

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207999Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 207999

SUPPL # n/a

HFD # 180

Trade Name OCALIVA

Generic Name obeticholic acid

Applicant Name Intercept Pharmaceuticals, Inc.

Approval Date, If Known May 29, 2016

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

c) Did the applicant request exclusivity?

YES NO

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

7 years

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

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:

Pivotal trial

Phase 3 trial 747-301- placebo controlled efficacy and safety study

Supportive trials

Phase 2 trial 747-201

Phase 2 trial 747-202

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 and # 3 YES NO

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

- b) For each investigation identified as "essential to the approval", does the investigation

duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 and # 3 YES NO

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

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

Pivotal trial phase 3 747-301

Phase 2 trial 747-201

Phase 2 trial 747-202

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

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

Investigation #1
IND # 63-307 YES ! NO
! Explain:

Investigation #2 and # 3
IND # 63-307 YES ! NO
! Explain:

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

None.

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: Dr. Lara Dimick-Santos, MD
Title: Cross Discipline Team Leader

Date: 3/24/2016

Name of Office/Division Director signing form: Dr. Dragos Roman
Title: Associate Director

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

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

/s/

ANISSA A DAVIS
04/25/2016

LARA DIMICK-SANTOS
04/25/2016

DRAGOS G ROMAN
04/25/2016

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 207999 BLA # n/a	NDA Supplement # n/a BLA Supplement # n/a	If NDA, Efficacy Supplement Type: n/a <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: OCALIVA Established/Proper Name: obeticholic acid Dosage Form: tablets		Applicant: Intercept Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a
RPM: CDR Anissa Davis-Williams		Division: Division of Gastroenterology and Inborn Errors Products
NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)	<p style="text-align: center;"><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></p> <ul style="list-style-type: none"> Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p style="margin-left: 20px;"> <input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity <i>(notify CDER OND IO)</i> Date of check: </p> <p><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>5/29/16</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 checked="" type="checkbox"/> Received
❖ Application Characteristics ³		

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

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

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

Review priority: Standard Priority
 Chemical classification (new NDAs only): Type 1
(confirm chemical classification at time of approval)

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

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

NDAs: Subpart H

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

Subpart I

- Approval based on animal studies

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

BLAs: Subpart E

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

Subpart H

- Approval based on animal studies

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

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input 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)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action(s) and date(s) 5/27/16
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input checked="" type="checkbox"/> Included
<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 <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i> 	<input 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) <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> Most-recent draft labeling 	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	10/27/15 (acceptable); 2/12/15 (non-acceptable)
<ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i> Review(s) <i>(indicate date(s))</i> 	10/26/15; 2/11/15
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input type="checkbox"/> None 8/31/15 DMEPA: <input type="checkbox"/> None 2/22/16 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input type="checkbox"/> None 4/29/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality: <input type="checkbox"/> 5/24/16 Other: <input checked="" type="checkbox"/> Maternal Health 2/23/16 None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	8/31/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

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

<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>indication granted orphan designation April 9, 2008</u> 	
<ul style="list-style-type: none"> ❖ Breakthrough Therapy Designation 	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> • Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) 	
<ul style="list-style-type: none"> • CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>) <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site</i>)</p>	
<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, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>) 	5/25/16;5/20/16;5/18/16;5/6/16;5/5/16;4/25/16;4/21/16;4/20/16;4/18/16;3/31/16;3/29/16;3/18/16;3/17/16;3/16/16;3/15/16;2/29/16;2/22/16;1/29/16;1/27/16;1/7/16;1/4/16;12/31/15;12/24/15;12/18/15;12/17/15;12/16/15;12/14/15;12/10/15;11/19/15;11/3/15;10/28/15;10/20/15;10/14/15;10/9/15;10/8/15;10/5/15;9/24/15;9/21/15;9/16/15;9/15/15;9/14/15;9/11/15;9/9/15;9/4/15;9/1/15;8/31/15;8/28/15;8/25/15;8/20/15;8/18/15;8/13/15;8/12/15;8/11/15;7/29/15;7/24/15;7/16/15;1/5/15;11/18/14;5/27/14
<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) 	12/28/15;9/28/15;9/11/15;8/17/15;8/6/15
<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 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 11/18/14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 8/5/10
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 10/27/15
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A 3/22/16
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) 	

❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	4/7/16
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/27/16
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/26/16
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/25/16
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 4
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) (<i>indicate date for each review</i>)	5/27/16
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	5/27/16 (pages 245-247 in Clinical Review)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 4/23/16 (COA); 2/1/16 (DBRUP);10/21/15 (QT-IRT)
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 4/12/16
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 2/12/16; 11/17/15; 4/11/16;2/24/16;2/16/16;;2/8/16;2/1/16;1/20/16;1/8/16;12/1/15; 9/1/15
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4/22/16; 3/8/16

Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/3/16 (Errata); 3/2/16
❖ OSI Clinical Pharmacology Inspection Review Summary <i>(include copies of OSI letters)</i>	<input type="checkbox"/> None requested 11/13/15;8/17/15
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 2/8/16
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None 1/7/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input type="checkbox"/> No carc 9/9/15
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 9/10/15;10/6/11 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary <i>(include copies of OSI letters)</i>	None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 5/24/16;4/19/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team <i>(indicate date of each review)</i>	<input type="checkbox"/> None 2/13/16;11/19/15
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Categorical exclusion granted (see OPQ review dated 4/19/16, pages 204-206)
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> Facilities inspections <i>(action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i>	<input checked="" type="checkbox"/> Acceptable 12/10/15 (see electronic archive printout and OPQ review dated 4/19/16, page 169) Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input type="checkbox"/> Done (<i>Send email to CDER OND IO</i>)
❖ For products that need to be added to the flush list (generally opioids): Flush List <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input type="checkbox"/> Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input 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 type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/

ANISSA A DAVIS
05/27/2016

Davis, Anissa

From: Davis, Anissa
Sent: Friday, May 20, 2016 4:08 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Label

Importance: High

Hello Linda:

The team would like for you to consider the following regarding the PI for NDA 207999 obeticholic acid:

For the monotherapy part in Section 14 of PI, we suggest to put the following information:

“OCALIVA Monotherapy:

Fifty-one PBC patients with baseline ALP \geq 1.67-times ULN and/or total bilirubin $>$ ULN were evaluated for a biochemical response to OCALIVA as monotherapy (24 patients received OCALIVA 10 mg once daily and 27 patients received placebo) in a pooled analysis of data from Trial 1 and from a randomized, double-blind, placebo-controlled, 3-month trial. At Month 3, 9 (38%) OCALIVA-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patient. The mean (95% CI) reduction in ALP in OCALIVA-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients.”

