

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206333Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 206333

SUPPL #

HFD # 540

Trade Name Kybella

Generic Name Deoxycholic acid

Applicant Name Kythera Biopharmaceuticals, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

N/A

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

N/A

d) Did the applicant request exclusivity?

YES NO

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

5 years

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

YES NO

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

N/A

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

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

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

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

YES NO

If yes, explain:

Name of person completing form: Matthew White
Title: Senior Regulatory Health Project Manager
Date: April 13, 2015

Name of Office/Division Director signing form: Kendall A. Marcus, MD
Title: Director, 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/

MATTHEW E WHITE
04/21/2015

KENDALL A MARCUS
04/21/2015

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 206333 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: Kybella Established/Proper Name: deoxycholic acid Dosage Form: injection		Applicant: Kythera Biopharmaceuticals, Inc. Agent for Applicant (if applicable): Diane Stroehmann
RPM: Matthew White		Division: DDDP
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="margin: 0;"><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>5/13/15</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. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1
(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 | |

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 checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input checked="" 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 (including approval letter with final labeling)	Action(s) and date(s) 4/29/15
Labeling	
❖ Package Insert (write submission/communication date at upper right of first page of PI)	
<ul style="list-style-type: none"> Most recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (write submission/communication date at upper right of first page of each piece)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling (if it is division-proposed labeling, it should be in track-changes format) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Original applicant-proposed labeling 	<input checked="" type="checkbox"/> Included
❖ Labels (full color carton and immediate-container labels) (write submission/communication date on upper right of first page of each submission)	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Letter – Kybella Denied: 8/12/14 Letter – Belkyra Granted: 12/18/14 Letter – Kybella Granted: 4/10/15 Review – Kybella Unacceptable: 8/5/14 Review – Belkyra Acceptable: 12/12/14 Review – Kybella Acceptable: 3/23/15
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (indicate date(s)) Review(s) (indicate date(s)) 	
❖ Labeling reviews (indicate dates of reviews)	RPM: <input type="checkbox"/> None 6/30/14 DMEPA: <input type="checkbox"/> None 12/8/14 DMPP/PLT (DRISK): <input type="checkbox"/> None 3/23/15 OPDP: <input type="checkbox"/> None 3/20/15 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting (indicate date of each review)	7/2/14
❖ 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 (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ 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 type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>12/3/14</u> If PeRC review not necessary, explain: _____ 	
<ul style="list-style-type: none"> ❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>) 	6/19/14: Information Request 6/30/14: NDA Acknowledge 7/10/14: Filing - Issues Identified 7/24/14: Method Validation Request 7/28/14: Method Validation Received 9/4/14: Information Request 10/2/14: Information Request 10/16/14: Information Request 10/22/14: Information Request 11/5/14: Information Request 1/16/15: Late-Cycle Backgrounder 1/20/15: Labeling/PMR 2/02/15: Labeling comments 3/06/15: Labeling comments 4/13/15: Labeling comments 4/23/15: Labeling/PMR comments 4/27/15: Labeling comments
<ul style="list-style-type: none"> ❖ 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) 	
<ul style="list-style-type: none"> ❖ 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 type="checkbox"/> No mtg 11/13/13
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 4/20/11
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 10/17/14
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 1/27/15
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	8/19/09: Guidance
<ul style="list-style-type: none"> ❖ Advisory Committee Meeting(s) 	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	3/9/15
Decisional and Summary Memos	
<ul style="list-style-type: none"> ❖ Office Director Decisional Memo (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4/24/15
<ul style="list-style-type: none"> Division Director Summary Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 4/3/15
<ul style="list-style-type: none"> Cross-Discipline Team Leader Review (<i>indicate date for each review</i>) 	<input type="checkbox"/> None 3/17/15
<ul style="list-style-type: none"> PMR/PMC Development Templates (<i>indicate total number</i>) 	<input type="checkbox"/> None 1
Clinical	

❖ Clinical Reviews		
• Clinical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (indicate date for each review)		Filing Review: 6/26/14 Clinical Review: 3/15/15
• Social scientist review(s) (if OTC drug) (indicate date for each review)		<input 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 (indicate date of review/memo)		
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (indicate date of each review)		<input type="checkbox"/> None ENTB/CDRH: 11/19/15 SEALD: 1/9/15 DPMH: 2/17/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (indicate date of each review)		<input checked="" type="checkbox"/> N/A
❖ Risk Management		
• REMS Documents and REMS Supporting Document (indicate date(s) of submission(s))		N/A
• REMS Memo(s) and letter(s) (indicate date(s))		N/A
• Risk management review(s) and recommendations (including those by OSE and CSS) (indicate date of each review and indicate location/date if incorporated into another review)		<input type="checkbox"/> None 4/3/15
❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators)		<input type="checkbox"/> None requested Inspection Summary: 2/17/15 Letter-Bhatia: 1/16/15 Letter-Monheit: 1/9/15
Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)		<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (indicate date for each review)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (indicate date for each review)		<input type="checkbox"/> None Filing Review: 6/27/14 Discipline Review: 12/19/14
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)		<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (indicate date for each review)		<input type="checkbox"/> None Filing Review: 6/30/14 Discipline Review: 12/16/14
❖ OSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)		<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 11/3/14
• Supervisory Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review 12/16/14
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/16/14
❖ 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	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)	<input type="checkbox"/> None Filing Review: 6/30/14 Discipline Review #1: 12/19/14 Final CMC Review: 4/24/15
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not needed Filing Review: 6/25/14 Discipline Review: 12/1/14
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ 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>)	
<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"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report; date completed must be within 2 years of action date) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁵</i>)	Date completed: Filing Review: 6/23/14 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

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

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)

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>)
❖ 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 checked="" 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

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

/s/

MATTHEW E WHITE
04/29/2015

From: White, Matthew
To: Diane Stroehmann (dstroehmann@kytherabiopharma.com)
Cc: Gould, Barbara
Subject: NDA 206333 for Kybella (deoxycholic acid) injection: Agency Proposed Label
Date: Monday, April 27, 2015 5:03:00 PM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kybella (deoxycholic acid) injection.

We have reviewed your draft package insert (PI) submitted April 24, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by April 28, 2015.



Agency Proposed
PI_4_27_15_NDA 206333

Regards,

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE

04/28/2015

Emailed to the Applicant on 4/27/15

From: White, Matthew
To: Diane Stroehmann (dstroehmann@kytherabiopharma.com)
Cc: Gould, Barbara
Subject: NDA 206333 for Kybella (deoxycholic acid) injection - Agency Proposed Labeling
Date: Wednesday, April 22, 2015 5:27:00 PM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kybella (deoxycholic acid) injection.

We have reviewed your draft package insert (PI) submitted April 13, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by April 24, 2015.



Agency Proposed
PI_NDA 206333_4_2:



Agency Proposed
Patient Labeling_NDA

We have also reviewed your draft carton and container labeling. The Agency's proposed edits are below. Please submit your concurrence with or your counterproposal to the Agency proposed carton and container labeling by April 24, 2015.

- Replace "tradename" with "Kybella" on the immediate container labels.

In addition, the Agency has modified the language for the postmarketing requirement that you acknowledged and submitted your timeline for on January 30, 2015. The modified PMR is below.

PMR Description: A safety assessment of deoxycholic acid treatment in subjects aged 65 years and older. This assessment is to be performed in the ongoing ATX-101-13-28 trial population of subjects aged 65 to 75 years. To the extent possible, all subjects should be continued through the planned end of the trial (even if a full course of treatment is not administered).

Trial Completion: 04/2016
Final Report Submission: 09/2016

Please submit your acknowledgment of the PMR and any revisions to the previously submitted timeline by April 24, 2015.

Contact me if you have any questions.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration
E-mail: matthew.white@fda.hhs.gov
Phone: 301-796-4997
Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/23/2015

From: White, Matthew
To: Diane Stroehmann (dstroehmann@kytherabiopharma.com)
Cc: Gould, Barbara
Subject: NDA 206333 for deoxycholic acid injection: Agency proposed label
Date: Monday, April 13, 2015 10:31:00 AM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid injection.

We have reviewed your draft package insert (PI) submitted March 19, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by April 16, 2015.



Agency Proposed
Label_NDA 206333_d



Agency Proposed
Patient Labeling_NDA

We have also reviewed your draft carton and container labeling. The Agency's proposed edits are below. Please submit your concurrence with or your counterproposal to the Agency proposed carton and container labeling by April 16, 2015.

Please revise both container carton labels as shown below:

- Display "Do not dilute" statement on both carton labels.
- In the ingredients list on the cartons, please include percentage composition of all ingredients in parentheses e.g.:
 - Deoxycholic acid (1%)

Regards,

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration

E-mail: matthew.white@fda.hhs.gov

Phone: 301-796-4997

Fax: 301-796-9895

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/s/

MATTHEW E WHITE
04/13/2015



NDA 206333

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Kythera Biopharmaceuticals, Inc.
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

ATTENTION: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs,
Pharmacovigilance and Research Compliance

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid Injection 20 mg/2 mL (10 mg/mL).

We also refer to your correspondence, dated January 19, 2015, received January 20, 2015, requesting review of your proposed proprietary name, Kybella.

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

If any of the proposed product characteristics as stated in your January 19, 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 Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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
04/10/2015

From: White, Matthew
To: [Diane Stroehmann \(dstroehmann@kytherabiopharma.com\)](mailto:dstroehmann@kytherabiopharma.com)
Cc: [Gould, Barbara](#)
Subject: NDA 206333 for deoxycholic acid injection
Date: Friday, March 06, 2015 1:42:00 PM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid injection.

We have reviewed your draft package insert (PI) submitted January 30, 2015. The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by March 16, 2015.



Agency Proposed
Label_3_6_15_NDA 2

We have also reviewed your draft carton and container labeling submitted February 9, 2015. The Agency's proposed edits are below. Please submit your concurrence with or your counterproposal to the Agency proposed carton and container labeling by March 16, 2015.

Carton Labeling:

- Include the statement "Single Use Vials. Discard Unused Portion" to the principal display panels, over the statement "four ready-to-use vials" (as presented on the other panels of the carton).

Regards,

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research Food
and Drug Administration

E-mail: matthew.white@fda.hhs.gov

Phone: 301-796-4997

Fax: 301-796-9895

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/s/

MATTHEW E WHITE
03/06/2015

From: White, Matthew
To: [Diane Stroehmann \(dstroehmann@kytherabiopharma.com\)](mailto:dstroehmann@kytherabiopharma.com)
Cc: [Gould, Barbara](#); [Attinello, Cristina](#)
Subject: NDA 206333 for deoxycholic acid injection: Carton and Container Labeling
Date: Monday, February 02, 2015 9:59:00 AM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid injection.

We have reviewed your draft carton and container labeling. The Agency's proposed edits are below. Please submit your concurrence with or your counterproposal to the Agency proposed carton and container labeling by February 9, 2015.

General Comments:

- 1- The presentation of the proprietary name, established name, dosage form and strength on every panel should be:

Trade name
(deoxycholic acid) Injection
20 mg/2 mL
(10 mg/mL)
For subcutaneous use only

- 2- The strength statements should be presented using the same font size as the established name and dosage form.

Immediate Container Labels (sample):

- 1- Include the route of administration statement "For subcutaneous use only". To achieve this you may reduce the size of the sample statement or shorten the sample statement to read "Sample"

Trade name
(deoxycholic acid) Injection
20 mg/2 mL
(10 mg/mL)
For subcutaneous use only

Carton Labeling:

- 1- Consider revising your color scheme. As currently presented, the (b) (4) font letters over the color background is difficult to read.
- 2- Relocate the sample statement to the bottom of the principal display panel. As currently presented, the samples statement is more prominent than more relevant information on the labels. Also, add another sample statement to the

back panel.

- 3- Include the statement "Single-use vials. Discard unused portion."
- 4- Relocate the route of administration statement "For subcutaneous use only" so that it does not intervene between the dosage form and strength statements, as these should be presented together (see General Comment 1).

Tradename
(deoxycholic acid) Injection
20 mg/2 mL
(10 mg/mL)

For subcutaneous use only

- 5- Revise the storage statement as shown below:
Store at 20° to 25°C (68° to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature]
- 7- Display barcode
- 8- The inactive ingredients should be listed alphabetically.
- 9- Remove "(b) (4)" from the ingredients list.
- 10- Insert the following after the statement "Each vial contains..."
2 mL sterile solution at pH 8.3

Regards,

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration

E-mail: matthew.white@fda.hhs.gov

Phone: 301-796-4997

Fax: 301-796-9895

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/s/

MATTHEW E WHITE
02/02/2015

From: White, Matthew
To: Diane Stroehmann (dstroehmann@kytherabiopharma.com)
Cc: Gould, Barbara; Attinello, Cristina
Subject: NDA 206333 for deoxycholic acid injection
Date: Tuesday, January 20, 2015 4:28:00 PM

Ms. Stroehmann,

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid injection.

