

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208081Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 208081

SUPPL #

HFD #

Trade Name Ameluz®

Generic Name aminolevulinic acid hydrochloride gel, 10% with BF-RhodoLED® lamp

Applicant Name Biofrontera Bioscience GmbH

Approval Date, If Known (PDUFA Date)

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

c) Did the applicant request exclusivity?

YES NO

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

3 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?

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# 020965

Levulan (aminolevulinic acid HCl) solution, 20%

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).

N/A

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

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

the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

ALA-AK-CT002: Phase III, randomized, multinational, reference therapy controlled and placebo-controlled, observer-blind to reference therapy and double-blind to placebo, parallel-group study (ratio 3:3:1)

ALA-AK-CT003: Phase III, randomized, double-blind, placebo-controlled, inter-

individual, 2-armed (2:1 ration), multi-center study

ALA-AK-CT007: Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group (2:1 ratio) study

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #3 YES NO

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

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

Investigation #1 YES NO

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Investigation #3 YES NO

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

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

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

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

Investigation #1
IND # 115412 YES ! NO
! Explain:

Investigation #2
IND # 115412 YES ! NO
! Explain:

Investigation #3
IND # 115412 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?

N/A

(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: Belainesh Robnett
Title: Regulatory Health Project Manager
Date: 05/10/2016

Name of Office/Division Director signing form: Kendall A. Marcus, MD
Director, ODE III, Division of Dermatology and Dental Products

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/

BELAINESH ROBNETT
05/10/2016

KENDALL A MARCUS
05/10/2016

EXCLUSIVITY SUMMARY

NDA # 208081

SUPPL #

HFD #

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505(b)(1)

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YES

NO

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

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YES NO

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

N/A

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #3	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input checked="" type="checkbox"/>

Investigation #3

YES

NO

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

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Investigation #1
IND # 115412 YES !
! ! NO
! Explain:

Investigation #2
IND # 115412 YES !
! ! NO
! Explain:

Investigation #3

IND # 115412

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?

N/A

(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: Belainesh Robnett
Title: Regulatory Health Project Manager
Date:

Name of Office/Division Director signing form: Kendall A. Marcus, MD
Director, ODE III, Division of Dermatology and Dental Products

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

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 208081 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Ameluz® Established/Proper Name: aminolevulinic acid hydrochloride with BF-RhodoLED® lamp Dosage Form: gel, 10%		Applicant: Biofrontera Bioscience GmbH Agent for Applicant (if applicable): Wayne F. Vallee/Cardinal Health Regulatory Sciences
RPM: Belainesh Robnett/Paul Phillips		Division: Dermatology and Dental Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="text-align: center;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p style="margin-left: 20px;"><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>	
❖ Actions		
<ul style="list-style-type: none"> Proposed action User Fee Goal Date is <u>May 10, 2016</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> Previous actions <i>(specify type and date for each action taken)</i> 		<input checked="" type="checkbox"/> 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 _____		<input type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only):
 (*confirm chemical classification at time of approval*)

- | | |
|-----------------------------------------------------------|---------------------------------------------------|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

(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

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> 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	<input checked="" type="checkbox"/> No <input type="checkbox"/> 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.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) 5/10/16
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> Most recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input checked="" type="checkbox"/> Included 5/5/16
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 7/10/15
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input checked="" type="checkbox"/> Device Labeling 5/5/16 <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (<i>if it is division-proposed labeling, it should be in track-changes format</i>) 	<input type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included 7/10/15
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included 4/14/16; 4/28/16
❖ Proprietary Name	
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	11/15/15 11/2/15
❖ Labeling reviews (<i>indicate dates of reviews</i>)	RPM: <input checked="" type="checkbox"/> 9/11/15 DMEPA: <input checked="" type="checkbox"/> 1/28/16 DMPP/PLT (DRISK): <input type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 3/16/16 SEALD: <input type="checkbox"/> None CSS: <input type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> 3/30/16 Other: <input type="checkbox"/> None DPMH 3/14/16 CDRH 3/17/16
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (<i>indicate date of each review</i>)	9/15/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included 5/10/16
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12/2/15</u> If PeRC review not necessary, explain: _____ 	
❖ Breakthrough Therapy Designation	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
❖ 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.) (<i>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</i>)	9/18/15 No Filing Review Issues Identified
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> 10/8/14 Pre-NDA
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	
❖ Advisory Committee Meeting(s) <ul style="list-style-type: none"> • Date(s) of Meeting(s) 	<input checked="" type="checkbox"/> No AC meeting
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 5/10/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 3/30/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)		3/22/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)		3/22/16 Page 13 Clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>) ⁵		<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 		<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)		<input checked="" type="checkbox"/> 3/4/16
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> 3/9/16
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> 3/8/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)		<input checked="" type="checkbox"/> 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 <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> 3/9/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews ⁶	
• Tertiary review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> Review #1 3/30/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> CDRH 5/6/16
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	3/30/16 Page 89 OPQ Review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections (<i>action must be taken prior to the re-evaluation date</i>) (<i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>)	<input checked="" type="checkbox"/> Acceptable OPQ Memo to Review 5/10/16 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> 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: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