One possible alternative to the last line above, for the ease of comparison of the two numbers, could be:

“The mean (95% CI) change in ALP in OCALIVA-treated patients was -246 (-327, -165) U/L compared to 17 (-7, 42) U/L in the placebo-treated patients.”

Rationale:

(b) (4)

The responder values are consistent with the results that you have provided in ISE (ise1.pdf, page 1491).

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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Anissa.Davis@fda.hhs.gov

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To Sponsor/Applicant

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/s/

ANISSA A DAVIS
05/20/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, May 18, 2016 2:07 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: RE: NDA 207999 OCALIVA (obeticholic acid): Labeling Negotiations

Hello Linda:

Regarding the label that I just forwarded concerning NDA 207999, I note the following:

It has come to our attention that there is an error in the results in Section 6.1 in the following text:

 (b) (4)

Please replace with the following:

The incidence of pruritus was higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration group, 70% and 56%, respectively. Discontinuation rates due to pruritus were also higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration group, 10% and 1%, respectively.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
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From: Davis, Anissa
Sent: Wednesday, May 18, 2016 1:43 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Labeling Negotiations

Hello Linda:

We have reviewed the Prescribing Information (PI) and Immediate Container Labels submitted for NDA 207999 Ocaliva (obeticholic acid) application review and made comments and/or edits. Please review below. Please ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).

Please submit your response officially to your application by close of business Monday, May 23, 2016 or sooner.

PI

<< File: NDA 207999 PI with FDA Edits.Comments 5.18.16.docx >>

Immediate Container Labels

Please revise the 5 mg tablet container to display: "Each tablet contains: 5 mg of obeticholic acid"

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
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/s/

ANISSA A DAVIS
05/18/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, May 18, 2016 1:43 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Labeling Negotiations

Hello Linda:

We have reviewed the Prescribing Information (PI) and Immediate Container Labels submitted for NDA 207999 Ocaliva (obeticholic acid) application review and made comments and/or edits. Please review below. Please ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).

Please submit your response officially to your application by close of business Monday, May 23, 2016 or sooner.



Immediate Container Labels

Please revise the 5 mg tablet container to display: "Each tablet contains: 5 mg of obeticholic acid"

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
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20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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ANISSA A DAVIS
05/18/2016

Davis, Anissa

From: Davis, Anissa
Sent: Friday, May 06, 2016 4:17 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: RE: NDA 207999 OCALIVA (obeticholic acid): Information Request- Revision to Item 1.d.
Importance: High

Hi Linda:

We have revised item 1.d. as follows:

1. Please provide additional analyses to address intra-subject variability in alkaline phosphatase (ALP) levels observed in your 747-301 trial. This should include, but is not limited to:
 - d. An analysis in the variability in ALP levels by tertiles of baseline ALP level, **by treatment group.**

The date to submit your response officially to your application is still Monday, May 9, 2016.

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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Senior Regulatory Project Manager

Food and Drug Administration

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From: Davis, Anissa
Sent: Thursday, May 05, 2016 5:38 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Information Request
Importance: High

Hi Linda:

As stated in the teleconference that we had earlier today, below is the information request we have drafted regarding your responses we received on April 29, 2016 for NDA 207999. Please submit all responses officially to the application.

Intercept: We request the following be submitted by COB Monday, May 9, 2016 or earlier.

1. Please provide additional analyses to address intra-subject variability in alkaline phosphatase (ALP) levels observed in your 747-301 trial. This should include, but is not limited to:
 - a. An outlier analysis
 - b. Separate lattice plots for ALP levels in individual patients, by treatment group and by age (<65, ≥65)
 - c. Evidence that the variability in ALP levels is related to liver ALP (this may be performed by correlation with GGT levels)
 - d. An analysis in the variability in ALP levels by tertiles of baseline ALP level, by dose
 - e. An attempt to understand specific sub-groups in whom greater variability is observed. If your explanation is that this is due to medication non-compliance, please provide data to support this explanation. In particular, we would like to know how long a patient would need to be non-compliant with UDCA and/or OCA to observe large changes (>60 U/L) in ALP. Please provide a reference for this information.

Intercept: We request the following be submitted as soon as possible, preferably no later than COB Wednesday, May 11, 2016:

2. Please provide longitudinal data on the natural history of ALP and TB levels (as continuous variables) over time, across all stages of PBC (by Rotterdam criteria and also in patients with known cirrhosis staged by compensated and decompensated), in patients not being treated with UDCA. This information should be available in the Global PBC Study Group database, which includes both treated and untreated early and advanced stages of PBC patients. Untreated patients can include patients from the pre-UDCA era, or patients discontinued from UDCA for any reason. The latter group should include only longitudinal data from the point of UDCA discontinuation on.
3. Provide the ages of the patients on whom you performed the ALP isoform analyses in trial 747-301.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
05/06/2016

Davis, Anissa

From: Davis, Anissa
Sent: Friday, May 06, 2016 9:10 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Labeling Negotiations 5/6/16

Importance: High

Hello Linda:

We have reviewed the Prescribing Information (PI) and Immediate Container Labels submitted for NDA 207999 Ocaliva (obeticholic acid) application review and made comments and/or edits. Please review below. Please ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions).