We have reviewed your draft package insert (PI). The FDA proposed edits are reflected in track changes in the attached labeling. Please submit your concurrence with or your counterproposal to the Agency proposed labeling by January 30, 2015.



Agency Proposed
Label_1_20_15_NDA

The Agency has identified the following postmarketing requirement (PMR) to be conducted post approval.

PMR Description: Complete the treatment and evaluation of subjects ages 65-75 years enrolled in the ongoing ATX-101-13-28 trial. Evaluation of subjects should continue through the end of the trial when achievable (even if treatment is not continued for the duration).

Trial Completion: _____
Final Report Submission: _____

Please submit to your NDA by January 30, 2015 your agreement to conduct the trial above and your timeline for trial completion and final report submission.

Matthew White

Regulatory Project Manager
Division of Dermatology and Dental Products
Center for Drug Evaluation and Research
Food and Drug Administration

E-mail: matthew.white@fda.hhs.gov

Phone: 301-796-4997

Fax: 301-796-9895

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/s/

MATTHEW E WHITE
01/28/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206333

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

Kythera Biopharmaceuticals, Inc.
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

ATTENTION: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs,
Pharmacovigilance and Research Compliance

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid Injection, 20 mg/2mL (10 mg/mL).

We also refer to your January 19, 2015, correspondence, received on January 20, 2015, notifying us that you are withdrawing your request for a review of the proposed proprietary name, (b) (4).

The proprietary name request for (b) (4) is considered withdrawn as of January 20, 2015.

Finally, we refer to your January 19, 2015, correspondence, received on January 20, 2015, requesting review of your proposed proprietary name, Kybella. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>.

Therefore, the user fee goal date is April 20, 2015.

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 Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Janet Anderson
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

JANET L ANDERSON
01/26/2015



NDA 206333

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Kythera Biopharmaceuticals, Inc.
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

ATTENTION: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs,
Pharmacovigilance and Research Compliance

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid Injection, 20 mg/2mL (10 mg/mL).

We also refer to your correspondence, dated and received September 29, 2014, requesting review of your proposed proprietary name, (b) (4).

We have completed our review of the proposed proprietary name, (b) (4) and have concluded that it is acceptable.

If any of the proposed product characteristics as stated in your September 29, 2014, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact 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 Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Deputy 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
12/18/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for deoxycholic acid injection, 10mg/mL.

We are reviewing your original NDA submission and have the following information request. We request a prompt written response by November 10, 2014.

- We understand that after outlining the planned treatment area a 1cm injection grid is applied to mark the injection sites. Provide details/diagram/methods of the grid that is applied to mark the injection sites.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

DAVID L KETTL
11/05/2014



NDA 206333

MID-CYCLE COMMUNICATION

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for deoxycholic acid injection, 10mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on October 17, 2014. The purpose of the teleconference was to provide you an update on the status of the review of your application.

A record of the teleconference is enclosed for your information.

If you have any questions, call Matthew White, Senior Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Mid-Cycle Communication



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MID-CYCLE COMMUNICATION

Meeting Date and Time: October 17, 2014 at 1:00 p.m.

Application Number: NDA 206333
Product Name: deoxycholic acid

Indication: For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults

Applicant Name: Kythera Biopharmaceuticals, Inc.

Meeting Chair: David Kettl, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Tatiana Oussova, MD, MPH, Acting Director, DDDP
Kendall A. Marcus, MD, Acting Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, MD, Clinical Reviewer, DDDP
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Hitesh Shroff, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Jamie Wilkins-Parker, PharmD, Acting Team Leader, DRISK
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Cristina Makela, Regulatory Health Project Manager, OSE
Matthew E. White, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Chelsea (So Hyun) Kim, Independent Assessor

APPLICANT ATTENDEES

Frederick Beddingfield III, MD, PhD, Chief Medical Officer
Diane Stroehmann, MSRA, RAC, Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
Jere Fellmann, PhD, Vice President, Clinical Operations
Todd Gross, PhD, Vice President, Clinical Development, Biostatistics and Data Management
Paul Lizzul, MD, PhD, MPH, MBA, Senior Medical Director
James McElvain, PhD, Vice President, Quality and Analytical

INTRODUCTION

We are providing these comments to you before we complete our review of the entire application to give you **preliminary** notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may or may not be able to consider your response before we take an action on your application during this review cycle.

SIGNIFICANT ISSUES

- No significant issues identified to date

OTHER ISSUES

- Additional product quality information required
- No nonclinical review issues have been identified to date

OUTSTANDING/NEW INFORMATION REQUESTS

- Product Quality information request sent October 16, 2014

Meeting Discussion:

The Applicant will submit the structural elucidation data in the same format as that for the API in section 3.1. The Applicant plans to amend the comparability protocol, and submit the amended protocol along with the requested structural elucidation data by October 24, 2014.

MAJOR SAFETY CONCERNS

- None at this time

RISK MANAGEMENT

- No REMS planned at this time

ADVISORY COMMITTEE MEETING

- Tentatively scheduled for February 9 or 10, 2015
- Potential Topics for Discussion:
 - General discussion of safety and efficacy of deoxycholic acid injection

POTENTIAL PMC/PMR's

- None identified to date

LATE CYCLE MEETING/OTHER PROJECTED MILESTONES

- Date range for late-cycle meeting: January 26 – January 28, 2015
- Target date for communicating proposed labeling and if necessary, any postmarketing commitment requests: January 23, 2015
- PDUFA action date: May 13, 2015

General Meeting Discussion:

There was a general discussion regarding the advisory committee membership and objectives. The Agency recommended an informal teleconference with the Applicant in advance of the late-cycle meeting to discuss advisory committee objectives.

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/s/

DAVID L KETTL
10/23/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid injection.

We also refer to your July 24, 2104 submission, containing your response to the Agency's filing communication dated July 10, 2014.

We are reviewing your submission and have the following comments and information requests. We request a written response by October 29, 2014.

1. In your July 24, 2014 submission, you provided a general description of the (b) (4) testing performed to monitor container closure integrity during stability testing. The description of this testing in your response (and in DMF (b) (4)) involves (b) (4).

You may provide a rationale stating why the (b) (4) study is adequate to test the container closure integrity of filled product vials. Alternatively, you should change your container closure integrity testing method to one that examines the integrity of intact vials.
2. Provide a description of how your biological indicators are cultured and handled (b) (4).

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

DAVID L KETTL
10/22/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid injection, 10 mg/mL.

We are reviewing your NDA and have the following comments and information requests. We request a written response by October 24, 2014.

Chemistry, Manufacturing and Controls (CMC)

1. You stated in Sec. 3.2.S.2.3.1 that the **starting material**, (b) (4) has been thoroughly characterized, (b) (4). Submit all of the aforementioned structure elucidation data to confirm the structure.
2. In Sec. 3.2.S.2.4.2 you have provided the specification of (b) (4). Submit structure elucidation data for these (b) (4).
3. In the drug substance specification table in Sec. 3.2.S.4 you have listed (b) (4). Submit structure elucidation data for these three impurities.
4. Regarding Comparability protocols, we have the following comments:
(b) (4)

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DAVID L KETTL
10/16/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (deoxycholic acid) injection, 10 mg/mL.

We also refer to your May 12, 2014 original NDA submission for (deoxycholic acid) injection, 10 mg/mL.

We are reviewing your submission and have the following information request. We request a prompt written response by October 8, 2014 in order to continue our evaluation of your NDA.

- In regards to the Clinical Outcome Assessment Evidence Dossier, please provide the body mass index (BMI) mean and range information for the concept elicitation (n=29) and cognitive (n=15) interview samples. In the clinical characteristics tables, we are able to locate only the means and ranges of height and weight of the two separate samples.

If you have any questions, please contact Matthew White, Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

DAVID L KETTL
10/02/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (deoxycholic acid) injection, 10 mg/mL.

We also refer to your May 12, 2014 original NDA submission for (deoxycholic acid) injection, 10 mg/mL.

We are reviewing the clinical pharmacology section of your submission and have the following information request. We request a prompt written response by September 17, 2014 in order to continue our evaluation of your NDA.

- Submit the full study report associated with and to support the summary results for in vitro cytochrome P450 enzyme inhibition and induction Study 100000544.

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

DAVID L KETTL
09/04/2014



NDA 206333

**ACKNOWLEDGE CORPORATE
ADDRESS CHANGE**

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

We acknowledge receipt on July 25, 2014, of your July 24, 2014 correspondence notifying the Food and Drug Administration (FDA) that the corporate address has been changed from

27200 West Agoura Road, Suite 200
Calabasas, CA 91301

to

30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

for the following new drug application (NDA):

NDA 206333 for (deoxycholic acid) injection, 10 mg/mL.

We have revised our records to reflect this change.

Please cite the NDA number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

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

If you have any questions, call me at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Matthew White
Senior Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW E WHITE
08/21/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206333

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Kythera Biopharmaceuticals, Inc.
30930 Russell Ranch Road, 3rd Floor
Westlake Village, CA 91362

ATTENTION: Diane Stroehmann, MSRA, RAC
Vice President Regulatory Affairs,
Pharmacovigilance and Research Compliance

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Deoxycholic Acid Injection, 10 mg/mL.

We also refer to:

- Your correspondence, dated and received May 23, 2014, requesting review of your proposed proprietary name, Kybella
- Your correspondence, dated and received July 25, 2014, providing information regarding change in address

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

The proposed proprietary name, Kybella, is unacceptable because this name could result in medication errors due to confusion with another product that is also under review. Therefore, the ultimate acceptability of your proposed proprietary name, Kybella, is dependent upon which underlying application is approved first. If another product is approved prior to your product, with a name that would be confused with your proposed name Kybella, you will be requested to submit another name.

We have taken into consideration that you intend to distribute Kybella directly to be dispensed from a physician's office and that the product is not intended to be sold to or dispensed by retail or hospital pharmacies. However, the distribution plan may not reduce risk associated with the confusion of similar names. We have reports of name

confusion with other products marketed under restricted distribution systems.^{1,2} Therefore, our safety concern is not diminished with your distribution plan for this product since the products could be prescribed and dispensed in the same medication use system.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Teena Thomas, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796- 0549. For any other information regarding this application, contact Matthew White, Regulatory Project Manager in the Office of New Drugs, at (301) 796- 4997.

Sincerely,

{See appended electronic signature page}

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

¹ Institute for Safe Medication Practices. Safety briefs: Don't Confuse TRACLEER (bosentan) with TRICOR (fenofibrate). ISMP Med Saf Alert Acute Care. 2003;8(13):2.

² Institute for Safe Medication Practices. Safety briefs: Mifepristone (MIFEPREX) and Misoprostol (CYTOTEC) mix-up. ISMP Med Saf Alert Community/Ambulatory Care. 2003;2(1):1.

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/s/

KELLIE A TAYLOR
08/12/2014



NDA 206333

**METHODS VALIDATION
MATERIALS RECEIVED**

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, VP Regulatory Affairs
27200 West Agoura Road
Suite 200
Calabasas, CA 91301

Dear Diane Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid, injection and to our July 14, 2014, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 24, 2014, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/28/2014



NDA 206333

**REQUEST FOR METHODS
VALIDATION MATERIALS**

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, VP Regulatory Affairs
27200 West Agoura Road, Suite 200
Calabasas, CA 91301
FAX: (818) 587-4591

Dear Diane Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Deoxycholic acid, injection.

We will be performing methods validation studies on Deoxycholic acid, injection, as described in NDA 206333.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

HPLC-CAD Methods: TM1226 and TM2465
HPLC-CAD Methods: CON-IM-0389 and CON-1689

Samples and Reference Standards

- 2 x 300 mg (b) (4) (DCA) reference standard for drug substance
- 200 mg substance drug substance
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) - (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 100 mg (b) (4) reagent grade
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) reference standard
- 25 mg (b) (4) (b) (4) reference marker
- 25 mg (b) (4) (b) (4) dimer reference marker

50 mg DCA resolution standard lot #02110052
10 mL placebo solution
20 vials ATX-101 drug product 10 mg/mL
20 vials ATX-101 drug product 20 mg/mL

Equipment

1 Pursuit 3 C18, 4.6 x 150 mm, 3 µm HPLC column

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
645 S Newstead
St. Louis, MO 63110

Please notify me upon receipt of this FAX. You may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy, Ph.D.
MVP coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/14/2014



NDA 206333

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
27200 West Agoura Road, Suite 200
Calabasas, CA 91301

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated and received May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for (deoxycholic acid) injection, 10 mg/mL.