BELAINESH ROBNETT
05/11/2016

**PeRC Meeting Minutes
December 2, 2015**

PeRC Members Attending:

Lynne Yao
Linda Lewis
Lily Mulugeta
Thomas Smith
Dionna Green
Gerri Baer
Daiva Shetty
Meshawn Payne
Shrikant Pagay
Belinda Hayes
Michelle Roth-Cline
George Greeley
Hari Cheryl Sachs NON-RESPONSIVE
Dianne Murphy NON-RESPONSIVE
Barbara Buch NON-RESPONSIVE
Adrienne Hornatko-Munoz NON-RESPONSIVE
Wiley Chambers
Greg Reaman NON-RESPONSIVE
Maura O'Leary NON-RESPONSIVE

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NON-RESPONSIVE

	NDA 208081	Ameluz (aminolevulinic acid hcl) Gel (Full Waiver) with Agreed iPSP	DDDP	Paul Phillips	Treatment of actinic keratosis (AK) of mild to moderate severity on the face and scalp (b) (4)
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NON-RESPONSIVE

NON-RESPONSIVE

6 Pages have been Withheld in Full as NON-RESPONSIVE immediately following this page

Ameluz (aminolevulinic acid hcl) Gel Full Waiver (with Agreed iPSP)

- Proposed Indication: Treatment of actinic keratosis (AK) of mild to moderate severity on the face and scalp [REDACTED] (b) (4)
- *PeRC Recommendations:*
- The PeRC concurred with the Division to grant a full waiver because the disease/condition does not exist in pediatric patients.

NON-RESPONSIVE

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/s/

GEORGE E GREELEY
12/15/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 208081

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Biofrontera Bioscience GmbH
c/o Cardinal Health Regulatory Sciences
Commerce Plaza II, Suite 300
7400 West 110th Street
Overland Park, KS 66210

ATTENTION: Wayne F. Vallee, R.Ph., RAC
Director, Regulatory Affairs and Product Development

Dear Mr. Vallee:

Please refer to your New Drug Application (NDA), dated and received July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Aminolevulinic Acid Hydrochloride Gel, 10%.

We also refer to your correspondence, dated and received August 26, 2015, requesting review of your proposed proprietary name, Ameluz.

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

If any of the proposed product characteristics as stated in your August 26, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

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

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

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Anderson, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0675. For any other information regarding this application, contact Robnett Belainesh, Regulatory Project Manager in the Office of New Drugs, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
11/15/2015



NDA 208081

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

Biofrontera Bioscience GmbH
C/o Cardinal Health Regulatory Sciences
Attention: Wayne F. Vallee, RPh, RAC
Director, Regulatory Affairs & Product Development
7400 West 110th Street, Suite 300
Overland Park, KS 66210

Dear Mr. Vallee:

Please refer to your New Drug Application (NDA) dated and received July 10, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for aminolevulinic acid HCl gel, 10% with BF-RhodoLED® lamp.

We also refer to your amendments dated July 22, August 17 and 26, 2015.

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 May 10, 2016.