Please submit your response officially to your application by close of business Wednesday, May 11, 2016.

PI



APPEARS THIS WAY ON ORIGINAL

NDA 207999 OCA NDA 207999 OCA
Label to Applic... Label to Applic...

Immediate Container Labels

- To be consistent with the PI please revise the storage conditions statement on the immediate container label as shown below:

Store at 20°C - 25°C (68°F-77°F); excursions permitted to 15°C -30°C (59°F-86°F) [See USP Controlled Room Temperature].

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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/s/

ANISSA A DAVIS
05/06/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, May 05, 2016 5:38 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Information Request

Importance: High

Hi Linda:

As stated in the teleconference that we had earlier today, below is the information request we have drafted regarding your responses we received on April 29, 2016 for NDA 207999. Please submit all responses officially to the application.

Intercept: We request the following be submitted by COB Monday, May 9, 2016 or earlier.

1. Please provide additional analyses to address intra-subject variability in alkaline phosphatase (ALP) levels observed in your 747-301 trial. This should include, but is not limited to:
 - a. An outlier analysis
 - b. Separate lattice plots for ALP levels in individual patients, by treatment group and by age (<65, ≥65)
 - c. Evidence that the variability in ALP levels is related to liver ALP (this may be performed by correlation with GGT levels)
 - d. An analysis in the variability in ALP levels by tertiles of baseline ALP level, by dose
 - e. An attempt to understand specific sub-groups in whom greater variability is observed. If your explanation is that this is due to medication non-compliance, please provide data to support this explanation. In particular, we would like to know how long a patient would need to be non-compliant with UDCA and/or OCA to observe large changes (>60 U/L) in ALP. Please provide a reference for this information.

Intercept: We request the following be submitted as soon as possible, preferably no later than COB Wednesday, May 11, 2016:

2. Please provide longitudinal data on the natural history of ALP and TB levels (as continuous variables) over time, across all stages of PBC (by Rotterdam criteria and also in patients with known cirrhosis staged by compensated and decompensated), in patients not being treated with UDCA. This information should be available in the Global PBC Study Group database, which includes both treated and untreated early and advanced stages of PBC patients. Untreated patients can include patients from the pre-UDCA era, or patients discontinued from UDCA for any reason. The latter group should include only longitudinal data from the point of UDCA discontinuation on.
3. Provide the ages of the patients on whom you performed the ALP isoform analyses in trial 747-301.

Anissa

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/s/

ANISSA A DAVIS
05/05/2016



NDA 207999

INFORMATION REQUEST

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
VP, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92121

Dear Dr. Robertson:

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

We also refer to your June 29, 2015 submission, containing your new drug application.

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

The analytical methods were validated by Division of Pharmaceutical Analysis, FDA (DPA). The following are the recommendations and information requests from DPA regarding the drug product analytical method validation.

- 1) The HPLC method for the determination of impurity ^(b)₍₄₎ in INT-747 film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM857/01
 - a) Two calibration data sets are collected in the experiment with 6 standard concentrations. Please clarify which data set in the specified sequence is used to determine the quadratic equation constants for system suitability and calculation.
- 2) The HPLC method for the determination of impurity ^(b)₍₄₎ and unspecified impurities in OCA film coated tablets 5mg, 10 mg and 25 mg— Quality Control Method QCM1069/01
 - a) In this method only 3 standard concentrations are prepared (see page 3 of this method) and used to generate a quadratic curve which will always result in a correlation coefficient (r) of 1 and always meet the system suitability requirement of \geq ^(b)₍₄₎. It is

recommended that more data points are used to build a calibration curve as performed in the method for Impurity (b) (4) (b) (4) point calibration curve).

- b) Two calibration data sets are collected in the experiment. Please clarify which data set in the specified sequence is used to determine the quadratic equation constants for system suitability and calculation.
- 3) Assay and Identification ((b) (4))
- a) In DPA's analysis, the concentration of the standard (b) (4) injection volume lead to overloading of the column resulting in poor peak shape and an inability to meet system suitability (Symmetry Factor). DPA reduced the injection volume by (b) (4), per USP<621> guidelines, and yielded sufficiently quantifiable results with better method performance.

If you have any questions, please contact me, at (240) 4025826 or at truong.quach@fda.hhs.gov. Please respond by **May 09, 2016**.

Sincerely,

Truong Quach, Pharm. D.
Regulatory Business Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Truong
Quach -S

Digitally signed by Truong Quach -S
DN: c=US, o=U.S. Government,
ou=FDA, ou=People,
cn=Truong Quach -S,
0.9.2342.19200300.100.1.1=20015119
49
Date: 2016.04.25 17:28:02 -04'00'

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, April 21, 2016 7:37 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): PMR/PMC Information Request

Importance: High

Hello Linda:

Below are the Postmarketing Requirement (PMR)s and Postmarketing Commitment (PMC) that the team has created for NDA 207999 (obeticholic acid). Please review and complete the dates for each one. If you have comments or need clarification, please let me know. **Please submit your final response officially to your application by April 27, 2016 or sooner.** Thanks

PMR 3057-X
Description: A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of obeticholic acid in patients with primary biliary cholangitis/cirrhosis (PBC) with Child-Pugh Classes B and C hepatic impairment, including Child-Pugh Class C patients with varying levels of MELD scores. You may conduct this as a stand-alone trial, or in a subset of patients in your confirmatory trial (PMR#3057-X).