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**.

Per the guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics* dated May 2014, Priority Review Designation is intended to facilitate and expedite review of NDAs submitted for drugs that treat a serious condition. A serious disease or condition is defined in 21 CFR 312.300(b)(1) as follows:

“ . . . a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible if it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.”

Moderate to severe convexity or fullness associated with submental fat in adults does not represent a serious disease or condition, therefore a Priority Review cannot be granted for this NDA.

This application is also subject to the provisions of “the Program” under the Prescription Drug User Fee Act (PDUFA) V (refer to <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>). Therefore, the user fee goal date is May 13, 2015.

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 January 23, 2015. In addition, the planned date for our internal mid-cycle review meeting is October 13, 2014. We are currently planning to hold an advisory committee meeting to discuss this application.

During our filing review of your application, we identified the following potential review issues and we have the following requests for information:

Clinical

1. Submit a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

Clinical Pharmacology

2.  (b) (4)

 (b) (4)

Statistics

3. Submit the SAS programs for creating the multiple imputation datasets and for analyzing the results for all of the primary and secondary endpoints for Studies 22 and 23. Include any necessary supporting information such as the randomization seed.

4. The file 'MRI Core Laboratory Documentation' (atx-101-11-22-e3-16-1-13.pdf) for Study 22 includes tables and listings for Study 23 instead. Submit a corrected file with tables and listings for Study 22.
5. Submit datasets comparable to ADMRI.xpt, ADMRIMI.xpt, and XM.xpt that include the MRI assessments that were originally not read by the vendor and not included in the locked database. The datasets should include all of the observations from the locked database and the observations from the subjects originally excluded from the database (30 subjects with missing baseline MRI measurements and 1 subject with missing Visit 9 measurements in Study 22 and 29 subjects with missing baseline MRE measurements and 1 subject with missing Visit 9 measurements in Study 23.)

Product Quality

6. Your application describes dye ingress studies to ensure container closure integrity. How did the preparation of the units used in dye ingress testing compare to production parameters? (In production, (b) (4) .) If parameters used to prepare units for dye ingress testing were different than those used in production, provide a rationale for the handling method that you describe.
7. Confirm that production sterilization parameters for the drug product include a (b) (4) .
8. Your application states that you use methods described in USP <85> for endotoxin testing, but you do not provide the results of method verification studies with the drug product. Provide a summary of any method verification studies.
9. Your application states that you use methods described in USP <71> for sterility testing, but you do not provide the results of method verification studies with the drug product. Provide a summary of any method verification studies.
10. Your application briefly describes the use of a (b) (4) test used to test container closure integrity in commercial production. Provide a more thorough description of the validation studies performed for this testing. Provide a description of test parameters, including positive and negative controls used in routine testing.
11. Describe culturing and handling methods for biological indicators (b) (4) requalification studies.
12. Your application states that endotoxin and container closure integrity will be tested as part of the stability program. State the specifications for these attributes, including test method and acceptance criteria.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of

deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

PRESCRIBING INFORMATION

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

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

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

Highlights (HL)

1. The margins on each side of the highlights section is 1 inch and it should be 1/2 inch.
2. There is no horizontal line to separate TOC from the FPI. The horizontal line between HL and TOC should be a single continuous horizontal line that spans the width of the page without any breaks.
3. Header titles should be centered in the columns; the horizontal lines on either side of the header titles should be created using the “hyphen” function not the “underline” function; the horizontal lines on either side of the section header titles should extend all the way to both the left and right margin of the columns.
4. There is white space between the HL Heading and HL Limitation Statement. There is white space between the product title and Initial U.S. Approval.
5. Each summarized statement of topic in HL must reference the section(s) or subsection(s) of the FPI that contain more detailed information. Not all statements and topics in HL have references. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement of topic.
6. Add “XXXX” as a place holder for the initial U.S. Approval date
7. “Dosage Forms” is not plural in the heading "Dosage Forms and Strengths"

8. Remove the brackets from “[and FDA-approved Patient Labeling]” in the Patient Counseling Information Statement.
9. The word “Revised” should be spelled out in the Revision Date.

Full Prescribing Information (FPI)

10. References should cite the section header not the subsection header. Correct cross-references in sections 7, 8.1, and 13.1.
11. As instructed in the guidance for industry, *Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products--Content and Format*, the statement instructing prescribers to advise patients to read the patient labeling should appear as the first statement in section 17. Also the current statement should be revised to read as follows: "Advise the patient to read the FDA-approved patient labeling (Patient Information)."

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by July 25, 2014. 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.

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

Please respond only to the above requests for information by July 25, 2014. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

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

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Acting 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
07/10/2014



NDA 206333

NDA ACKNOWLEDGMENT

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
27200 West Agoura Road
Suite 200
Calabasas, CA 91301

Dear Ms. Stroehmann:

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

Name of Drug Product: (deoxycholic acid) injection, 10 mg/mL

Date of Application: May 13, 2014

Date of Receipt: May 13, 2014

Our Reference Number: NDA 206333

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 11, 2014, in accordance with 21 CFR 314.101(a).

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

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

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

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

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

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

If you have any questions, call me at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Matthew White
Senior Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

MATTHEW E WHITE
06/30/2014



NDA 206333

INFORMATION REQUEST

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
27200 West Agoura Road
Suite 200
Calabasas, CA 91301

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for (deoxycholic acid) injection, 10 mg/mL.

We also refer to your May 12, 2014 submission, containing an original NDA for (deoxycholic acid) injection, 10 mg/mL.

We are reviewing the clinical pharmacology section of your submission and have the following comments and information requests. We request a prompt written response by June 20, 2014 in order to continue our evaluation of your NDA.

- For your population pharmacokinetic analysis report KYTH-01-13, provide (or provide the location of) your electronic files listed in your Appendix D (Base Model Development, Covariate Model Selection, Final Model Selection, and Final Data Set).

If you have any questions, please contact Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

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/s/

DAVID L KETTL
06/19/2014



IND 079726

MEETING MINUTES

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Clinical Quality
27200 West Agoura Road, Suite 200
Calabassas, CA 91301

Dear Ms. Stroehmann:

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

We also refer to the meeting between representatives of your firm and the FDA on November 13, 2013. The purpose of the meeting was to discuss the development program for (deoxycholic acid) injection.

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

If you have any questions, call Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: November 13, 2013, at 10:30 a.m.
Meeting Location: White Oak Building 22, Room 1309

Application Number: IND 079726
Product Name: (deoxycholic acid) injection
Proposed Indication: For improvement in appearance of moderate to severe convexity or fullness associated with excess submental fat in adults

Sponsor Name: Kythera Biopharmaceuticals, Inc.

Meeting Chair: Dr. Susan J. Walker
Meeting Recorder: Matthew White

FDA ATTENDEES

Susan J. Walker, MD, FAAD, Director, DDDP
Stanka Kukich, MD, Deputy Director, DDDP
Tatiana Oussova, MD, MPH, Deputy Director for Safety, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jill Merrill, PhD, Pharmacology Reviewer, DDDP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Yuqing Tang, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP3
An-Chi Lu, MS, PharmD, Clinical Pharmacology Reviewer, DCP3
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Tarun Mehta, PhD, Product Quality Reviewer, DNDQA II, Branch IV
Roy Blay, PhD, Reviewer, DGCAB
Matthew E. White, Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

So Hyun Kim, Independent Assessor

SPONSOR ATTENDEES

Frederick Beddingfield, MD, PhD, Chief Medical Officer

Diane Stroehmann, MSRA, RAC, Vice President, Regulatory Affairs, Pharmacovigilance and Clinical Quality

Deepak Chadha, MS, MBA, RAC, Vice President, Regulatory Affairs

Jere Fellmann, PhD, Vice President, Clinical Operations

Todd Gross, PhD, Vice President, Clinical Affairs, Biostatistics and Data Management

Nancy Jorgesen, MA, MBA, Vice President, Product, Systems and Alliance Management

Dan Lee, MS, Senior Director, Clinical Affairs

Paul Lizzul, MD, PhD, MPH, MBA, Medical Director

James McElvain, PhD, Senior Director, Quality and Analytical

(b) (4) Consultant Toxicologist

(b) (4) Consultant Statistical Scientist (b) (4)

(b) (4) Consultant (b) (4)

(b) (4) Consultant (b) (4)

Richard Nkulikiyinka, MD, MRCP, Head of Dermatology, Bayer Global Clinical Development

Clemens Guenter, Ph.D., Safety Consumer Care, Bayer Healthcare (participated via phone)

Purpose of the Meeting:

To discuss the development program for (deoxycholic acid) injection

Regulatory Correspondence History

We have had the following meeting(s)/teleconference(s) with you:

- 8/19/2009: Guidance meeting
- 4/20/2011: End-of-Phase 2 meeting

We have sent the following correspondences:

- 11/28/2008: Advice letter (2)
- 5/7/2009: Advice letter
- 6/17/2009: Information request letter
- 12/8/2009: Advice/information request letter
- 1/21/2010: Advice/information request letter
- 6/10/2010: Advice/information request letter (2)
- 8/13/2010: Advice/information request letter
- 2/18/11: Advice letter
- 3/31/2011: Advice/information request letter
- 4/13/2011: Advice/information request letter
- 8/1/2011: Advice/information request letter
- 8/4/2011: Advice/information request letter
- 11/3/11: Advice/information request letter
- 12/5/11: Information request letter (electronic)
- 12/16/11: Special protocol – agreement letter
- 3/21/12: Advice/information request letter
- 6/6/12: Advice letter
- 3/28/13: Agreed iPSP letter

- 5/13/13: Agreed PSP letter
- 5/20/13: Advice letter

Chemistry, Manufacturing and Controls (CMC)

Question 1:

The CMC information planned for inclusion in the NDA filing is summarized in Section 5. Kythera believes that the CMC data is adequate to support the filing and review of an NDA for ATX-101. Does the Agency agree?

Response:

Your planned CMC information for NDA filing is reasonable with one exception that is related to sterilization validation. We recommend that the sterilization validation package include three commercial scale batches and be submitted at time of NDA submission.

Additional Comment:

The qualification of (b) (4) for the proposed product should include data/information indicating that the (b) (4) can maintain its physical integrity without (b) (4) during the in-use period.

Meeting Discussion:

The sponsor stated there is (b) (4) terminal sterilization. The sponsor has completed sterilization validation using a matrix approach with surrogate products on three batches at full commercial scale. The surrogate product has a higher viscosity than the drug product and represents the worst case scenario. The Agency recommended that the sponsor submit their proposed sterilization validation package with data to the IND. The Agency will review the proposal and provide comments.

The sponsor stated that 12 months of stability data will be included in the initial NDA submission. The Agency agreed to accept any additional stability data within 30 days following NDA submission.

Pharmacology/Toxicology

Question 1:

The completed nonclinical program is discussed in Section 6 and a table of all nonclinical studies to be included in the NDA is presented in Appendix A. Kythera believes the nonclinical program is complete and is adequate to support NDA filing and review. Does the Agency agree?

Response:

Yes. The completed nonclinical program appears to be adequate to support NDA filing and review.

Clinical/Clinical Pharmacology

Question 1:

The overall clinical development program, including results from recently completed Phase 3 studies, is summarized in Section 7 of this briefing document. Appendix B provides a tabulated overview of all studies to be included in the NDA as well as ongoing and planned studies. Kythera believes that the clinical development program for ATX-101 is complete and that no additional studies are necessary to permit filing and review of the ATX-101 NDA for the proposed indication. Does the Agency agree?

Response:

The overall clinical development plan appears adequate to support NDA filing. Your application will be reviewed under the PDUFA V “Program” for NME’s. As such, it is expected that the application will be complete upon its original submission. As an NME, this application may be referred for Advisory Committee discussion.