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 March 30, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please 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:

Chemistry, Manufacturing and Controls

1. We recommend that you develop an in vitro release test (IVRT) methodology and propose in vitro release acceptance criteria (range) for your drug product to be used at release and during stability as a quality control parameter. Your proposed acceptance criteria should be based on generated data for the final to-be-marketed batches. Submit all the generated data in electronic format.
2. Along with the proposed in vitro release specification, include the IVRT method development and validation report. The IVRT method development report should contain (but is not limited to) justification for the selection of the following methodology components:
 - a. Diffusion Apparatus
 - b. Receptor Medium Selection
 - c. Membrane Selection
 - d. Sampling Time Points
 - e. Temperature
3. The IVRT method validation report should contain (but is not limited to) the following validation components:
 - a. Linearity and Range
 - b. Accuracy/Precision and Reproducibility
 - c. Mass Balance
 - d. Sensitivity and Specificity
 - e. Selectivity
 - f. Robustness
 - g. Membrane Inertness
 - h. Receptor Solution Solubility/Stability
4. The IVRT method's sensitivity, specificity, selectivity and robustness need to be performed with altered product lots that contain 50% and 150% of the label claim of active pharmaceutical ingredient (API) in the reference product, with the test evaluating a minimum of one run of 6 diffusion cells each per product concentration, including the reference.
5. The August 31, 2015, communication from the drug product manufacturer (b) (4) indicated that:

(b) (4)

Finished drug product will be manufactured in November 2015, after changes a – c are implemented. These changes in the equipment and the manufacturing process (including updated batch records) must therefore be submitted as an amendment to the current application NDA 208081 for review by the Agency.

Clinical Pharmacology

6. The dose of BF-200 ALA 10% gel applied in the maximal use pharmacokinetic (PK) trial (ALA-AK-CT006) was 2g to a 20cm² surface area of the face. [REDACTED] (b) (4)
[REDACTED]
[REDACTED] Clarify the maximum dose and application area you propose to be used clinically (e.g., one 2 g tube and application area of 20 cm²) and provide justification on how the dose and application area used in the maximal use PK trial would support your proposed clinical use.
7. The maximal use PK trial assessed systemic exposure following application to the face only, while you are seeking an indication of the face and scalp. Drug absorption may be different when applied to face compared to scalp. Provide a detailed rationale on how the systemic exposure data obtained following application to the face in the maximal use PK trial would support an indication in the scalp.
8. In your bioanalytical report (CRS study no. 199/12-03.AA) for the maximal use PK trial, submit the incurred sample reanalysis (ISR) results for Protoporphyrin IX (PpIX).
9. Provide additional long term storage stability data to support long term storage of 5-ALA plasma samples for (b) (4) months (current report provides data to cover only 13 months of stability at -20°C).

Clinical

10. Provide rationale for assuming the applicability of foreign data to U.S. population/practice of medicine or identify location in the application.
11. Provide justification for not conducting a thorough QT study.
12. Submit an annotated CRF in order to trace the SDTM data to its origin.
13. In trial ALA-AK-CT007, 94 (22%) of records in ADAE are not traceable to SDTM. Provide clarification.
14. In trial ALA-AK-CT002 and trial ALA-AK-CT007, there are subjects with missing baseline laboratory (LFTs) results. Provide the missing data or clarify.
15. In trial ALA-AK-CT002, there are subjects without any laboratory (LFTs) tests. Provide the missing data or clarify.

Device

16. In the User Manual on page 11/25, section 7.2.2 shows the Home Screen which includes a place for lamp settings. You stated that the US version has output energy and time fixed. You should clarify what is the function of the setting feature in the US model or provide a statement that this feature has been disabled in the US model.
17. On page 4/25, Intended Use, the intended use is given as "...used exclusively in combination Ameluz gel for [REDACTED] (b) (4) We recommend that the intended use state the specific indication for use that will be granted for aminolevulinic acid HCl in this NDA. Since the lamp will be sold as a separate item and it is possible that aminolevulinic acid HCl gel may obtain approval for indications outside the US not granted in the US, the US model's User Manual should clearly state the US approved indication for use.
18. Since the last step in the treatment of actinic keratosis using aminolevulinic acid HCl will be light exposure, it seems appropriate that the lamp User Manual also include any warnings or precautions associated with possible photosensitive side-effects from the treatment. Addition of these precautions to the BF-RhodoLED User Manual would be appropriate since the light exposure is the last step in the treatment process.

