampling day by up to 7 days. To minimize risk of any shift in endogenous concentration, we recommend that the baseline sampling day be as close as possible to the post dose sampling day (e.g., separated by 1 day).

Administrative Comments

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

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block

letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

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

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

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

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

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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 Division of Pediatric and Maternal Health at

301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in 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.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

DATA STANDARDS FOR STUDIES

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product

registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm).

505(b)(2) REGULATORY PATHWAY

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

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

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

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

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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

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

/s/

KENDALL A MARCUS
05/08/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 117635

MEETING MINUTES

Aclaris Therapeutics, Inc.
Attention: Christopher Powala
Chief Operating Officer
101 Lindenwood Drive, Suite 400
Malvern, PA 19355

Dear Mr. Powala:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for hydrogen peroxide topical solution, 40%.

We also refer to the meeting between representatives of your firm and the FDA on September 28, 2016. The purpose of the meeting was to discuss the development plan for hydrogen peroxide topical solution, 40%.

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 Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	September 28, 2016, 10:30 – 11:30 AM EST
Meeting Location:	FDA, White Oak Building 22
Application Number:	IND 117635
Product Name:	hydrogen peroxide topical solution, 40%
Proposed Indication:	For the treatment of seborrheic keratoses in adult patients
Sponsor Name:	Aclaris Therapeutics, Inc.
Meeting Chair:	Strother D. Dixon
Meeting Recorder:	Kendall A. Marcus, MD

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
David Kettl, MD, Clinical Team Leader, DDDP
John Kelsey, DDS, MBA Dental Reviewer, DDDP
Jianyong (Jerry) Wang, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III (DB III)
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Jie Wang, PhD, Acting Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3 (DCP 3)
Yanhui Lu, PhD, Clinical Pharmacology Reviewer, DCP3
Yichun Sun, PhD, Quality Assessment Lead, Division of New Drug Products II (DNDP II)/New Drugs Product Branch V (NDPB V)
Sarah Ibrahim, PhD, Product Quality Reviewer, DNDP II/NDPB V
Roy Blay, PhD, Reviewer, Division of Good Clinical Practices Assessment Branch (DGCAB)
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Christopher Powala, Chief Operating Officer, Aclaris
(b) (4), Consultant
Christopher Phillips, Vice President, Manufacturing, Aclaris
(b) (4), Consultant
Kim Forbes-McKean, PhD, Senior Vice President, Drug Development, Aclaris
(b) (4)
Matt Stroschein, Vice President, Project Management, Aclaris

1.0 BACKGROUND

The purpose of the meeting is to discuss the development plan for hydrogen peroxide topical solution, 40%

Regulatory Correspondence History
We have had the following meetings/teleconferences with you:

- December 11, 2015 – Final Responses
- May 6, 2015 – Type B/End-of-Phase 2
- February 25, 2015 – Type C/Guidance
- April 24, 2013 – Type B/Pre-IND

We have sent the following correspondences:

- April 29, 2016 – Advice
- April 29, 2016 – Proprietary Name Granted
- April 8, 2016 – Advice
- October 29, 2015 – Pediatric Study Plan Initial Agreement
- September 29, 2015 – Advice
- September 17, 2015 – Pediatric Study Plan Written Response
- March 4, 2015 – Advice
- November 6, 2014 – Advice
- October 30, 2013 – Study May Proceed
- September 26, 2013 – Information Request

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

Question 5:
Does the Division agree with the planned content and format of the quality information for the NDA? (Section 6.4)

FDA Response to Question 5:
Refer to ICH guideline M4Q(R1), *The Common Technical Document for the Registration of Pharmaceuticals for Human Use- Quality Overall Summary of Module 2 and Module 3: Quality*, for the format and content of the quality information that should be provided in the NDA submission.

We refer you to our End-of-Phase 2 Meeting Minutes regarding informational elements necessary for your drug delivery system for your NDA submission.

2.2. Pharmacology/Toxicology

Question 6:
Does the Division agree that the information provided in SN0018 adequately addresses their previous comments and that safety pharmacology, hERG, genetic toxicology,

carcinogenicity, and reproductive toxicology studies are not required? (Section 6.5)

FDA Response to Question 6:
Yes, we agree.