We have the following additional comments:

1. You should address the effects of intrinsic factors (e.g., hepatic and renal impairment) on the pharmacokinetics (PK) of your drug and potential impact on safety.
2. You stated that there is little or no potential drug interaction, but details were not provided. Refer to draft guidance for industry *Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - February 2012* for detailed recommendations.
3. It is noted that the mean C_{max} from the supra-therapeutic dose in your QT/QTc trial (Study 24) was slightly lower than the mean C_{max} from your maximal use PK trial (Study 32). Provide rationale supporting the adequacy of the QT interval assessment.
4. Provide in the NDA a table listing of all clinical trials and the associated formulation used in each trial.
5. At the time of your NDA submission, you should include bioanalytical reports and associated method validation reports for all trials with PK assessment. The bioanalytical report for each trial should outline the duration of sample storage and supporting long-term storage stability information.
6. Provide in the NDA raw and calculated PK parameters for all trials with PK assessments in SAS Transport format (.xpt). Include a data definition file.

Meeting Discussion:

The sponsor considers the QT/QTc studies appropriate and will submit their rationale to the NDA. The Agency agreed that this approach is reasonable.

Question 2:

Exposure to ATX-101 in clinical studies and overall study duration is discussed in Section 7.3.2. Over 2,500 human subjects have been enrolled in 17 clinical studies of ATX-101. Of those, over 1600 subjects have been exposed to at least one dose of ATX-101 and will be included in the NDA submission as part of the safety database. Of these, over 700 subjects have been exposed to

up to six monthly treatments using the dosage/injection regimen intended for the proposed indication, and were followed for 6 months after last treatment. Additional long term (12 months or more) safety information has been collected from 360 subjects treated with ATX-101 at or above the concentration intended for the proposed indication.

Kythera believes the requirements of ICH E1A Guidance have been met in terms of the total safety exposure and that long term safety data adequately characterize the safety profile of the product and permit filing and review of the ATX-101 NDA for the proposed indication. Does the Agency agree?

Response:

Your proposed safety database appears to be adequate for filing and review.

Question 3:

The Integrated Summary of Safety (ISS) is discussed in Section 7.6. The ISS will include integrated safety data from 14 SMF studies, including two long-term follow-up studies (12 [ongoing] & 26). Four additional Phase 1 and 2 studies (04, 05, 10, (b) (4)) of ATX-101 were conducted for non-SMF indications; these studies will not be included in the pooled analyses but will be discussed in the ISS. Other ongoing studies will not be included in the original ATX-101 NDA ISS (Section 7.9). The safety population will include all subjects who received at least one dose of study drug. Three safety analysis groups will be utilized for the ISS analyses:

ISS Analysis Group	Studies Included
Group 1: Pivotal U.S. Phase 3 Studies	22, 23
Group 2: Phase 2 and 3 Placebo Controlled SMF Studies	03, (b) (4) 15, 16, 17, 22, 23
Group 3: All Submental Fat Studies	03, (b) (4) 12, 15, 16, 17, 19, 22, 23, 24, 26, (b) (4) 32
Individual Study Summaries (where appropriate)	04, 05, 10, (b) (4)

Does the Agency agree with this approach?

Response:

The proposed safety analysis groups are a reasonable approach. Include all available safety data from study 1403740 in the ISS as a component of the additional group (Group 4) with data from studies 12 and 26.

The following data should be included:

- Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation from the trials conducted with your product. Case narratives should include past medical history, concomitant medications, ATX-101 exposure data, detailed event description, outcome, and discussion on causality,

- Case report forms (CRFs) for all serious AEs, all severe AEs, and for all subjects who discontinued from the studies for any reason. A study's CRFs should be placed in a CRF folder under the applicable study with a file tag of "case-report-forms." Also provide the following:

Electronic links for:

- a. all serious AEs
- b. all severe AEs
- c. all patients discontinued regardless of reason
- d. all deaths

CRFs should be referenced under the study in which it belongs and tagged as "case-report-forms" in that study's stf.xml file. CRFs that are not submitted should be readily available upon request.

- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq 1\%$.
- Adverse event tables $\geq 1\%$ regardless of causality.
- Line listings for all safety data.

Question 4:

The Integrated Summary of Efficacy (ISE) is discussed in Section 7.7. The ISE will include pooled efficacy results from U.S. Phase 3 Studies 22 and 23 to support the primary indication and will include pooled efficacy results from EU Phase 3 Studies 16 and 17 as supporting evidence. Studies 03, 07, 12, 15, and 26 will be integrated in the ISE database, but they will not be pooled for analyses. Individual study results will be summarized in a common format and layout and, where appropriate, used to support the U.S. Phase 3 pooled analyses.

ISE Analysis Group	Studies Included
Group 1: Pivotal U.S. Phase 3 Studies	22, 23
Group 2: EU Phase 3 Studies	16, 17
Individual Study Summaries (where appropriate)	03, 07, 12, 15, 26

Does the Agency agree with this approach?

Response:

Your proposal for the ISE appears reasonable to support the NDA filing.

Note that the following items should be included for your Phase 2 and Phase 3 studies in your submission:

1. The electronic datasets for clinical studies in SAS transport form (.xpt). You should submit both SDTM datasets (raw data directly from the CRF in standardized format) and analysis datasets. You might refer to the Analysis Data model (ADaM) Examples in Commonly Used

Statistical Analysis Methods for guidance regarding analysis datasets:

http://www.cdisc.org/stuff/contentmgr/files/0/5aee16f59e8d6bd2083dbb5c1639f224/misc/adam_examples_final.pdf. Each analysis dataset should include the treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies.

2. Include dataset documentation (define.xml and define.pdf) for SDTM and analysis datasets. Definition files for raw datasets modeled according to CDISC/SDTM IG 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. 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.
3. Statistical programs for any non-standard analyses.
4. 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).
5. The generated treatment assignment lists and the actual treatment allocations (along with date of enrollment) from the trials.
6. 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. You may request dataset(s) analysis for CDISC specifications compliance as part of the test submission. For additional information, contact the Electronic Submission Support Team at esub@fda.hhs.gov, or for standardized data submission questions, contact edata@fda.hhs.gov.
7. Refer to the CDER eCTD webpage for all current versions of specifications and guidances related to the eCTD:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>
8. Contact esub@fda.hhs.gov for any further questions related to preparing or submitting your eCTD submission.

Question 5:

The clinical data demonstrate that the benefits of ATX-101 outweigh the risks (Section 7.5). Clinically meaningful improvements in SMF have been clearly demonstrated, as reflected by the appearance of submental convexity/fullness and objective MRI volume measurements, and the majority of subjects treated with ATX-101 in the clinical development program reported high satisfaction with their treatment and improvement in self perceptions related to SMF. Overall, AEs observed following treatment with ATX-101 were transient, and mild to moderate in severity. To provide for the safe use of ATX-101, Kythera will make available comprehensive injection training and sufficient directions for injection technique and associated risks in the proposed labeling (Section 7.8). Therefore, Kythera does not intend to include a Risk Evaluation and Mitigation Strategy (REMS) in the NDA. Does the Agency agree with this approach?

Response:

Yes, this approach seems reasonable.

Question 6:

The development of and analytical approaches employed to evaluate and confirm the measurement properties and interpretability of the clinician and patient reported outcome scales are detailed in Section 7.2. Prior to use in Phase 3 studies, the reliability, construct-related validity, sensitivity and interpretability of the Clinician-Reported and Patient-Reported Submental Fat Rating Scales (CR-SMFRS and PR-SMFRS) and the Patient-Reported Submental Fat Impact Scale (PR-SMFIS) were assessed using Phase 2 clinical study data. Kythera developed and validated these scales in accordance with FDA's PRO Guidance (December 2009).

- a. Does the Agency agree with the planned analytical approaches (Section 7.2.3) to be utilized to confirm the measurement properties and interpretability of these instruments using data from the Phase 3 clinical program?
- b. Following the End-of-Phase 2 Meeting, a PR-SMFIS evidence dossier was submitted to the Agency for review (28 October 2011). If the Agency has completed their review of the PR-SMFIS dossier, Kythera would appreciate receiving any comments or advice. Kythera acknowledges the Special Protocol Assessment Agreement letter dated 16 December 2011, wherein the Agency indicated that the adequacy of the PR-SMFIS as a measure to support labeling claims would be addressed at the time of NDA submission.

Response:

Your proposed analytical approach for the assessment scales reviewed under SPA appears adequate for review. As stated in SPA agreement letter (dated 12/16/2011), (b) (4)

Question 7:

For the 120-day safety update, Kythera intends to update the integrated safety database with data from Studies 12, 35 and 1403740 and amend the ISS accordingly. Individual study information for planned Studies 27, 28, and 36 will be provided as follows: 1) description of the study, 2)

status of the study, including demographics and disposition, and 3) summary of available study results, including the most frequent and most serious adverse experiences by body system and safety reports submitted to the Agency. Additional detail is provided in Section 7.9.

Does the Agency agree with this approach?

Response:

Do not amend the initial ISS with new safety data from Studies 12, 35 and 1403740, but submit separately 120-day safety data update from studies 12, 27, 28, 36 and 1403740 in the same format as the ISS.

Meeting Discussion:

The sponsor agreed to segregate new data in the 120 day safety update and provide datasets.

Regulatory

Question 1:

ATX-101 (deoxycholic acid injection) is a new molecular entity that if approved will provide a safe and effective therapy to improve the appearance of submental convexity/fullness associated with excess submental fat where no satisfactory alternative nonsurgical or pharmacological therapy exists, to date. Current options for patients with undesirable submental fat include surgical procedures such as liposuction and neck lift and use of unapproved and unregulated, nonsterile pharmacy-compounded PC/DC products, which pose a potentially high safety risk (Section 4.1). Additional details are provided in Section 4.2 and 7.5 of this meeting briefing document. A new NDA may be classified as a Priority Review if the drug product has the potential to provide, in the treatment, prevention, or diagnosis of a disease, a safe and effective therapy where no satisfactory alternative therapy exists, including nondrug products or therapies. Does the Agency agree that the NDA for ATX-101 is eligible for Priority Review?

Response:

You are referred to the draft guidance for industry *Expedited Programs for Serious Conditions-Drugs and Biologics*. You may request priority review designation when you submit the original NDA.

We do not anticipate that the NDA for ATX-101 would be granted Priority Review.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND or NDA might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21 CFR 54 and 21CFR 314.50(k).

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that a REMS is not anticipated.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application:

12 months of stability data will be included in the initial NDA submission. The Agency agreed to accept any additional stability data within 30 days following NDA submission.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

NDA NUMBER: LATE COMPONENT - QUALITY

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. The PSP must contain an outline of the pediatric study or studies that

you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Pediatric and Maternal Health Staff at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the following labeling review resources: the Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products, labeling guidances, and a sample tool illustrating the format for Highlights and Contents (Table of Contents) available at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>.

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.				

DATA SUBMISSION

The Agency prefers Sponsor to submit datasets based on the [Study Data Specifications](#) (currently 2.0). However, in general, the Agency accepts datasets, which comply, within a reasonable timeframe, with previous versions of the Study Data Specifications and other related guidance; based on the timing of protocol design, protocol initiation, and data collection.

The Agency expects Sponsor to evaluate the risk involved converting study data collected to standardized data, if applicable. The Agency prefers Sponsor to submit study data conversion explanation and rationale. The study data conversion rationale and explanation should address either scenario; decision rationale for not converting or decision rationale for converting. The Agency expects Sponsor’s evaluation and rationale include study data scientifically relevant to the application’s safety and efficacy representation. As such, the evaluation and explanation may include rationale based on the pooling/integrating of data from multiple studies.

The [PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2013 THROUGH 2017](#) guidance provides specific requirements for electronic submissions and standardization of electronic drug application data. Sponsor should design and implement data standardization in all research protocols to be included in regulatory submissions, as required based on the timing for implementation of the research. The non-clinical and clinical research study designs should include concise and complete explanation for implementation of data standardization in the data collection section of the protocol. Sponsor should use the Clinical Data Interchange Standards Consortium (CDISC) Technical Road Map to design end-to-end harmonized data standardization, including the Clinical Data Acquisition Standards Harmonization ([CDASH](#)) standard for design and implementation of data collection instruments.

The Agency's methodology and submission structure supports research study design, as indicated in the [Guidance to Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications](#) and the [Study Data Specifications](#). The Agency's methodology and submission structure also supports integrating study data collection for Safety and Efficacy study submission. Each study should be complete and evaluated on its own merits. Sponsor should maintain study data independently in the SEND datasets for non-clinical tabulations, SDTM datasets for clinical tabulations, and ADaM datasets for analyses tabulations. (See [SEND](#), [SDTM](#) and [ADaM](#) as referenced in [Study Data Specifications](#)). Study analyses datasets should be traceable to the tabulations datasets.