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 42 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:

You did not provide a review and summary of the available literature to support the content in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of

labeling. Submit the following information on topical aminolevulinic acid HCl use in pregnant and lactating women or provide a rationale for not doing so:

- Review and summary of all available published literature
- A revised labeling incorporating the above information (in Microsoft Word format) that complies with PLLR

In addition, you should submit any data on a drug's negative impact on fertility, if applicable.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by October 21, 2015. 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.

Please respond only to the above requests for information by October 21, 2015. 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.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

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

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), 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 Belainesh Robnett, Regulatory Project Manager, at (240) 402-4236.

Sincerely,

{See appended electronic signature page}

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

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/s/

KENDALL A MARCUS
09/18/2015



PIND 115412

MEETING MINUTES

Biofrontera Bioscience GmbH
Cardinal Health Specialty Solutions
Attention: Wayne F. Vallee, RPh, RAC
Director, Managing Consultant
7400 West 110th Street, Suite 300
Overland Park, Kansas 66210

Dear Mr. Vallee:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Ameluz[®] Gel, 78 mg/g with BF-RhodoLED[®] red light illumination.

We also refer to the teleconference between representatives of your firm and the FDA on October 8, 2014. The purpose of the teleconference was to discuss the planned NDA submission for the entire combination product comprised of Ameluz[®] 78 mg/g gel with the BF-RhodoLED[®] red light illumination.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 8, 2014, 8:30 AM
Meeting Format: Teleconference

Application Number: PIND 115412
Product Name: Ameluz[®] (5-aminolevulinic acid hydrochloride) Gel, 78 mg/g with BF- RhodoLED[®] red light illumination
Proposed Indication: (b) (4) treatment of actinic keratosis of mild to moderate intensity on the face and scalp
Sponsor Name: Biofrontera Bioscience GmbH

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Cristina Attinello

FDA ATTENDEES

Kendall A. Marcus, M.D., Acting Deputy Director for Safety, DDDP
Gordana Diglisic, M.D., Clinical Team Leader, DDDP
Denise Cook, M.D., Clinical Reviewer, DDDP
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Jiaqin Yao, Ph.D., Pharmacology Reviewer, DDDP
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III
Carin Kim, Ph.D., Biostatistics Reviewer, DB III
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Chinmay Shukla, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Jessica Weintraub, Pharm.D., Safety Evaluator, OSE/DPV I
Carolyn McCloskey, Pharm.D., Epidemiology Medical Officer, OSE/DEPI I
Roy Blay, Ph.D., Reviewer, DGCAB
Lisa Lin, Senior Regulatory Analyst, OBI
Richard Felten, Device Reviewer, CDRH
Maria R. Walsh, R.N., M.S., Associate Director for Regulatory Affairs, ODE III
Cristina Attinello, M.P.H., Senior Regulatory Health Project Manager, DDDP
Janet Anderson, Pharm.D., Safety Regulatory Project Manager, OSE

SPONSOR ATTENDEES

Hermann Lübbert, Ph.D., Managing Director, CEO, Biofrontera Bioscience GmbH

Montserrat Foguet, Ph.D., Head of RA and Production, Biofrontera Bioscience GmbH
Beate Schmitz, Ph.D., Project Manager, Biofrontera Bioscience GmbH

(b) (4)

Wayne F. Vallee, RPh, RAC, Director, Managing Consultant, Cardinal Health, U.S. Agent

(b) (4)

Purpose of the Meeting:

To discuss the planned NDA submission for the entire combination product comprised of Ameluz[®] 78 mg/g gel with the BF-RhodoLED[®] red light illumination

Regulatory Correspondence History

We have had the following teleconference with you:

- July 11, 2012: Pre-IND Meeting

Regulatory

Question 1:

In the Pre-IND meeting, Biofrontera suggested using 505(b)(1) as regulatory basis for NDA filing. Having reconsidered its position, the company plans to base the NDA on 505(b)(2).

Does the Agency agree with the proposed approach?

Response:

Yes, if you plan to rely upon published literature that is necessary for approval, your application will be a 505(b)(2) NDA. Refer to the 505(b)(2) Regulatory Pathway section below for further information regarding 505(b)(2) NDAs, particularly with respect to providing a scientific justification for reliance on published literature.