2.3. Clinical Pharmacology

We have the following general Clinical Pharmacology comments regarding your NDA submission.

To have a complete Clinical Pharmacology section of your NDA submission, you need to provide drug metabolism and drug-drug interaction information of your product. Alternatively, you should provide justification why the drug metabolism and drug-drug interaction information is not available for your product.

We noted that in Attachment 3 (Draft NDA TOC) of your briefing document, there are no bioanalytical assay validation reports for the pharmacokinetic (PK) and bioavailability studies. We recommend that you provide the bioanalytical assay validation reports in Module 5.3.1 of your NDA.

2.4. Clinical/Biostatistics

Question 1:
Does the Division agree with not including certain sections and have any other comments on the draft package insert? (Attachment 1)

FDA Response to Question 1:
Comprehensive review of labeling will not occur until submission of the NDA. In the application, you should provide a rationale for not including Sections 7 and 9 in your application. See Clinical Pharmacology Comments above.

For further information related to Section 7, refer to21 CFR 201.57(c)(8), as well as draft guidance for industry: *Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*

For further information related to Section 9, refer to 21 CFR 201.57(c)(10).

Question 2:
Does the Division agree with the planned submission regarding format, case report tabulations, case report forms, and clinical datasets? (Section 5)

FDA Response to Question 2:
The planned submission format is generally acceptable.

Your proposal to submit raw datasets in accordance with CDISC SDTM version 1.3: Implementation Guide version 3.1.3 and/or in accordance to the general considerations of the Study Data Specifications version 2.0 is acceptable. In addition, your proposal to submit analysis datasets in accordance with ADaM version 2.1: Implementation Guide version 1.1, and/or in accordance to the general considerations of the Study Data Specifications version 2.0 is acceptable.

For the analysis datasets, we have the following general comments:

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

Question 3:
Does the Division have any comments on the draft NDA table of contents? (Attachment 3)

FDA Response to Question 3:
From a technical standpoint (not content related) , the proposed Table of Contents for the planned NDA appears reasonable.

Review of the content of the application will not occur until NDA review.

Question 4:
Does the Division agree with the planned location of the ISE/ISS within the eCTD? (Section 6.3)

FDA Response to Question 4:
Yes. Additional background can be found in the Agency guidance, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

Question 7:
Does the Division have any comment on the revised secondary endpoint and the subsequent analysis plan? (Section 6.6.2)

FDA Response to Question 7:
Provided that your Phase 3 trials have not been unblinded and analyzed, your revised

secondary efficacy endpoint (i.e., the proportion of subjects that have at least 3 of 4 target lesions judged to be "clear" on the PLA at Visit 8 (Day 106)) is acceptable.

We note that you have changed the primary method for the handling of missing data from multiple imputation to non-responder imputation. In addition, we note that your amended statistical analysis plan (SAP) does not include sensitivity analyses for the handling of missing data. We recommend that the SAP include sensitivity analyses that use alternate assumptions to those of the primary imputation method to ensure that the results of the study are not driven by the method of handling missing data.

Meeting Discussion:
The sponsor noted no major issues with the Agency advice. They stated that a revised protocol and revised SAP would be submitted within several weeks. They will include a multiple imputation analysis proposal in this submission.

Question 8:
Does the Division agree with the proposed ISS plans? (Section 6.6.3)

FDA Response to Question 8:
Your proposed approach for the integrated summary of safety (ISS) appears generally reasonable. Section 2.5.5 should contain the Overview of Safety, Section 2.7.4 should contain the Summary of Clinical Safety and Section 5.3.5.3 should contain the Integrated Summary of Safety (ISS).

You should submit Case Report Forms (CRFs) and narratives for all serious adverse events (AEs) regardless of relationship to the study product, pregnancies, severe adverse events and all discontinuations regardless of the reason, for all trials in the development program. In addition, provide narratives for subjects who experienced hair discoloration.

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

a. all serious AEs

b. all patients discontinued regardless of reason

c. all pregnancies

Guidelines for narrative summary content are provided on page 26 of guidance for industry *Premarketing Risk Assessment* at http://www.fda.gov/cder/guidance/6357fnl.pdf.

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).

Ensure that the adverse event (AE) data set contains the following:

a) Full MedDRA Hierarchy
b) Primary and secondary SOCs
c) All data in same version of MedDRA

Include the full text version of any referenced articles.