In addition, please reference the [CDER Common Data Standards Issues Document](#) for further information on data standardization in submissions.

Additional Comments:

- Do not provide placeholders for sections that will not be submitted (e.g. 1.1.1. Form FDA 1571, N/A). Placeholders are only required when submitting ANDAs.
- Providing a linked reviewer's aid/ reviewer's guide for an original application in module 1.2, as a separate document from the cover letter, to briefly describe where information can be found throughout the application, can be helpful to the reviewers.
- Regarding m1.3.2; Notify the ORA office by letter, of your NDA eCTD submission, making explicit reference to the drug, application number, etc. State in the letter that "the application is being submitted in eCTD format to the Division of XXX, and as the field offices have access to the complete submission on the FDA network, an individual field copy is no longer required". A copy of this letter is what you place in m1.3.2. For regional and district office addresses, please refer to: <http://www.fda.gov/ICECI/Inspections/IOM/ucm124008.htm>
- For archival purposes, you should submit a pdf file of any labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.
- Providing a single 3.2.S and 3.2.P section with attribute of "ALL" and differentiating documents by leaf title, is acceptable. Additionally, indicating the substance/product/strength/manufacturer/excipient, etc., at the beginning or end of a leaf title, helps searching abilities
- Module 4 and 5 study reports and document leaf titles should be clear and indicative of the content. "Study 0009 clinical report; study 0009 protocol" will be examples of good leaf titles and "009 study report.pdf" will be a good example of a file name.
- Regarding use of the m5-3-7 heading element, FDA doesn't use module 5.3.7 CRFs. Instead, case report forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications, tagged as "case report form" and reside with the study's information. Do not use 5.3.7 as a heading element in the index.xml

- Datasets should be referenced under the appropriate study's STF to which they belong and tagged, accordingly. Please refer to [Study Data Specifications](#).
- If this is your first eCTD submission, it is recommended that a sample eCTD be completed prior to submitting an actual eCTD submission. Please refer to the eCTD Sample Web page for more information, located at:
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

Additional Links:

[Electronic Regulatory Submissions and Review Helpful Links](#)
[Electronic Common Technical Document \(eCTD\)](#)
[Study Data Standards Resources](#)

CLINICAL INVESTIGATOR SITE INFORMATION

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

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

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (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

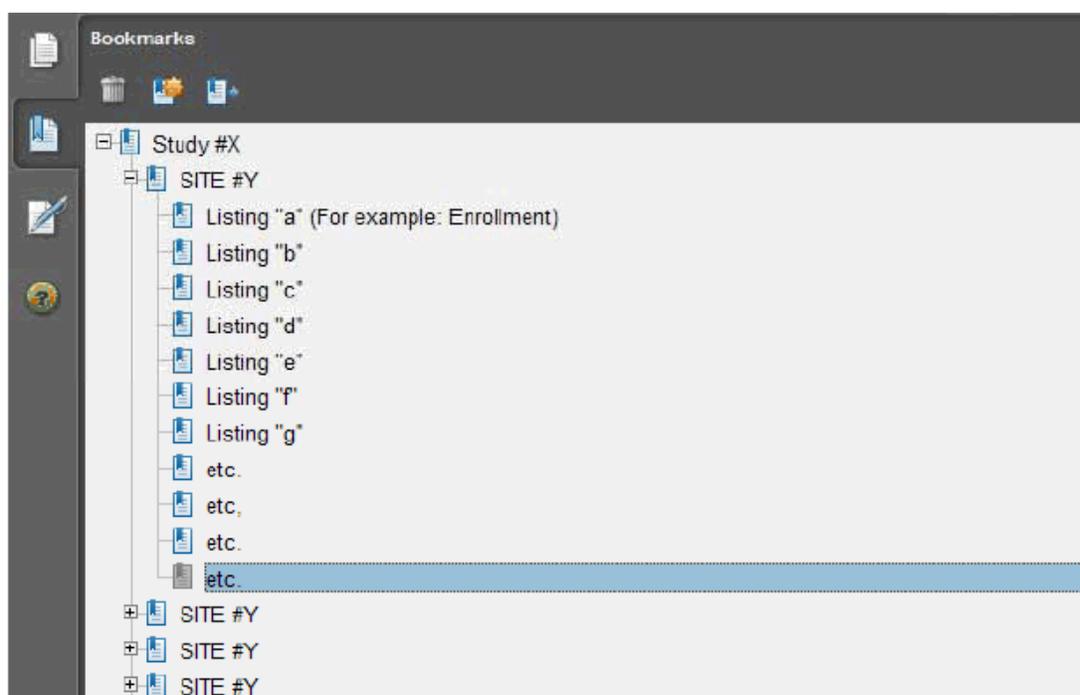
clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

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.

**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 Item¹	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.

References:

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

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

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/

SUSAN J WALKER
12/03/2013



IND 079726

MEETING MINUTES

Kythera Biopharmaceuticals, Inc.
Attention: Patricia Walker, M.D., Ph.D.
Chief Medical Officer
27200 West Agoura Rd., Suite 200
Calabasas, CA 91301

Dear Dr. Walker:

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

We also refer to the meeting between representatives of your firm and the FDA on April 20, 2011. The purpose of the meeting was to discuss the development program for (sodium deoxycholate) Injection.

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

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

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: April 20, 2011; 9:00 a.m. (EDT)
Meeting Location: FDA W.O. Bldg. 22, room 1309

Application Number: IND 079726
Product Name: (sodium deoxycholate) Injection
Proposed Indication: reduction of submental fat
Sponsor/Applicant Name: Kythera Biopharmaceuticals, Inc.

Meeting Chair: Susan J. Walker, M.D.
Meeting Recorder: Paul Phillips

FDA ATTENDEES

Susan J. Walker, M.D., F.A.A.D., Director, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Milena Lolic, M.D., Clinical Reviewer, DDDP
Gary Chiang, M.D., M.P.H., Clinical Reviewer, DDDP
Elektra Papadopoulos, M.D., Medical Officer, SEALD
Lucie Yang, M.D., Clinical Team Leader, DMIP
Mohamed Alesh, Ph.D., Biostatistics Team Leader, DB III
Yuqing Tang, Ph.D., Biostatistician, DB III
Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Roy Blay, Ph.D., Reviewer, DSI
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Deepak Chadha, M.S., M.B.A., V.P., Regulatory Affairs
Nancy Jorgesen, Product Team Leader
Daniel Lee, M.S., Director, Clinical Affairs
Patricia Walker, M.D., Ph.D., Chief Medical Officer
(b) (4) Chief Scientist & Regulatory Advisor, (b) (4)
(b) (4) Consultant Biostatistician, (b) (4)

1.0 BACKGROUND

We have had the following meeting with you:

- 08/19/2009: Guidance Meeting

We have sent the following correspondences:

- 11/28/2008: Advice/IR letter (1)
- 11/28/2008: Advice/IR letter (2)
- 05/07/2009: Advice/IR letter
- 06/17/2009: Advice/IR letter
- 12/08/2009: Advice/IR letter
- 01/21/2010: Advice/IR letter
- 06/10/2010: Advice/IR letter (1)
- 06/10/2010: Advice/IR letter (2)
- 08/13/2010: Advice/IR letter
- 02/18/2011: Advice/IR letter
- 03/31/2011: Advice/IR letter

2.0 DISCUSSION

In your briefing package you submitted the findings of your dose ranging study (Study 15) which was designed with your stated objectives of : (i) evaluating the safety and efficacy of the 5 mg/ml ATX-101 and 10 mg/ml ATX-101 transcutaneous injections in the submental fat area and (ii) evaluating the psychometric performance of the three measures of submental fat size and impact, namely; (a) Clinician-Reported Submental Fat Rating scale (CR-SMFRS), (b) Two single item Patient-Reported Submental Fat Rating Scale (PR-SMFRS) and (c) The six item Patient-Reported Submental Fat Impact Scale (PR-SMFIS). The main enrollment criteria in the study were for a subject to have score of 2 or 3 on the 5-categories (0 to 4) CR-SMFRS scale and a score 0, 1 or 3 on the subject Self Rating scale (SSRS). Based on the findings of your study you propose a success criteria based on composite endpoint of 1-grade change at minimum on both the CR-SMFRS and PR-SMFRS scales.

It is not clear whether the study design of Study 15 can address the stated objectives of the trial. In particular, we have concerns about:

- (i) assessment of the reliability and validity of the scales when subjects enrolled in only 2 categories out of the 5 categories of the CR-SMFRS,
- (ii) the accuracy of treatment effect when the enrollment criteria disregard one of the two components for the composite endpoint used to evaluate treatment effect at the end of the trial,
- (iii) the utility of the MRI measurements (thickness and volume) when the success criteria is based on an arbitrary data-driven threshold ((b) (4) (b) (4)).
- (iv) the first component of the proposed Patient-Reported Submental Fat Impact Scale (PR-SMFIS), which is the key secondary endpoint, is in the opposite direction of the

remaining 5 components yet the analysis is based on the sum of the items divided by their number, which is 6.

Based on the findings of your Phase 2 trial, you submitted protocols for Phase 3 trials which have the same limitations on study enrollment and success criteria as your completed Phase 2 trial. With the above concerns about design and findings from the completed Phase 2 trial, the Agency would encourage you to address the reliability and validity of the scales used and the reliability of the estimate of treatment effect from the Phase 2 trials in light of the Agency-recommended endpoint, as conveyed to you in previous communication, of success on the composite endpoint based on CR-SMFRS and PR-SMFRS scales with 2 grades improvement at a minimum on each.

Clinical/ Biostatistics

Question 1:

Does the Agency agree that the CR-SMFRS and PR-SMFRS have been demonstrated to be reliable and valid clinician-reported and patient-reported measurement instruments that may be used to assess reduction of SMF in pivotal studies?

Response:

No. The CR-SMFRS and the PR-SMFRS have the potential to be adequately well-defined and reliable (b) (4). However, neither of these scales directly measure fat, rather they measure degree of visible submental “bulge,” which may result from factors unrelated to fat (e.g., neck anatomy, muscle tone, skin laxity, and subject position). Although the CR-SMFRS includes palpation of submental soft tissue, without also minimizing the impact of head and neck position on the visual assessment of submental fat, the CR-SMFRS cannot be considered to be a valid measure of SMF size.

Meeting Discussion:

The sponsor stated that they will submit revised proposed labeling that matches the concepts measured.

We provide the following comments for the three scales that you identified as suitable measurement instruments for use in pivotal trials.

CR-SMFRS:

You have proposed standardizing the position of the subject by use of the Frankfort plane; however, the Frankfort plane indicated in the CR-SMFRS can only be approximated and may be difficult to replicate. In addition, it is possible to move the chin anteriorly and significantly change the neck contour without raising the chin, or changing the Frankfort plane parallel to the floor. You may consider the use of a method to better standardize the position of the head and neck (e.g., using a right angle or standard form to fit the head with a constant height of the chin from the floor for each patient).

We are also concerned that the photo-guide includes examples of individuals who appear to be significantly overweight with generalized neck and facial adiposity, which does not appear to be consistent with the patient population described in your indication (see also our response to Q3). Additionally, the photo-guide includes among its examples an individual who has the appearance of having a recessed chin which can interfere with the evaluation of submental fat.

According to the summary of intra-rater reliability, each rater's first session rating agreed with his/her second session rating for over 60% of subjects; this implies that for up to 40% of patients there was disagreement. You provided the intraclass correlation coefficient (ICC) for the intra-rater reliability and the inter-rater reliability. Please also provide the weighted kappa for assessment of both intra-rater and inter-rater reliability for comparison.

PR-SMFRS:

1. Our comments with regard to standardization of patient position also apply to the PR-SMFRS.
2. The PR-SMFRS lacks detailed verbal descriptors or graphics (e.g., photoguide) to assist patients in selecting their responses. This is of particular concern in light of the high response rate in the placebo-treated group using the PR-SMFRS in Study 15.
3. You provided a summary of the development of the PR-SMFRS, but did not submit the entire PRO dossier with complete qualitative study reports. Thus our comments are preliminary.

PR-SMFIS:

On reading the Patient-Reported Submental Fat Impact Scale (PR-SMFIS), we are concerned about whether the items are adequately defined to allow a description of the scale's results ^(b)₍₄₎. For example, when responding to the item, "How much older do you look because of your chin fat?" patients may be evaluating different concepts related to looking older depending on the patient's age and other factors such as body image. Therefore, we view the PR-SMFIS as an exploratory outcome assessment.