Chemistry, Manufacturing and Controls (CMC)

Question 10:

Does the Agency agree with the proposed release specifications for Ameluz[®] drug product and drug substance?

Response:

We agree that the proposed specifications are reasonable to support NDA submission. The adequacy of the specifications to support NDA approval will be determined in the NDA review. We notice that minimal fill and packaging integrity are not included in your proposed drug product specification. We recommend that minimal fill be added to drug product release specification and packaging integrity (interior and exterior) be added to drug product release and stability specifications.

Question 12b:

Does the Agency agree to the time plan of submitting follow-up data for drug substance and drug product stability during NDA review?

Response:

Yes, the proposed stability update by month 5 is acceptable, provided that 12 months of stability data from three registration stability batches will be included in the initial submission as stated for both drug substance and drug product.

Additional Comments

1. Provide weight loss data for the three drug product registration stability batches.
2. Provide (b) (4) potential data for Phase 3 clinical and registration stability batches.
3. Include information regarding drug substance manufacturing/testing facilities and your proposed drug substance regulatory specification in Module 3.

Meeting Discussion:

The sponsor inquired about the rationale for (b) (4)
(b) (4)
The Agency agreed to provide further feedback once the sponsor submits their proposal to address this issue.

Pharmacology/Toxicology

Question 9:

Does the Agency agree that the nonclinical studies appear to be adequate for review in support of Ameluz[®] registration in the proposed indication considering the minimal systemic exposure after topical application?

Response:

Based on the summary information provided in your briefing document, nonclinical information including nonclinical studies conducted with your drug substance/product and published data derived from literature appears to be adequate to support an NDA submission of your drug product. However, the adequacy of these nonclinical studies and publications from literature will be determined after review.

Because a slight, transient increase in plasma levels of 5-aminolevulinic acid (ALA) following topical treatment with Ameluz[®] was observed in the maximal use pharmacokinetic study (ALA-AK-CT006), nonclinical information should be submitted in an appropriate format to address the nonclinical requirements for an NDA in your original submission. A copy of each publication from literature to support your NDA should be submitted. The literature references should be organized in your NDA submission to allow for determination of what nonclinical information is provided in each literature reference. Appropriate wording in nonclinical sections of labeling for your drug product should be carefully proposed based on either nonclinical studies conducted or information provided in submitted literature references.

Because complete data are not currently available, the perceived nonclinical data requirements may change during review of the NDA.

Clinical Pharmacology

Question 2:

The briefing book provides a summary of the clinical pharmacology, pharmacokinetic and efficacy/safety studies. In particular, the company has considered the advice obtained in the Pre-IND meeting and will present additional clinical data, including data from two Phase I safety studies, a dermal sensitization study in accordance with FDA guidance and a maximal use PK study as well as an additional Phase III study for the treatment of mild to moderate AK with Ameluz[®] in combination with BF-RhodoLED[®].

Does the Agency agree that the updated clinical database is adequate for review in consideration of approval of the combination product Ameluz[®] / BF-RhodoLED[®] for the proposed indication?

Response:

From a clinical perspective, the clinical database is acceptable for review in consideration of approval of the combination product Ameluz[®] / BF-RhodoLED[®] for the proposed indication with the following exception:

We note that in your maximal use pharmacokinetic (PK) trial (ALA-AK-CT006) you have applied 2 g dose to a 20 cm² surface area of the face. It is not clear what dose and surface area you intend to propose for clinical use and how they relate to the conditions you studied in the maximal use PK trial. We also note that you are planning on seeking an indication to treat AK on both face and scalp and you have not assessed drug exposure following application on the scalp. We cannot comment on the adequacy the maximal use PK trial at this time. Provide a detailed rationale in your NDA.

Clinical/Biostatistics

Question 3:

An ISE outline describing the overall analysis approach and the statistical methods to be employed for analysis of efficacy will be provided in the briefing documents. Does the Agency agree with the company's approach to the ISE for the combination product Ameluz[®] / BF-RhodoLED[®]?

Response:

Your proposed approach for the ISE appears reasonable. In addition to the pooled Phase 3 results, the ISE should include comprehensive in-depth analysis of the total efficacy results, and should discuss the extent to which the results of the relevant studies reinforce or do not reinforce each other. This may require additional discussion beyond individual study summaries and a pooled analysis. For additional information on the content of the ISE, refer to guidance for industry *Integrated Summary of Effectiveness* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079803.pdf>).