PMR 3057-X Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMR 3057-X
Description: A randomized, placebo-controlled trial to evaluate the safety and efficacy of OCALIVA used as monotherapy in patients with primary biliary cholangitis/cirrhosis (PBC) who are intolerant of or non-responsive to ursodeoxycholic acid (UDCA). Enroll patients across all stages of PBC, by the Rotterdam criteria. You may conduct this as a stand-alone trial, or in a sub-set of patients in your confirmatory trial (PMR # 3057-X).

PMR 3057-X Schedule Milestones:	Final Protocol Submission:	MM/DD/YYYY
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMR 3057-X
Description: A randomized, double-blind, placebo-controlled trial to verify and describe that OCALIVA-induced reductions in alkaline phosphatase and/or total

bilirubin are associated with improvements in the composite clinical endpoint of progression to cirrhosis, death, transplant, decompensation events and hepatocellular cancer. Your ongoing trial (747-302) should be revised to include patients across the spectrum of stages of primary biliary cholangitis/cirrhosis (PBC), including patients with early, moderately advanced and advanced PBC by the Rotterdam criteria, and should be adequately powered to demonstrate benefit in each stage.

PMR 3057-X Schedule Milestones:	Draft Amended Protocol Submission:	<u>MM/DD/YYYY</u>
	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

PMC 3057-X Description:	Develop a formulation that would allow once daily dosing for patients with hepatic impairment. Conduct a (b) (4) study in healthy subjects to characterize the relative bioavailability of the new formulation. Submit your (b) (4) study protocol once you have a new formulation.
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PMR 3057-X Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
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/s/

ANISSA A DAVIS
04/21/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, April 20, 2016 10:57 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: RE: NDA 207999 (obeticholic acid): Clinical Information Request- Revised

Importance: High

Hello Linda:

See revisions **in red** in the information request below which was sent to you on Monday, April 18, 2016. The due date remains the same-April 29, 2016.

1. Provide data and analyses for the measurement of within patient variability (i.e., intra-subject/day-to-day variability) for each patient's ALP concentration (in units/liter) overtime by treatment group for trials 747-301, 747-201 and 747-202. Please separately designate placebo patients who were inadvertently treated with OCA.
 - Provide separate graphical patient profiles for each patient's ALP concentration (in units/liter) over time by treatment group for trials 747-301, 747-201 and 747-202.
 - **Please show the 15% reduction from baseline as a dashed line in the graph.**
2. Please provide separate responder analyses of ALP by different thresholds (i.e., achieving a percent reduction from baseline of at least 5%, 10%, 15%, 20%, 25%, 30% 35%, and 40%) for all treatment groups (**placebo, titration arm and 10mg OCA arm**) at each time point (i.e., at 2 weeks, 3 months, 6 months, 9 months and 12 months) for trial 747-301.
3. Please provide expert opinion and literature to address the question of whether the natural history of the disease results in reduction of ALP, and the extent of ALP reduction with more advanced stages of PBC along with onset of cirrhosis.
4. Please answer whether OCA has an effect on ALP levels independent of its effect in the diseased state. This may be assessed by examining ALP data from healthy volunteer studies of at least 2 weeks duration.

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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From: Davis, Anissa
Sent: Monday, April 18, 2016 4:32 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Request
Importance: High

Hello Linda:

We have the following clinical information request for NDA 207999 OCALIVA:

1. **Provide data and analyses for the measurement of within patient variability (i.e., intra-subject/day-to-day variability) for each patient's ALP concentration (in units/liter) overtime by treatment group for trials 747-301, 747-201 and 747-202. Please separately designate placebo patients who were inadvertently treated with OCA.**
 - **Provide separate graphical patient profiles for each patient's ALP concentration (in units/liter) over time by treatment group for trials 747-301, 747-201 and 747-202.**
2. **Please provide separate responder analyses of ALP by different thresholds (i.e., achieving a percent reduction from baseline of at least 5%, 10%, 15%, 20%, 25%, 30% 35%, and 40%) for all treatment groups at each time point (i.e., at 2 weeks, 3 months, 6 months , 9 months and 12 months) for trial 747-301.**
3. **Please provide expert opinion and literature to address the question of whether the natural history of the disease results in reduction of ALP, and the extent of ALP reduction with more advanced stages of PBC along with onset of cirrhosis.**
4. **Please answer whether OCA has an effect on ALP levels independent of its effect in the diseased state. This may be assessed by examining ALP data from healthy volunteer studies of at least 2 weeks duration.**

Please submit your response officially to your application by April 29, 2016.

Thank you!

Anissa

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/s/

ANISSA A DAVIS
04/20/2016

Davis, Anissa

From: Davis, Anissa
Sent: Monday, April 18, 2016 4:32 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Request

Importance: High

Hello Linda:

We have the following clinical information request for NDA 207999 OCALIVA:

- 1. Provide data and analyses for the measurement of within patient variability (i.e., intra-subject/day-to-day variability) for each patient's ALP concentration (in units/liter) overtime by treatment group for trials 747-301, 747-201 and 747-202. Please separately designate placebo patients who were inadvertently treated with OCA.**
 - Provide separate graphical patient profiles for each patient's ALP concentration (in units/liter) over time by treatment group for trials 747-301, 747-201 and 747-202.**
- 2. Please provide separate responder analyses of ALP by different thresholds (i.e., achieving a percent reduction from baseline of at least 5%, 10%, 15%, 20%, 25%, 30% 35%, and 40%) for all treatment groups at each time point (i.e., at 2 weeks, 3 months, 6 months , 9 months and 12 months) for trial 747-301.**
- 3. Please provide expert opinion and literature to address the question of whether the natural history of the disease results in reduction of ALP, and the extent of ALP reduction with more advanced stages of PBC along with onset of cirrhosis.**
- 4. Please answer whether OCA has an effect on ALP levels independent of its effect in the diseased state. This may be assessed by examining ALP data from healthy volunteer studies of at least 2 weeks duration.**

Please submit your response officially to your application by April 29, 2016.

Thank you!