Meeting Discussion:

The sponsor agreed to use improved standardization of the head and neck position when obtaining assessment by CR-SMFRS and PR-SMFRS

The sponsor agreed to develop a patient-reported outcome measure that includes line drawings representing different degrees of submental convexity as response options. This measure will be included as an additional endpoint in the phase 3 studies and will serve as another anchor for interpretation of change on the CR-SMFRS and PR-SMFRS.

The Agency requested the sponsor to provide detailed information as well as data related to reliability and validation of the proposed CR-SMFRS and PR-SMFRS scales, as Study 15 included subjects with CR-SMFRS scores of 2 or 3 only. The requested data should include description of the reliability/ validation study set up, number of subjects enrolled, statistical methodology for reliability and validation analysis, ratings of each subject enrolled in the study as well as the study results.

Question 2:

Does the Agency agree that a composite primary efficacy endpoint in which a responder is defined as a subject with at least a 1-grade improvement in CR-SMFRS and at least a 1-grade improvement in PR-SMFRS is appropriate for pivotal studies of ATX-101 for the reduction of SMF?

Response:

Your proposed 1-grade improvement might not be sufficient to garner an efficacy claim.

1. We do not agree that a 1 point change is a meaningful treatment benefit (from the perspective of the individual seeking SMF reduction) on the basis of the results from Study 15 where 1 grade improvement was observed in placebo treated subjects at the rate of 60% (by subjects). Provide your explanation for this magnitude of response in the placebo group.
2. CR-SMFRS and PR-SMFRS scales are both 5-point categorical over continuum scales where one grade improvement may be difficult to correlate clinically. For example, difference between higher end of grade 1 and lower end of grade 2 represents 1 point scale difference, but not necessarily a meaningful clinical difference. With setting the effect threshold to at least 2-grade reduction from the baseline measurement, we increase the probability that scale grade difference represents the true, meaningful difference in the treatment. This is particularly important, when the effect of the drug may not be robust, and when placebo effect is high.
3. You suggest that reduction of 2 grades (from 2 to 0 or 3 to 1) may not be desirable or may not provide additional benefit (from the subject's prospective). However, you base that conclusion on the results of Study 15, which utilized incompletely-developed measurement instruments. It appears that only half of discontinued subjects (6/11) had PR-SMFRS recorded at the time of discontinuation, and it is not clear whether subjects' scoring prompted discontinuation.
Provide data that justify 1-point grade improvement as meaningful and desirable benefit from the subject's perspective as well as data to support your position that a two grade change is undesirable.
4. You suggest that reduction of 2 grades may not be achievable due to the lack of available tissue to be injected and provided the summary of 11 subjects who discontinued due to lack of submental fat (as assessed by investigator). However, according to your statement 5 out of 11 discontinued subjects achieved 2 or 3 grade reduction at your primary efficacy evaluation time point despite observed lack of available tissue 12 weeks earlier.

Meeting discussion:

The sponsor offered a new proposal for dichotomized composite primary endpoint that would include two grade improvement (for example from grade 2 to 0 and from 3 grade to 1). The Agency requested that the sponsor submit the proposal to the IND; the Agency offered to provide comments expeditiously.

Question 3:

Does the Agency agree that data from Study 15 demonstrate that use of ATX-101 results in objective reductions in SMF as assessed by MRI volume and thickness?

Response:

Your results from Study 15 demonstrate the trend in reduction of SMF as assessed by MRI volume measurement of the submental area: 99mm³ (placebo arm), 404mm³ (0.5% arm), and 617 mm³ (1% arm). The trend was also seen, but without dose response, in thickness reduction (0.4 mm, 1.7 mm, and 1.7 mm for respected arms).

We have the following comments:

1. Subject position could affect measurement, thus you should standardize use of MRI for submental fat assessment including, for example, use of a subject positional aid and verification of subject position and the technical adequacy of images prior to each MRI measurement.
2. We anticipate that intra-and inter-reader variability may pose significant challenges in obtaining interpretable measurement. Where two independent readers perform image interpretation, we recommend a pre-determined level of reader discrepancy be set, with values outside this level subject to adjudication by a third reader.
3. For multiple imaging sites, we recommend using a central facility to monitor the processes and services associated with imaging (related to an independent radiographic assessment).

It would be difficult to interpret the MRI results of SMF reductions as a stand alone, meaningful outcome without identification of a clinically meaningful threshold. Establishing meaningful threshold might be more appropriate for volume than for thickness reduction because: a) according to your results, volume measurement showed better dose response and b) volume reduction is the same concept assessed by other instruments (CR-SMFRS and PR-SMFRS scales).

Meeting discussion:

The sponsor stated that they agreed with the Agency's recommendation to standardize procedures for obtaining MRI images and for interpretation of the images, and had done so in their phase 2 study. The sponsor agreed to submit this information to the IND.

Question 4:

In the proposed Phase 3 Studies 22 and 23, Kythera has included a secondary 3-item composite efficacy endpoint comprising 1-grade improvements in CR-SMFRS and PR-SMFRS and a threshold change in MRI thickness or volume:

- a. Does the Agency agree that such a 3-item composite endpoint is a reasonable secondary endpoint in the proposed Phase 3 trials?
- b. Does the Agency agree with setting the MRI thickness and volume thresholds based on placebo group data in the Phase 3 studies?

Response:

- a. A secondary end-point should be clinically meaningful and supportive of the primary-end point. At this time we can not agree that a 1-grade improvement in CR-SMFRS and PR-SMFRS and that the proposed threshold in MRI thickness or volume would represent a clinically meaningful change (see response to questions 2).

- b. You proposed to define the MRI threshold as (b) (4). However, the threshold should be a static criterion (b) (4). Propose and justify a clinically-meaningful minimum reduction from that of the corresponding baseline measurement as the threshold for the classification of a MRI responder. It should also be noted that such threshold should be related to the success criteria based on CR-SMFRS and PR-SMFRS (see response to question 3).

Meeting Discussion:

The Agency requested the sponsor to provide full MRI data including the distribution for all subjects and to clarify why the number of subjects having MRI data is smaller than that of CR-SMFRS and PR-SMFRS although the same subjects were used for all assessments. The sponsor will submit a revised proposal for how MRI will be used in Phase 3 trials with regard to endpoints. The sponsor agreed to provide such information to the IND.

Question 5:

Does the Agency agree that the proposed U.S. Phase 3 clinical studies are adequate to support approval with respect to the other study design aspects? Such aspects include the following:

- a. Inclusion and exclusion criteria
- b. Secondary and safety endpoints
- c. Assessment of skin laxity
- d. Statistical approach

Response:

Your inclusion/exclusion criteria do not appear to identify the population described by your proposed indication.

- Clarify why you exclude patients with SMF of 4 (even though BMI may be 40 or less).
- Clarify why your inclusion criteria do not include threshold on the PR-SMFRS given that results from that scale contribute to the composite primary-end point (see statistical approach below). Your study enrollment criteria should specify minimum scores for the primary measures used for assessment of treatment effect.
- Clarify why you include subjects who are “neither satisfied nor dissatisfied with their chin appearance” (score 3 on the SSRS) when your inclusion criterion calls for dissatisfaction with the submental area.
- Clarify why you exclude subjects older than 65 years of age. Do you anticipate age-related safety issues in this population with your product?
- Clarify why you require use of contraception in female subjects of child-bearing potential who are not sexually active.

Regarding secondary end-points:

- You have proposed 7 secondary endpoints. Secondary endpoint intended for labeling should be clinically meaningful and few in number along with multiplicity adjustment to control Type I error rate.

Regarding safety monitoring:

- Proposed intervals for safety evaluation appear adequate. In addition to AE, laboratory testing and assessment of the treatment area, any signs of dysphonia/dysphagia will need to be actively assessed.

Regarding skin laxity:

- The skin laxity scale (SMSLG) is still under development. (b) (4)

You are encouraged to continue its development and to submit results to IND when available.

Regarding the statistical approach:

- Your sample size calculation is based on the proportion of subjects with 1-grade CR-SMFRS and PR-SMFRS improvement. However, you should power your Phase 3 study for the composite endpoints recommended by the Agency which would form the basis for establishing the efficacy claim. You are encouraged to obtain reliable estimates of treatment effects for powering your Phase 3 studies. Proceeding to Phase 3 absent any data to inform the powering of the Phase 3 trials would be at your risk.
- The proposed endpoints for efficacy evaluation are based on CR-SMFRS and PR-SMFRS; however, for subject enrollment, the protocol specified a score of 2 or 3 on the CR-SMFRS and a score of 0, 1, 2, 3 on SSRS. The enrollment criteria should be based on the same scales used for efficacy evaluation, but we note that PR-SMFRS is not part of your enrollment criteria. It is not clear how a subject with “a slight amount of chin fat” on PR-SMFRS would be assessed at the end of the trial, given that we do not agree with one point grade improvement as definition for responder. Furthermore, your SSRS is a 7-point scale expressed in a different direction of the CR-SMFRS, which makes it difficult to interpret the study findings.
- In addition, you also planned to use PR-SMFIS which includes 6 questions each rated on an 11-point scale. You also proposed the analysis to be carried out by averaging the scores from the 6 questions. Please note that the 1st question is expressed in a different direction from the rest of the questions and may cause difficulties for interpretation.
- You proposed to use the logistic regression controlling for baseline CR-SMFRS for the primary analysis, while the Agency-recommended endpoint for establishing an efficacy claim is a composite endpoint based on the clinical and subject evaluation. Your statistical method should be designed for the recommended endpoint. In addition, we are also interested in assessing center-to-center variability, thus the study should be designed taking into account that randomization as well as analysis should investigate center to center variability.
- In addition to the primary method of using multiple imputations to handle missing data, you should propose alternate methods for imputing missing data as sensitivity analyses to ensure that the efficacy results are not driven by the handling of missing data.
- You stated that a statistical analysis plan (SAP) will be finalized prior to breaking the study blind. It should be noted that for Phase 3 trials intended to establish an efficacy

claim, the statistical analysis methodology should be part of the study protocol or submitted in a separate document along with the protocol.

Meeting Discussion:

As the treatment effect based on the CR-SMFRS differs substantially from that based on PR-SMFRS, the Agency requested that the sponsor address how the results of the study would be applicable for powering their future Phase 3 trials. The sponsor agreed to provide their rationale in their follow up submission.

Question 6:

Kythera believes that the indication, “ATX-101 is indicated for [REDACTED] (b) (4) [REDACTED]” would be supported by the proposed ATX 101 clinical program. Does the Agency concur?

Response:

You propose a novel indication. Per 21CFR 201.57(2), labeling must state that a drug is indicated for the treatment of a “...recognized disease or condition, or of a manifestation of a recognized disease or condition.” We understand that you propose [REDACTED] (b) (4) [REDACTED]

To garner an indication, you need to establish the safety and efficacy of your product in that population. Your inclusion/exclusion criteria do not appear to enroll the population described in your indication (see response to Q5). We recommend enrollment of a broader population which will be more representative of the real-world population who will use your product based on the indication.

Question 7:

Kythera believes that the expected number of subjects to be exposed in the ATX 101 clinical program, including Phase 3 trials and a planned QT/QTc trial, would be adequate to support approval. Does the Agency concur?

Response:

Your estimated number of subjects from ATX 101 development program at the time of NDA filing is approximately 2200 out of which about 1300 would be from active arms. Our understanding is that the database for ATX 101 development program will include studies conducted under two INDs (IND [REDACTED] (b) (4) [REDACTED] for the treatment of superficial lipomas and IND 79,726 for the treatment of submental fat. Per the ICH E1A Guidance, the minimum anticipated number of exposed subjects should be a) 1500 total and b) 300-600 treated for 6 months; your total safety data base appears to be smaller than this. As described in the guidance, if the benefit from the drug is small or a new safety signal is detected, larger numbers may be needed to make a risk/benefit decision.

Question 8:

Does the Agency agree that following subjects who completed the three Phase 2 SMF studies for at least 12 months will be sufficient to address long-term safety and duration of response for ATX-101?

Response:

No. Within three Phase 2 studies there are 3 different ATX-101 concentrations (0.5%, 1%, and 2%) and two different administration patterns (volume/grid combinations) studied.