While you plan to conduct hierarchical statistical testing in “four strata” (page 32), it should be noted that establishing an efficacy claim would be based on efficacy data from individual Phase 3 trials along with a replication of study findings.

Question 4:

An ISS outline describing the overall analysis approach and the statistical methods to be employed for analysis of safety will be provided in the briefing document. Does the Agency agree with the company’s approach to the ISS for the combination product Ameluz[®] / BFRhodoLED[®]?

Response:

Your approach for the ISS is reasonable. We have the following additional comments:

- TEAEs for the pivotal trials and those that occur during long term safety should be reported separately.
- Provide separate summary tables for TEAEs that occur with a frequency of $\geq 1\%$ for both all TEAEs and those determined to be related to drug/device.

Question 5:

Does the Agency agree that no Risk Management Plan / Risk Evaluation and Mitigation Strategy is necessary for the combination product Ameluz[®] / BF-RhodoLED[®]?

Response:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Question 6:

Biofrontera proposes to provide Financial Certification and/or Disclosure information (Form FDA 3454/3455) only for investigators who participated in the two pivotal studies as well as the additional phase III study under conduct and not for any other study.

Does the Agency agree that this is acceptable?

Response:

This is acceptable.

Question 7:

Biofrontera proposes to provide narratives and case report forms for patients from all clinical studies who meet the following criteria:

- Deaths within 3 months after the last PDT
- Any SAE, regardless of causality

- Any AE leading to study drug discontinuation, regardless of causality

The submitted CRFs will be indexed with study subject ID. Additional CRFs are available upon request.

Does the Agency agree with the plan of providing case report forms and patient narratives?

Response:

This is acceptable.

Question 8:

All datasets that will accompany the clinical study reports will be submitted in CDISC SDTM Version 3.1.2. (phase I trials) and 3.1.3 format (phase II and phase III trials), respectively. As specified in the company position in [Question 10.3](#) , the ISE will include a presentation of the phase II study and a pooled presentation of efficacy data of phase III studies. Safety data will be presented in an ISS as outlined in [Question 10.4](#) and will include phase I data as well as a pooled presentation of data from phase II and phase III studies. The integrated databases of efficacy and safety will be submitted in CDISC SDTM Version 3.1.3 format. Since CDISC datasets will be provided, no additional legacy datasets will be submitted for traceability of the original study report data.

SAS files will be submitted to accompany the NDA submission documents. Does the Agency agree with the proposed plan for submission of SAS files to accompany the submission?

Response:

It is acceptable to submit datasets as SAS transport (xpt) files. In terms of “traceability”, the database for the Phase 3 trials should include datasets containing raw variables directly from the CRF, and you should submit both the study-level data tabulations (SDTM format datasets) and the study-level analysis datasets as SAS transport files. If the SDTM data being submitted is not traceable directly back to the CRFs, then you must submit the intermediary legacy data which is traceable back to the CRFs and that was used to generate the SDTM datasets.

Meeting Discussion:

In response to the Agency’s inquiry regarding an intermediary legacy dataset between the CRF and the SDTM, the sponsor clarified that their SDTM is the raw dataset that traces directly back to the CRFs. The sponsor stated that they would submit individual SDTM, ADaM datasets for each Phase 3 trial and also submit pooled datasets for the ISE and ISS.

In particular, note the following:

1. Each analysis dataset should include the treatment assignments, baseline assessments, study site variable, 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.

2. The analysis dataset documentation (define.pdf file) should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. The documentation should indicate which variables are derived.
3. Definition files for raw datasets modeled according to CDISC/SDTM and standards should be submitted as .xml file types (define.xml). Refer to CDISC's Define.XML page for assistance/guidance related to creating define.xml files for CDISC/SDTM data. Also, for ease of viewing by the reviewer and printing, submit corresponding define.pdf files in addition to the define.xml.
4. Statistical programs for any non-standard analyses should be submitted.
5. 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).
6. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

You are encouraged to arrange a test submission, prior to actual submission. Please refer to the Submit a Sample eCTD or Standardized Data Sample to the FDA Website (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>) for guidance on sending a test submission.