Anissa

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ANISSA A DAVIS
04/18/2016

From: [Cherry-France, Cheronda](#)
To: ["Linda Robertson"](#)
Cc: [Davis, Anissa](#); [Hong, Cindy](#)
Subject: NDA 207999/OCA: Comments Regarding Erratum for FDA Clin Pharm AC Package: IR Due By Friday, April 1st
Date: Thursday, March 31, 2016 9:13:48 AM
Importance: High

Hi Linda:

The team has the following comments for the Erratum for FDA Clin Pharm AC Package for NDA 207999 OCA. **IR is due by COB, Friday, April 1st.**

-
Clinical/Biostatistics

1. Page 13: You state that "The risk of adverse outcomes associated with inadequate or no response to UDCA (as determined primarily by ALP and, in more advanced disease, bilirubin as well) is substantial."
We believe this statement overstates the facts and should be corrected to state "data from the Global PBC study group supports that patients who have elevated ALP and TB after one year of treatment with UDCA have an increased risk of death or liver transplant."
2. Page 13: While UDCA has had a marked impact on clinical outcomes in PBC, ALP remains abnormally elevated in 70% of patients taking a therapeutic dose of UDCA.
Please provide a reference for this statement or, alternatively, change 70% to the 40% quoted in the Lammers paper, and define "abnormally elevated".
3. Page 14: You state "Activation of FXR regulates bile acid homeostasis enterohepatically, as well as inflammation and fibrosis in response to liver injury."
Please clarify the data that supports this statement. We believe this to be nonclinical data, but you should specify what type of data supports this statement.
4. Page 14: "Mean total bilirubin levels increased in the placebo group and were maintained in the OCA treatment groups, suggestive of a slowing of disease progression with OCA."
Your trial was not designed to test for a "slowing of disease progression with OCA", therefore this statement is misleading. Furthermore, as the changes in TB were all within normal limits, and the normal variability in TB levels in the PBC population is not known, we do not agree with this statement. You need to clarify that these changes in TB were all within normal limits and specify the amount/percent of change observed, and acknowledge that your trial was not designed to test this hypothesis.
5. Page 14: "Placebo patients crossed over to OCA treatment in the LTSE exhibited improvements in both ALP and bilirubin after 1 year of therapy"
Again the improvements in TB are minimal and the TB remains within normal limits, the clinical meaningfulness of which is not known. You need to clarify that for the patients with normal TB at entry, the TB levels all remained within normal limits, and specify the percent change in TB for these patients vs. the percent change in the placebo group. You should also specify the number of patients with above normal TB at entry and the number of these patients who experienced normalization of TB.
6. Page 15: "OCA treatment resulted in significant improvements in secondary endpoints associated with liver damage secondary to cholestasis (eg, GGT, ALT and AST), as well as exploratory markers of immune status and inflammation (eg, IgM and CRP). An evaluation of

transient elastography that was available in a smaller subset of patients indicated that progression of fibrosis was significantly attenuated in the OCA 10 mg group compared with placebo.”

You are overstating the significance of these changes. You need to clarify this statement as the changes in ALT and AST were not clinically relevant. You may state the baseline and the mean change from baseline in each of these parameters. In addition, you overstate the elastography findings. These endpoints were all considered exploratory. This should be stated.

7. Page 18: **Correct the graphic presentation to reflect that serum bilirubin, albumin and platelets do not change until cirrhosis is present.**
8. Page 20: “Up to 70% of patients who are currently being treated or are intolerant to UDCA have an elevated ALP (Lammers 2014).”
Lammers paper quotes 40% of patients have an inadequate response. Correct the percent, or provide us with the location of this statement within the Lammers paper.
9. Page 24: “In fact, doubling of bilirubin was the regulatory endpoint used to support initial approval of UDCA in the US.”
Doubling of bilirubin was only part of the clinical benefit endpoint used for approval of UDCA. Clarify that UDCA approval was based on clinical benefit as well as changes in TB. “main efficacy end point measured during this study, was defined as death, need for liver transplantation, histologic progression by two stages or to cirrhosis, development of varices, ascites or encephalopathy, marked worsening of fatigue or pruritus, inability to tolerate the drug, doubling of serum bilirubin and voluntary withdrawal” and “reduction in the proportion of patients exhibiting a more than 50% increase in serum bilirubin; median percent decrease in bilirubin, transaminases, and alkaline phosphatase; incidence of treatment failure; and time to treatment failure. The definition of treatment failure included: discontinuing the study for any reason; a total serum bilirubin level greater than or equal to 1.5 mg/dL or increasing to a level \geq two times the baseline level; and the development of ascites or encephalopathy.”
10. Page 29: “Long-term safety data has been collected out to over 5 years in the open-label LTSE studies.”
Clarify the number of patients for which you have 5 year data in the LTSE study.
11. Page 32: The primary mechanism of action of OCA in the treatment of PBC is improved bile acid homeostasis, together with anti-inflammatory and anti-fibrotic activity in the liver.
Clarify that this statement is based on in vitro and nonclinical studies in animal models of a different disease and is not proven in humans
12. Page 48: You refer to “key secondary efficacy analyses” and “The key secondary efficacy endpoints were to be considered confirmatory...”. And “A 2-sided test at the 5% level of significance was used for all endpoints. The following rank order for the testing of statistical significance was used for the key secondary efficacy analyses:
The multiplicity adjustment in your SAP allowed for testing of your primary endpoint and key secondary endpoint. Your statements above imply multiple secondary endpoints were considered to be confirmatory. Please correct.
13. Page 52: Demographics and baseline characteristics were typical of a PBC population and included a high risk population of advanced or cirrhotic patients.
This statement is inconsistent with the stage of disease of enrolled patients based on the

Rotterdam criteria, as specified in your Statistical Analysis Plan. Please correct.