Submit a tabulated summary of ECG results from Phase 2 and Phase 3 trials to the NDA.

You should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), and an annotated copy of the Case Report Form (which maps variables in the datasets to the CRF).

Question 9:
Does the Division agree with the proposed ISE plans? (Section 6.6.4)

FDA Response to Question 9:
Your proposed approach for the integrated summary of efficacy (ISE) appears reasonable.

It should be noted that the objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, analyses based on pooled efficacy data are considered exploratory. Establishing an efficacy claim would be based on efficacy data from the individual Phase 3 trials along with a replication of study findings.

Findings from subgroup analyses are important for investigating consistency of treatment effect across subgroups; consequently, they are useful for the interpretation of clinical trial findings. You are encouraged to present results of the subgroup analyses for efficacy and safety for each trial individually as well as for the pooled data.

Question 10:
Does the Division agree with the proposed eCRFs and narratives to be included in the NDA (deaths, other serious adverse events, discontinuations due to adverse events)? (Section 6.6.5)

FDA Response to Question 10:
You should submit Case Report Forms (CRFs) and narratives for all serious adverse events (AEs) regardless of relationship to the study product, pregnancies, severe adverse events and all discontinuations regardless of the reason, for all trials in the development program. See, in addition, responses to Question 8.

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 26, 2016 communication granting this meeting, if, at the time of

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

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on PDUFA V and the Program is available at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. 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. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the 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 Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products. The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft

guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

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

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

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

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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.

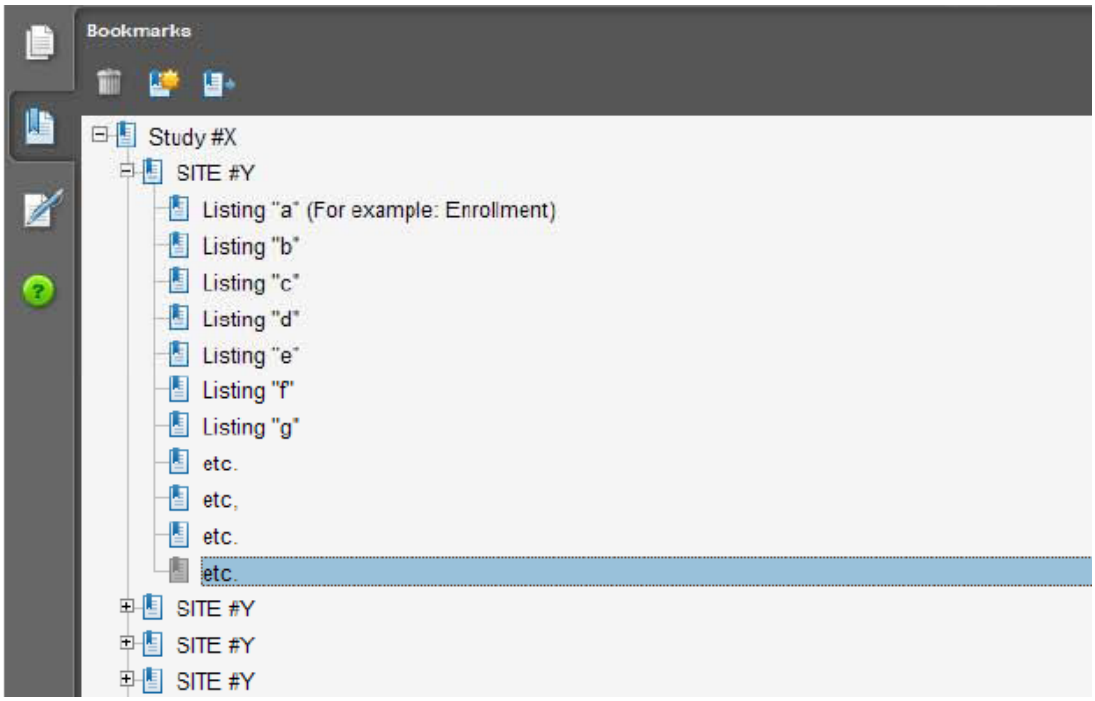
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

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.

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

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

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

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

References:

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

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

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

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

/s/

KENDALL A MARCUS
09/28/2016