Question 11:

Does the Agency agree that the proposed BF-RhodoLED[®] information and positioning within the NDA, along with the supporting documentation are adequate for review leading to approval?

Response:

The Center for Devices and Radiological Health (CDRH) does agree that use of the STED format is acceptable in terms of how the device information is presented. We would like to advise you that using this format does not relieve you of the need to provide adequate information demonstrating device safety. It is assumed that a detailed user manual will also be included in the device submission. Also see response to Question 12 for including the information in the eCTD electronic format.

In reviewing the list of performance standards applied, in Table 10-11 it was noted that you used IEC 62304:2006 for software. Although this standard is recognized by CDRH it does not include requirements for the information required by CDRH related to software verification and validation. It is recommended that you obtain a copy of the CDRH guidance document *Software Verification and Validation for Premarket Submissions*. This guidance can be located on the FDA web site at www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm089543.htm

Question 12a:

For the phase III trials ALA-AK-CT002 and ALA-AK-CT003 6- and 12-month follow-up data will be presented at the time of submission. The primary efficacy and safety analysis for the ongoing clinical phase III trial (protocol ALA-AK-CT007) will be presented in the NDA.

Does the Agency agree that no follow-up data for the study ALA-AK-CT007 is necessary for review in consideration of approval of the combination product Ameluz[®]/ BF-RhodoLED[®]?

Response:

The follow-up safety data from trial ALA-AK-CT007 should be presented in the 120 day safety update.

Question 12c:

Does the FDA agree that the contents of the NDA seem appropriate for review and that no additional data, other than agreed-upon updated stability data , are required for the filing of the NDA?

Response:

We recommend that the application be submitted in eCTD format, according to guidance for industry: *Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

A. General eCTD comments:

- 1.6.3 Correspondence regarding meetings – a single pdf file can be provided (instead of separate pdf files for each document) with proper bookmarks of all correspondence, table of contents and hyperlinks.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 (tabular format), should be linked to the referenced studies in m5.
- To submit the descriptive portion (only) of a post marketing report in eCTD format, it should be provided as a single pdf file with bookmarks, table of contents and hyperlinks in eCTD section, m5.3.6. Ensure that the leaf title of the report includes the reporting period, since each report is for a specific time period.
- Except otherwise agreed upon by the Division, use m5.3.5.4 for Companion Diagnostic/Device Clinical Data or Study Reports and use m3.2.P.7 if you are submitting the structure of the device and how it interacts with the drug.
- Remember to provide proper page orientation for all pdf files.

B. Device constituent part location using eCTD format:

Generally, the information for the device should be located in the same module that would provide similar information for the drug or biological product. Do not use eCTD module 3.2.R for this information. Instead use the following principles.

1. For eCTD format and use of the system, adhere to eCTD headings as defined per ICH and FDA specifications. In the specifications, these may be identified as leaf nodes or elements. Specifically, any title that is associated with a numerical item should not change; i.e., Item 3.2.P.7 should say “Container Closure System.”
2. Do not use "node extensions" to create new elements. Although this is described in the eCTD specification, and may be acceptable in some regions, it is not acceptable in submissions to FDA.
3. When including and referencing device information, we recommend the following:
 - a. You may reference files under 3.2.P.7 which are not currently listed as numerical items in ICH and FDA specifications and guidance.
 - b. In 3.2.P.7 you could include a leaf titled something similar to the following, “Table of Contents for the BF-RhodoLED.” This leaf/document could provide reference links to the other files in module 3.2.P.
 - c. The leaf titles should be clear, concise and indicative of the document's content.
4. Module 1.4.4 cross reference to other applications is a location where you can provide references to other applications and you can include copies of an application’s table of contents, reference tables, or other similar documents. If you are cross referencing another company's application or master file, include the appropriate letters of authorization from the other companies in modules 1.4.1 - 1.4.3 (1.4.1 Letter of authorization, 1.4.2 Statement of right of reference, 1.4.3 List of authorized persons to incorporate by reference). If there are standards you will reference in the Performance Specifications which also meet these criteria, then put them in module 1.4.4. The Performance Specifications section should link to this information.
5. All device information pertaining to manufacturing or assembly of the finished combination product and documents necessary to demonstrate compliance with 21 CFR Part 4 - Current Good Manufacturing Practice Requirements for Combination Products accessible at <https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products>. All applicable documents should be located in Section 3.2.P.3.
 - a. The list of manufacturing facilities provided on the Form FDA 356h, or as an attachment to the form, should explicitly describe the manufacturing, assembly, or testing processes taking place at each site with regards to the device constituent part.
6. Provide an "Information to Reviewers” or “Reviewers Guide” document in Module 1.2 Cover letters. This document would be separate from the cover letter and referenced after the cover letter. It would provide a high level overview (with reference links) of the submission’s content and list where the information is located in the eCTD. For example, it would identify where drug, device and combination product information and all manufacturing information is located.