Long term safety data should be collected from the relevant population treated at dosage levels at or above those intended for clinical use, thus only subset of the Phase 2 population may be adequate. Consider including a longer extension to characterize adverse events associated with greater latency (e.g. nodules, fibrosis). Unless only one cycle of ATX-101 will be administered per lifetime in an anatomic location, we need to understand the safety and efficacy of repeated cycles of treatment.

Nonclinical

Question 9:

Based on agreements reached at the 19 August 2009 Guidance Meeting and the completion of the additional pharmacology and toxicology studies, Kythera believes that the completed nonclinical program is adequate to support both Phase 3 clinical studies and a future NDA filing for ATX 101 manufactured using synthetic DCA. Does the Agency concur?

Response:

Yes. The completed nonclinical program appears to be adequate to support both Phase 3 clinical studies and NDA filing.

Chemistry, Manufacturing, and Controls

Question 10:

Kythera has previously submitted IND CMC amendments providing for ATX 101 manufactured with synthetic DCA drug substance formulated in PBS with benzyl alcohol preservative. Kythera believes that the available and proposed chemistry, manufacturing, and controls information, particularly with respect to impurities and stability, is adequate to support Phase 3 clinical studies and will be adequate to support a future NDA filing for ATX 101. Does the Agency concur?

Response:

Yes, the agency agrees that available ATX 101 CMC information is adequate to support the Phase 3 clinical studies. As to whether it is adequate for NDA filing, it is a review issue. Please add numeric limits for both known and unknown related substances to drug substance and drug product specifications as per ICH guidelines. Please monitor the stability of the proposed clinical batches.

Clinical Pharmacology/Biopharmaceutics

There were no specific clinical pharmacology or biopharmaceutics questions identified in this briefing document. We have the following comments:

We acknowledge the summary of the results of the PK (b) (4) of your drug product following injection into submental fat that was included in this briefing document. However, we also note that you indicated that the drug product formulation used in the PK study is substantially different from the formulation to be used in the Phase 3 clinical trials. For example, the drug substance changed from animal-derived sodium salt of deoxycholate (NaDC) to synthetic deoxycholic acid (sDCA) as well as some other excipient changes. Therefore, the PK information obtained with the original formulation cannot be used to definitively define the PK characteristics of your final to-be-marketed formulation. Based on the aforementioned, we recommend that you conduct a study to characterize the PK of your final to-be-marketed formulation.

We also recommend that you address potential metabolic Drug-Drug Interactions for your drug product during your clinical development.

Meeting discussion:

Sponsor agreed to provide non clinical data and rationale to support their request for waiving the need for new PK study using new product formulation.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is

waived or deferred.

5. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
6. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
7. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).
8. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

3.0 DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced documents that provide specifications for sponsors regarding implementation and submission of study data in a standardized format. These documents will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. These documents may be found at the following webpage:

<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

4.0 ACTION ITEMS

Action Item/Description	Owner
Provide revised proposed labeling	Sponsor
Provide rationale and nonclinical data to support request for waiving the need for PK study using new product formulation	Sponsor
Provide validation data, including statistical analyses, for instruments/scales	Sponsor
Provide explanation of how investigator and subject rating scales are related	Sponsor
Submit detailed information on procedure for obtaining MRI images	Sponsor
Submit proposal for dichotomized primary endpoint	Sponsor
Provide comments on sponsor proposal for dichotomized primary endpoint	FDA
Submit proposal for use of another anchor (i.e. line drawings) as an additional endpoint in Ph 3	Sponsor
Submit proposal for how MRI will be used in Ph 3 trials with regard to endpoint	Sponsor

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

/s/

SUSAN J WALKER
04/28/2011



IND 79,726

MEETING MINUTES

Kythera Biopharmaceuticals, Inc.
Attention: Patricia Walker, M.D., Ph.D.
Chief Medical Officer
27200 West Agoura Rd., Suite 200
Calabasas, CA 91301

Dear Dr. Walker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ATX-101 (sodium deoxycholate) for injection, for the reduction of localized subcutaneous fat deposits in the submental area.

We also refer to the meeting between representatives of your firm and the FDA on August 19, 2009. The purpose of the meeting was to discuss the development plan of ATX-101.

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

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance Meeting

Meeting Date and Time: August 19, 2009; 9:00 a.m. (EDT)
Meeting Location: FDA White Oak Campus
Bldg. 22, Conf. Room 1315

Application Number: IND 79,726
Product Name: ATX-101 (sodium deoxycholate)
Indication: Reduction of localized subcutaneous fat deposits in the submental area
Sponsor/Applicant Name: Kythera Biopharmaceuticals, Inc.

Meeting Chair: Susan J. Walker, M.D.
Meeting Recorder: J. Paul Phillips

FDA ATTENDEES

Susan Walker, M.D., F.A.A.D., Director, DDDP
Stanka Kukich, M.D., Deputy Director, DDDP
Tatiana Oussova, M.D., M.P.H., Deputy Director of Safety, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Milena Lolic, M.D., Clinical Reviewer, DDDP
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Anjum Khan, M.D., Medical Officer, DONED/ENTB
Robert C. Smith, M.D., J.D., Medical Officer, DRARD/RDB
Keith Wear, Ph.D., Research Physicist, DIAM
Yunbo Liu, Ph.D., Visiting Scientist (Physicist), DSFM
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DPA II, Branch III
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DB III
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Barbara Gould, M.B.A.H.C.M., Chief, Project Management Staff, DDDP
J. Paul Phillips, M.S., Regulatory Health Project Manager, DDDP
Jeannine Helm, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Patricia Walker, M.D., Ph.D., Chief Medical Officer
Deepak Chadha, M.S., M.B.A., RAC, Vice President, Regulatory Affairs
Dan Lee, M.S., Director, Clinical Affairs
Robert Hodge, Director, Manufacturing
Nancy Jorgensen, Project Team Leader

(b) (4) Consultant Biostatistician (b) (4)

PURPOSE

This meeting was to discuss the development plan for ATX-101 (sodium deoxycholate).

DISCUSSION

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Kythera submitted an IND CMC amendment providing a new phosphate-buffered saline (PBS) formulation of ATX-101 drug product. Kythera believes the submitted information is adequate to allow use of this formulation in the Phase 3 clinical program. Does the Agency concur?

Response:

Yes, we concur.

Question 2:

Kythera believes that available and proposed CMC information on ATX-101 is adequate to support the Phase 3 development program. Does the Agency concur?

Response:

Yes, we concur.

Additional CMC Comments:

1. Make sure that your assay and related substances method(s) for drug substance is stability-indicating and sensitive. A method using (b) (4) is usually not sensitive. We are concerned about its ability to quantitate low level impurities.
2. The HPLC-CAD chromatogram of ATX-1-1 drug substance (p. 29 of the briefing package) shows a shoulder in the peak of deoxycholic acid. Address this peak purity issue if HPLC-CAD is selected as the regulatory method for the related substances in drug substance.
3. You state in Submission S/N 0024 (page 6) that (b) (4) is not clearly resolved by the CAD method and it elutes between (b) (4). Clarify how you plan to monitor/quantitate (b) (4) in the stability studies of drug substance and drug product since they elute so closely.
4. Revise drug substance specification for the following:
 - Under the test on Residual Solvents please specify the (b) (4) which you plan to routinely test.
 - It should be Microbiological test rather than (b) (4).
 - Add a test on optical rotation with an appropriate acceptance criterion.

- Clarify if the assay on sodium deoxycholate is performed (b) (4).

Nonclinical

(b) (4)

(b) (4)

Question 4:

Kythera believes that the completed and proposed nonclinical pharmacology/toxicology program is adequate to support the Phase 3 development program (see Attachment 1 under Section IV, Nonclinical Overview). Does the Agency concur?

Response:

The completed and proposed nonclinical program appears to be adequate to support Phase 3. However, if new concerns arise, additional studies may be necessary.

Clinical/Biostatistics

Question 5:

Kythera believes that the proposed Phase 3 clinical studies are adequate to support approval with respect to design, primary and secondary endpoints, statistical methods, etc. Does the Agency concur?

Response:

No, we do not concur.

In regard to end points, we have the following comments:

1. In order to provide more objective primary endpoint we recommend that imaging with precise measurements of the submandibular fat thickness be utilized as co-primary end point. You can select any imaging modality provided that is safe and that you can prove that it is effective and reliable for before and after treatment comparison of fat thickness. A method should be defined for measuring the fat deposit in a consistent site. We recommend that the measurement be taken prior to the first treatment and at every scheduled visit afterwards.

This measurement can further be used to assist with decision making about the need for additional treatments during each visit.

2. In addition, second co-primary endpoint should consist of investigator and subject assessment. To be considered a success, a subject should win on both, as a single composite end point (consisting of both investigator's assessment and subject's self-assessment). The composite end-point may be more reflective of true success in specific patient eliminating possible discrepancy between patient and investigator.
3. The agency recommends evaluating the proposed co-primary endpoints by considering the following:
 - a. For the components of the composite endpoint, namely, (i) the investigator sub mental score and (ii) the subject satisfaction with appearance, each should be evaluated on a 5-point scale at the same time points, with success being defined as a minimum of 2-grade reduction from the corresponding measurements at the baseline. A subject is considered a treatment success on this composite endpoint if he/she meets the success criteria on each of the component endpoints.
 - b. For the co-primary endpoint assessing the reduction of the submandibular fat thickness the sponsor should propose a clinically meaningful minimum reduction threshold from that of the corresponding baseline measurement. Subjects who do not achieve such minimum threshold reduction (their thickness reduction being less than is clinically meaningful) should be treated as treatment failure.
 - c. As the success criteria above require a subject to meet each of co-primary endpoints in (a) and (b), there is no multiplicity adjustment for testing of treatment effect. However, multiplicity adjustment would be required if the sponsor plan to investigate efficacy in more than one dose. Also, multiplicity adjustment would be required for multiple secondary endpoints which are clinically meaningful and are intended for labeling claim.
 - d. As efficacy evaluation is based on subjective scales and expected adverse events might indicate the treatment used, this raises the possibility for a potential bias in the efficacy evaluation. The sponsor should propose an approach for ensuring study blinding in order to reduce the possibility of bias.
 - e. The sponsor should propose statistical methodologies appropriate for analysis of the recommend endpoints.
4. To reduce the chance of under powering future Phase 3 trials such trials should be sufficiently powered for the co-primary endpoints recommended by the Division using reliable estimates of treatment effect derived from Phase 2 trials which evaluated the same endpoints. As the sponsor's clinical development program did not evaluate treatment effect for the recommend endpoints thus it would be difficult to appropriately power future Phase 3

trials. The sponsor is encouraged to conduct phase 2 trials evaluating the co-primary endpoints recommend by the Division using valid investigator and subject scales. Furthermore, in such phase 2 trials the sponsor might investigate the interaction between number of treatments a subject would require and possible baseline factors (e.g., thickness, age, weight, etc...). This information will be helpful in planning future Phase 3 trials as well as for possible labeling.

Meeting Discussion:

The sponsor agreed to the utility of an objective assessment such as using MRI. The sponsor asked if the objective assessment/imaging could be evaluated apart from the Phase 3 trial. The Agency agreed to review such a proposal when submitted.

In regard to your proposed scales we have the following comments:

The validity of your scales (both SSRS and SMFRS) has not been established.

1. The validity of the investigator rating scale, the Submental Fat Rating Scale (SMFRS), has not been established.
 - a. A description of scale development, including evidence of expert consensus is valuable in establishing scale content validity. Content validity is defined as evidence from qualitative research with a representative sample of those who will be completing the questionnaire that the concept measured and represented by the score is the intended concept and that study results can be interpreted in a meaningful way. The study (ATX-101-08-11) can only allow assessment of the reliability and does not support the validity of the SMFRS. Assessment of measurement properties (e.g., test-retest reliability) does not replace the need for adequate evidence of scale content validity.
 - b. The rating of subjects who manifest increased skin laxity and the rating of obese subjects may be difficult as it requires the rater to distinguish localized submental fat from lax skin and the effects of generalized obesity, respectively. Evidence should be provided that investigators understand and use the scale as intended (i.e., for the measurement of localized submental fat).
 - c. The photographic guide was not provided in the submission for Agency review and comment. Any guides, manuals and training instructions should be provided with the scale, as all of these items comprise the rating instrument and can affect the overall adequacy of an instrument to support claims in labeling.
 - d. It is not possible to ascertain whether the grades within the SMFRS are properly selected, because the content validity of the scale has not been established.
2. Labeling claims of “(b) (4)” are not appropriate on the basis of the SSRS for the following reasons.