14. Page 52: Demographics and baseline characteristics were typical of a PBC population, middle to advanced aged females, and reflective of a high-risk population primarily earlier in disease but with fair (~30%) representation of more advanced or cirrhotic patients (based on current or prior evidence of cirrhosis), 9% of patients had elevated bilirubin levels at baseline).
By the Rotterdam criteria there were only 21 (10%) patients in the phase 3 trial with moderately advanced disease and no patients with advanced PBC. Please correct this by using the Rotterdam criteria, as specified in your Statistical Analysis Plan. If you include other criteria as well you need to specify the criteria were established post-hoc.
15. Page 62: Statistically significant differences compared to placebo were observed for both OCA titration and OCA 10 mg groups for IgM (the hallmark immunoglobulin increased in PBC) and hsCRP (Figure 30). Together, these findings support the immune modulatory and anti-inflammatory properties of OCA observed in preclinical studies.
There was no adjustment for multiplicity after your primary and key secondary endpoint, therefore this is considered an exploratory endpoint that is of nominal statistical significance. . Please correct.
16. Page 63: Transient elastography (Fibroscan®) is one of the best current surrogate markers of liver fibrosis in PBC (Corpechot 2012).
Transient elastography has not been approved by the FDA for diagnosis of liver fibrosis. It was approved for accurate assessment of kilopascals in phantom objects, not in livers. It has not been shown to be accurate in detecting changes in liver fibrosis from stage to stage, and has only shown accuracy in some studies in detecting cirrhosis vs. not cirrhosis. There is little data to support accuracy with detecting fibrosis progression in patients with PBC. Clarify this statement with the above facts or provide supporting data from clinical trials that compare transient elastography by stage with histology.
17. Page 63: Progression of fibrosis as assessed by percentage increase in transient elastography was statistically significantly reduced in the 10 mg OCA group (2.9%) versus placebo (21.7%; $p < 0.05$), but not in the OCA titration group (22.1%) (Figure 32).
See answer to #15 above
18. Page 65: The impact of OCA on fibrosis was further evaluated using the serological based marker AST to Platelet Ratio Index (APRI; Figure 33). There was a statistically significant improvement in the LS mean APRI with both OCA titration ($p = 0.0004$) and 10 mg ($p = 0.0005$) after 12 months of treatment.
There was no adjustment for multiplicity after your primary and key secondary endpoint; therefore, this is an exploratory endpoint that is of nominal statistical significance. Please correct
1. Page 71: These results are clinically meaningful given that improvements in bilirubin, when within the normal range, have been found to have prognostic utility (Lammers 2014).
We do not see anywhere in the Lammers paper that states improvements in the TB levels within normal limits predict clinical benefit, nor was your study designed to test this. Please delete the statement.
20. Page 72: In summary, the pivotal study demonstrated clinically meaningful improvement in the primary composite endpoint shown to be associated with clinical benefit.
The pivotal study demonstrated statistically significant reductions in the surrogate biomarker, ALP. The composite endpoint has not yet been shown to be “associated with

a clinical benefit". Please correct this overstatement.

21. Page 88: Ursodeoxycholic acid (UDCA) is the only medicine currently approved to treat PBC, but up to 70% of UDCA-treated patients either fail to respond or have a suboptimal response.

Lammers paper quotes 40% with suboptimal response. Correct this number.

22. Page 91: The majority of patients with PBC who are treated with OCA can expect clinically meaningful (and in some instances substantial) improvements in ALP and total bilirubin. These benefits are particularly notable as up to 50% of patients with PBC have a suboptimal response to the standard of care UDCA.

Lammers paper quotes 40%, correct the number or provide references.

Clinically meaningful benefit has yet to be evaluated. This should be changed to statistically significant improvements in ALP. You have not demonstrated a statistically significant improvement in TB.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
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/s/

CHERONDA L CHERRY-FRANCE
03/31/2016

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, March 29, 2016 4:42 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Information Request

Importance: High

Hello Linda:

Please review the below clinical information request concerning NDA 207999 and submit your response officially to your application by close of business tomorrow, March 30, 2016. Thank you!

1. Clarify the number of patients in the trial 747-301 who had early stage and moderately advanced stage disease (according to Rotterdam criteria).
 - a. In the 747-301 CSR 92% patients were shown to have an early stage disease.
 - b. Clinical IR response submitted to NDA 207999 Sequence 0057(58) sent on 3-21-2016 you responded 90% patients had early stage disease in trial 747-301.
 - c. Clinical IR response submitted to NDA 207999 Sequence 0055 (56) sent on 3-16-2016, 91% patients were classified as early stage disease in the trial 747-301.

2. Please provide the graphs *for mean total bilirubin* over time (i.e. baseline→month 12) using mg/dL as well as $\mu\text{mol/L}$ for trial 747-301 and similar graphs for 747-301 LTSE trial from baseline→over time for the data threshold available up to the 120 day safety update.

For both trials-Re-Scale the graph at vertical axis to start the TB variable at "0" instead of "8" $\mu\text{mol/L}$. Add a horizontal line to depict the upper limit of normal for TB.

3. How many patients did you identify comparable to trial patients (ALP at baseline \geq 1.67X ULN, UDCA=1 and SG_DSRDAM=1) from the Global PBC database for the biomarker validation analysis (out of 4,845).