Additional Comments

1. Provide in the NDA a full summary of worldwide safety data of your combination product to date.
2. Include in the NDA, at a minimum, for all clinical trials the protocols, line listings of adverse events, SAEs, vital signs, laboratory results including biopsies, along with summary tables.
3. Submit the PK data from your maximal use PK trial (ALA-AK-CT006) in SAS transport format. Also submit the bioanalytical method validation reports and bioanalysis reports in your NDA.
4. If you intend to market your product under a proprietary name, you must submit your proposed proprietary name for review. Refer to guidance for industry: *Contents of a Complete Submission for the Evaluation of Proprietary Names* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).
3. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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 EOP2 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 Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

Meeting Discussion:

As there was no End-of-Phase 2 Meeting, the sponsor was advised to submit the initial PSP as soon as possible to the PIND. The sponsor agreed, understanding that the agreed PSP must be in place prior to NDA submission.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

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

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

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)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

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.

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).

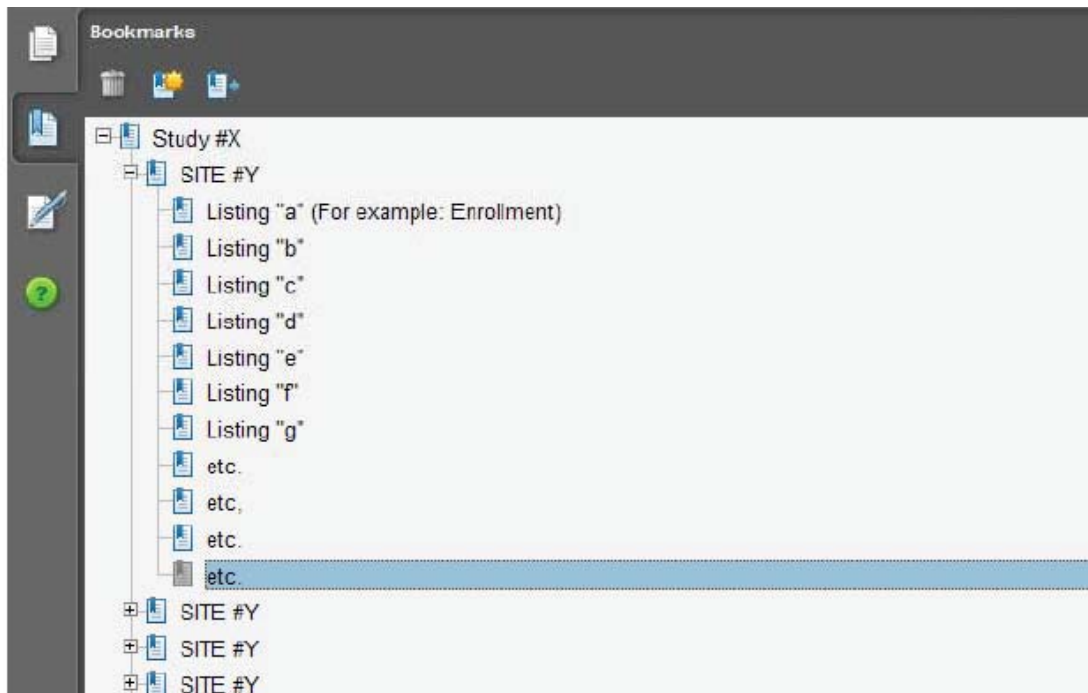
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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

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/s/

KENDALL A MARCUS
10/10/2014