- a. The content validity of the Subject Satisfaction Rating Scale (SSRS) was not described. Evidence of patient input in instrument development including qualitative research demonstrating patient understanding was not provided for Agency review and comment.
 - b. The SSRS is a single-item subject-reported outcome in which the subject is asked to rate on a 7-point scale his/her level of satisfaction as follows: “Considering your appearance in association with your face and chin, how satisfied do you feel with your appearance at the present time?” It is unclear whether this statement describes a well-defined and reliable treatment effect as many factors can influence subject satisfaction with their face and chin.
 - c. In addition, a claim of (b) (4) would not be supported by a general single question because (b) (4) is influenced by multiple aspects of the patient treatment experience such as convenience, dosage form, all aspects of efficacy, and adverse events. The SSRS does not measure (b) (4), because other aspects of treatment (e.g., adverse events, time spent, convenience or worries related to study medication) are omitted.
3. We refer you to our draft Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071975.pdf>).

We have the following comments regarding the protocol and the design of the trial:

- The design of your Phase 3 trial is based on two Phase 2 trials where end points were assessed 16 weeks after the last dose. Your current draft protocol proposes assessment 12 weeks after the last dose. Provide rationale for this change.
- Safety evaluation is inadequate:
 1. Subjects should be followed for a minimum of 12 months after completion of the trial. Any persistent change e.g. hardness or nodularity of the treated area should be evaluated per standard of care.
 2. Active assessment of difficulties with swallowing and speech should be performed on every visit.
 3. Active assessment of local skin reactions should be pre-defined, and quantified.
- Your product can cause bruising. Laboratory testing should include coagulation parameters (aPTT, PT).

Meeting Discussion:

The Agency recommended that the sponsor provide information demonstrating consistency between the objective assessment measurements and the composite endpoint of physician and

subject assessment. There should be agreement on the physician and subject scoring scales as a first step before proposing the study including an objective measurement. This information would inform the appropriate design of Phase 3 trials. The Agency agreed to review an investigational plan prior to study initiation.

Additional Agency Comments:

Regarding the report for study ATX-101-08-11 entitled, “Inter-rater and Intra-rater Evaluation of a Rating Instrument for Submental Fat.”

- The reliability data for the SMFRS are provided under optimal conditions. Investigators underwent intensive training in which they rated both photographs as well as live subjects prior to rating the 66 test subjects. In addition, they performed the initial and repeat assessment on the same day as the training. In a clinical trial setting, investigators’ scoring practices may deviate from the methods described during training, especially over a study period lasting weeks.
- The patient-level data that included individual SMFRS ratings by all 7 raters (in addition to the mean ratings) was not provided for Agency review. Please provide.
- Please also provide other patient-level information such as age, gender, race, and BMI.

Regarding the study report for protocol ATX-101-07-M1 entitled, “Self-assessment Survey of Submental Fat.”

- This study’s stated objective was to “evaluate reactions toward various ATX-101 draft product profiles, identify decision drivers for product trial, and gauge the likelihood of Botox/filler users to adopt ATX-101 as a treatment.” This study does not address the validity or reliability of either the SMFRS or the SSRS.

Question 6:

Kythera believes that the proposed indication, i.e., [REDACTED] (b) (4) [REDACTED] would be supported by the Phase 3 clinical program. Does the Agency concur?

Response:

Ultimately, the indication garnered will represent the population studied and for whom safety and effectiveness has been established. Without agreement on endpoints, we cannot agree that the program you propose would support the indication you are pursuing. Additionally, it is difficult to agree on a proposed indication until Phase 3 trials are conducted and reviewed.

You need to provide data regarding the long-term safety and duration of response for your product.

Question 7:

Kythera believes that the expected number of subjects exposed in the ATX-101 clinical program, including the two Phase 3 trials, is adequate to support approval. Does the Agency concur?

Response:

At this time it is not possible to comment on the number of subjects since that may change significantly based upon different end-points. The number of subjects needed to establish safety may exceed that needed to establish efficacy.

Question 8:

Kythera requested waiver from pediatric studies according to 21 CFR §314.55(c)(2) under IND #79,726 and will submit it in a future NDA. Kythera believes that pediatric studies are not required for ATX-101 when used for the reduction of localized SMF. Does the Agency concur?

Response:

A waiver from pediatric studies may be acceptable for the ATX-101 when used for the reduction of (b)(4) SMF indication. A formal request with rationale should be provided in the marketing application for the pediatric age groups for which the sponsor requests a waiver.

Additional Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
3. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is waived or deferred.
4. 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.
5. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue

early in development.

6. We remind you that effective June 30, 2006, all submissions must include content and format of prescribing information for human drug and biologic products based on the new Physicians Labeling Rule (see attached website <http://www.fda.gov/cder/regulatory/physLabel/default.htm> for additional details).

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
IND 79726	GI 1	KYTHERA BIOPHARMS	ATX-101
IND 79726	GI 1	KYTHERA BIOPHARMS	ATX-101
IND 79726	GI 1	KYTHERA BIOPHARMS	ATX-101

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/s/

SUSAN J WALKER
08/21/2009

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 206333

LATE-CYCLE MEETING MINUTES

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Rd., 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) dated May 13, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for deoxycholic acid injection, 10 mg/mL.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on January 27, 2015.

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

If you have any questions, call Matthew White, Regulatory Project Manager at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Late Cycle Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF LATE-CYCLE MEETING MINUTES

Meeting Date and Time: January 27, 2015 at 11:00 a.m.
Meeting Format: Teleconference

Application Number: NDA 206333
Product Name: deoxycholic acid injection, 10 mg/mL
Applicant Name: Kythera Biopharmaceuticals, Inc.

Meeting Chair: David Kettl, MD
Meeting Recorder: Matthew White

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Amy G. Egan, MD, MPH, Deputy Director, ODE III
Maria R. Walsh, RN, MS, Associate Director for Regulatory Affairs, ODE III
Kendall A. Marcus, MD, Director, DDDP
David Kettl, MD, Clinical Team Leader, DDDP
Milena Lolic, MD, Clinical Reviewer, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Elektra Papadopoulous, MD, MPH, Endpoints Team Leader, SEALD
Sarrit Kovacs, PhD, MS, Endpoints Reviewer, SEALD
Tamara Johnson, MD, MS, Medical Officer, DPMH
Carol Kasten, MD, Medical Officer, DPMH
Roy Blay, PhD, Reviewer, DGCAB
Nyedra Booker, PharmD, MPH, Risk Management Analyst, DRISK
Gabriella Anic, PhD, Epidemiologist, DEPI I
Matthew White, Senior Regulatory Health Project Manager, DDDP

EASTERN RESEARCH GROUP ATTENDEES

Christopher Sese, Independent Assessor

APPLICANT ATTENDEES

Frederick Beddingfield, MD, PhD, Chief Medical Officer
Diane Stroehmann, MS, Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
Nancy Jorgesen, Vice President, Project Management and Corporate Operations
Paul Lizzul, MD, PhD, Senior Medical Officer
Todd Gross, PhD, Vice President, Clinical Development, Biostatistics and Data Management
Jere Fellmann, PhD, Vice President, Clinical Operations
James McElvain, PhD, Vice President, Quality and Analytical

1.0 BACKGROUND

NDA 206333 was submitted on May 13, 2014 for deoxycholic acid injection, 10mg/mL

Proposed Indication: For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults

PDUFA Goal Date: May 13, 2015

FDA issued a Background Package in preparation for this meeting on January 16, 2015.

2.0 DISCUSSION

1. Introductory Comments

2. Discussion of Substantive Review Issues

- No substantive review issues have been identified to date.

3. Discussion of Minor Review Issues

- Labeling discussions pending
- Additional edits to the label may be forthcoming to bring the label into compliance with Final Pregnancy and Lactation Labeling Rule which takes effect June, 2015

Meeting Discussion:

The Applicant intends to submit their counterproposal to the Agency proposed package insert (sent January 20, 2015) by January 30, 2015. Additional Agency comments regarding the carton and container labeling are forthcoming.

4. Discussion of Upcoming Advisory Committee Meeting

5. REMS or Other Risk Management Actions

- No issues related to risk management have been identified to date.

6. Postmarketing Requirements/Postmarketing Commitments

- Postmarketing Requirement (PMR) to submit data from the ongoing safety and efficacy trial under protocol ATX-101-13-28 reflecting ATX-101 use in population 65-75 years of age

Meeting Discussion:

The Applicant intends to submit their proposed timeline by January 30, 2015.

7. Review Plans

- The Office of Compliance inspection results for the manufacturing sites are pending
- The Office of Scientific Investigation (OSI) inspection results are pending
- We plan to take an official action in accordance with the PDUFA goal dates.

8. Wrap-up and Action Items

This application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, this meeting did not address the final regulatory decision for the application.

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/s/

DAVID L KETTL
02/02/2015



NDA 206333

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Kythera Biopharmaceuticals, Inc.
Attention: Diane Stroehmann, MSRA, RAC
Vice President, Regulatory Affairs, Pharmacovigilance and Research Compliance
30930 Russell Ranch Rd., 3rd Floor
Westlake Village, CA 91362

Dear Ms. Stroehmann:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for deoxycholic acid injection, 10mg/mL.

We also refer to the Late-Cycle Meeting (LCM) scheduled for January 27, 2015. Attached is our background package, including our agenda, for this meeting.

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Late-Cycle Meeting Background Package

LATE-CYCLE MEETING BACKGROUND PACKAGE

Meeting Date and Time: January 27, 2015 at 11:00 a.m.
Meeting Format: Teleconference

Application Number: NDA 206333
Product Name: deoxycholic acid injection, 10mg/mL

Proposed Indication: For improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults
Applicant Name: Kythera Biopharmaceuticals, Inc.

INTRODUCTION

The purpose of a Late-Cycle Meeting (LCM) is to share information and to discuss any substantive review issues that we have identified to date, Advisory Committee (AC) meeting plans (if scheduled), and our objectives for the remainder of the review. The application has not yet been fully reviewed by the signatory authority, division director, and Cross-Discipline Team Leader (CDTL) and therefore, the meeting will not address the final regulatory decision for the application. We are sharing this material to promote a collaborative and successful discussion at the meeting.

During the meeting, we may discuss additional information that may be needed to address the identified issues and whether it would be expected to trigger an extension of the PDUFA goal date if the review team should decide, upon receipt of the information, to review it during the current review cycle. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, if an AC is planned, we may not be prepared to discuss that new information at this meeting.

BRIEF MEMORANDUM OF SUBSTANTIVE REVIEW ISSUES IDENTIFIED TO DATE

1. Discipline Review Letters

No Discipline Review letters have been issued to date.

2. Substantive Review Issues

No substantive review issues have been identified to date.

ADVISORY COMMITTEE MEETING

Date of AC meeting: March 9, 2015

Date AC briefing package to be sent under separate cover by the Division of Advisory Committee and Consultant Management: February 17, 2015

Potential questions and discussion topics for AC Meeting are as follows:

Considering potential risks and benefits, do the available data support approval of deoxycholic acid injection for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat in adults?

We look forward to discussing our plans for the presentations of the data and issues for the upcoming AC meeting. Final questions for the Advisory Committee are expected to be posted two days prior to the meeting at this location:

<http://www.fda.gov/AdvisoryCommittees/Calendar/default.htm>

REMS OR OTHER RISK MANAGEMENT ACTIONS

No issues related to risk management have been identified to date.

LCM AGENDA

1. Introductory Comments – 5 minutes
 - Welcome, Introductions, Ground rules, Objectives of the meeting
2. Discussion of Minor Review Issues – 5 minutes
 - Labeling discussions pending
 - Additional edits to the label may be forthcoming to bring the label into compliance with Final Pregnancy and Lactation Labeling Rule which takes effect June, 2015
3. Discussion of Upcoming Advisory Committee Meeting – 5 minutes
4. Postmarketing Requirements/Postmarketing Commitments – 5 minutes
 - Postmarketing Requirement (PMR) to submit data from the ongoing safety and efficacy trial under protocol ATX-101-13-28 reflecting ATX-101 use in population 65-75 years of age — propose timeline.
5. Review Plans – 5 minutes
 - The Office of Compliance inspection results for the manufacturing sites are pending

- The Office of Scientific Investigation (OSI) inspection results are pending
- We plan to take an official action in accordance with the PDUFA goal dates.

6. Wrap-up and Action Items – 5 minutes

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/s/

KENDALL A MARCUS
01/16/2015