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

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/s/

ANISSA A DAVIS
03/29/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, March 17, 2016 8:12 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Clinical Information Request

Importance: High

Hello Linda:

We have the following clinical information request regarding NDA 207999:

Please use the following laboratory values reference range for analyses of these data for the following questions: ALP ULN = 118.3 U/L (Females) and 124.2 U/L (Males); Total Bilirubin ULN: 19.32 $\mu\text{mol/L}$ (Female) and 25.48 $\mu\text{mol/L}$ (Male); Albumin LLN: 35 g/L

1. Please clarify the IR response sent on 3-16-2016 electronically to NDA 207999, Serial 0055 the following
 - a. The number of patients in each group i.e., placebo group, OCA titration arm, OCA 10 mg, OCA 25 mg, OCA 50 mg group in respective trials (using baseline ALP, TB and Albumin) disease stage based on Rotterdam criteria.
 - b. The number of patients in each group i.e., placebo group, OCA 10 mg, OCA 25 mg, OCA 50 mg group in respective trials for the baseline ALP and TB in trial 747-201 and 747-202.
2. Using the Rotterdam criteria to classify disease severity, please tabulate the hepatic adverse events that occurred in each clinical trial (747-201, 747-202 and 747301) for placebo and OCA. Include as hepatic adverse events including hepatic decompensation or any elevations of total bilirubin above 2 x ULN for patients with normal TB at baseline and TB above 2 x baseline for patients with elevated TB at baseline. Also include as hepatic adverse events elevations in transaminases above 3 x baseline. Tabulate by patient ID number, dose and severity of event and by trial.). Please use the data submitted to the FDA for hepatic adverse events as reported in the integrated summary of safety and in the clinical study report (and not based on the recent/post-hoc adjudication for hepatic events submitted for the OCA labeling). Provide a clinical narrative for each patient (if not provided in NDA submission in CSR), including in the narrative the patients' laboratory values (including liver parameters, chemistries including serum creatinine; hematology and coagulation profile) at baseline, during the event and in recovery and at end of trial or end of contact with the patient. Present your analyses of the data and note if any difference were seen in the frequency of adverse events in the patients who were in moderately advanced disease or advanced disease category compared with patients in early disease stage.
3. Referring to the IR sent on 3-16-2016, please add the following information to the column:

For patients who had low albumin at baseline, provide the ALP, TB, conjugated bilirubin and Albumin at baseline and at the end of treatment to assess outcomes. Please use the threshold for normal reference as mentioned above in the IR such that results are comparable across trials. Were there any differences in the hepatic adverse events both hepatic decompensation and liver biochemistry elevations or lipid profile changes observed in patients with moderately advanced stage and advanced stage disease compared to early stage disease from baseline to end of treatment? Please provide these data for the three trials (747-201, 747-202, and 747-301) separately. Tabulate by patient ID number, dose and severity of event and by trial.

4. You have utilized different reference range for total cholesterol, HDLc and LDLc for trial 747-201/747-202 and trial 747-301. You have not provided the laboratory normal reference range for trial 747-205 in the CSR. Using the CURRENT standardized reference range utilizing the guidelines currently used in clinical practice in the US, please provide the results for patients for the all the trials (747-201, 747-202, 747-301 and 747-205) such that results are comparable. This clinical request was sent to you in an IR sent on 3-16-2016.

- a. Provide the changes in mean total cholesterol, mean HDLc and mean LDLc laboratory values in mg/dL in the trial 747-205 at baseline and end of trial (8 weeks). Please provide these data in mg/dL. For patients who had abnormal baseline levels, provide the amount of change from baseline to end of treatment.
- b. Provide a tabulated list of patients who had changes in the total cholesterol, HDLc and LDLc that were below lower limit of normal (LLN) or above upper limit of normal at end of treatment in trials 747-205 and 747-301 trial. Please present the data in mg/dL instead of mmol/L. For patients who had abnormal baseline levels, provide the amount of change from baseline.
- c. Also include a table of patients who had TC, LDLc, HDLc change that were 2 Standard Deviation above or below the reference range respectively, at the end of trial (i.e. baseline to end of study/month12 or day 85 or 8 weeks) in the trials (747-201, 747-202, 747-301, 747-205). Tabulate by patient ID number, dose and severity of event and by trial.

Please submit your response officially to you application by 3-20-2016

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

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/s/

ANISSA A DAVIS
03/17/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, March 16, 2016 2:46 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Information Request

Importance: High

Hello Linda:

Please see the attached document regarding a clinical information request for NDA 207999. Please submit your response officially to your application by March 17, 2016. Thank you@!



03/16/2016

APPEARS THIS WAY ON
ORIGINAL

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

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NDA 207-999 Clinical IR date 3/16/2016

Please send a response to the IR by 3-17-2016.

1. For the subset of patients in Trial 747-301 who had elevated TB at baseline, please provide the individual data for TB and ALP change from baseline to month 12 using the following thresholds. If the albumin level was lower than LLN provide the data by adding another column to the Table. Please use the threshold provided below:

ALP ULN = 118.3 U/L (Females) and 124.2 U/L (Males)

Total Bilirubin ULN: 19.32 $\mu\text{mol/L}$ (Female) and 25.48 $\mu\text{mol/L}$ (Male)

Albumin LLN: 35 g/L

Patient ID#	Baseline Total bilirubin	Baseline Alkaline phosphatase	Month 12 Total bilirubin	Month 12 Alkaline phosphatase
PLACEBO ARM				
Patient ID				
OCA titration arm	Baseline Total bilirubin	Baseline Alkaline phosphatase	Month 12 Total bilirubin	Month 12 Alkaline phosphatase
Patient ID				

OCA 10 mg arm				
Patient ID				

2. Similarly as shown in the Table above in a separate Table for the subset of patients in Trial 747-201 and 747-202 who had elevated TB at baseline, please provide the individual data for TB and ALP change from baseline to month 12. If the baseline albumin was low, please provide the albumin at baseline and month 12 in an additional column. Please use the following thresholds.
 - a. ALP ULN = 118.3 U/L (Females) and 124.2 U/L (Males)
 - b. Total Bilirubin ULN: 19.32 $\mu\text{mol/L}$ (Female) and 25.48 $\mu\text{mol/L}$ (Male)
 - c. Albumin LLN: 35 g/L

3. Please provide the mean of total bilirubin for the treatment arm for trial 747-201 and 747-202 and change overtime (i.e. baseline to Day 85/end of study).

4. Provide the changes in mean total cholesterol, mean HDLc and mean LDLc laboratory values in mg/dL in the trial 747-205 at baseline and end of trial (8 weeks).

5. Provide a tabulated list of patients who had changes in the Total cholesterol, HDLc and LDLc that were below lower limit of normal (LLN) or above Upper limit of normal at end of treatment in trials 747-205 and 747-301 trial. Please present the data in mg/dL instead of mmol/L. For patients who had abnormal baseline levels, provide the amount of change from baseline.

6. Also include a table of patients who had TC, LDLc, HDLc change that were 2 SD above or below the reference range respectively, at the end of trial (i.e. baseline to end of study/month12).

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/s/

ANISSA A DAVIS
03/16/2016

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, March 15, 2016 4:36 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: RE: NDA 207999 OCALIVA (obeticholic acid): Clinical Information Request-Addition
Importance: High

Hello Linda:

In addition to the clinical information request below concerning NDA 207999 (obeticholic acid), please respond to the following (same response date as below):

While categorizing patients for the Stages of disease please also state:

How many patients were categorized as moderately advanced disease on basis on Albumin versus TB i.e., moderately advanced disease (Albumin n (%) and Total Bilirubin n (%)).

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
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From: Davis, Anissa
Sent: Tuesday, March 15, 2016 1:47 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Clinical Information Request
Importance: High

Hello Linda:

We have the following clinical information request regarding NDA 207999 OCALIVA (obeticholic acid):

1. Please fill the number of patients in each category for baseline criteria (use the mean of the screening and baseline levels). If you have patient (s) in different category (ies) which are not mentioned add them in separate column. ? Please use ALP ULN: 118.3 U/L (females), 124.2 U/L (males); TB ULN 19.32 $\mu\text{mol/L}$ (females), 25.48 $\mu\text{mol/L}$ (males).

Table 1: ALP and TB at baseline be each trial (mean baseline and screening values)

Trials	ALP $\geq 1.67 \times$ ULN AND TB < ULN	ALP $\geq 1.67 \times$ ULN AND TB $\geq 1.0 \times$ ULN and < $2.0 \times$ ULN	ALP $\geq 1.67 \times$ ULN AND TB $\geq 2 \times$ ULN	ALP < $1 \times$ ULN AND TB < $1 \times$ ULN	ALP < $1 \times$ ULN AND TB $\geq 1.0 \times$ ULN and < $2.0 \times$ ULN
747-201					
747-202					
747-301					

2. Stages of disease: Using the Rotterdam criteria of classifying the disease stage i.e.,

Stages of disease

- a. Early disease: Normal Albumin, Normal total bilirubin (TB), elevated ALP
- b. Moderately advanced disease: Either Low Albumin or High TB
- c. Advanced Disease: Both Low Albumin+ High TB

Please use ALP ULN: 118.3 U/L (females), 124.2 U/L (males); TB ULN 19.32 $\mu\text{mol/L}$ (females), 25.48 $\mu\text{mol/L}$ (males). Please use a uniform albumin cut off criteria (Albumin=3.5 g/L as lower limit of normal (LLN)):

Rotterdam Criteria	747-201	747-202	747-301
Early stage disease, n (%)			
Moderately advanced n (%)			
Advanced disease n (%)			

3. Summary of Clinical Safety, Section 3.2.2.2 and Section 3.2.5.2.2.1 of the please clarify “exposure-adjusted incidence” whether this analysis addresses the exposures of different duration OR different doses of OCA.

Please submit your response officially to your application by tomorrow, March 16, 2016.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

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ANISSA A DAVIS
03/15/2016

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, March 15, 2016 1:47 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Clinical Information Request

Importance: High

Hello Linda:

We have the following clinical information request regarding NDA 207999 OCALIVA (obeticholic acid):

1. Please fill the number of patients in each category for baseline criteria (use the mean of the screening and baseline levels). If you have patient (s) in different category (ies) which are not mentioned add them in separate column. ? Please use ALP ULN: 118.3 U/L (females), 124.2 U/L (males); TB ULN 19.32 $\mu\text{mol/L}$ (females), 25.48 $\mu\text{mol/L}$ (males).

Table 1: ALP and TB at baseline be each trial (mean baseline and screening values)

Trials	ALP $\geq 1.67 \times$ ULN AND TB < ULN	ALP $\geq 1.67 \times$ ULN AND TB $\geq 1.0 \times$ ULN and < $2.0 \times$ ULN	ALP $\geq 1.67 \times$ ULN AND TB $\geq 2 \times$ ULN	ALP < $1 \times$ ULN AND TB < $1 \times$ ULN	ALP < $1 \times$ ULN AND TB $\geq 1.0 \times$ ULN and < $2.0 \times$ ULN
747-201					
747-202					
747-301					

2. Stages of disease: Using the Rotterdam criteria of classifying the disease stage i.e.,

Stages of disease

- a. Early disease: Normal Albumin, Normal total bilirubin (TB), elevated ALP
- b. Moderately advanced disease: Either Low Albumin or High TB
- c. Advanced Disease: Both Low Albumin+ High TB

Please use ALP ULN: 118.3 U/L (females), 124.2 U/L (males); TB ULN 19.32 $\mu\text{mol/L}$ (females), 25.48 $\mu\text{mol/L}$ (males).
Please use a uniform albumin cut off criteria (Albumin=3.5 g/L as lower limit of normal (LLN)):

Rotterdam Criteria	747-201	747-202	747-301
Early stage disease, n (%)			

Moderately advanced n (%)			
Advanced disease n (%)			

3. Summary of Clinical Safety, Section 3.2.2.2 and Section 3.2.5.2.2.1 of the please clarify “exposure-adjusted incidence” whether this analysis addresses the exposures of different duration OR different doses of OCA.

Please submit your response officially to your application by tomorrow, March 16, 2016.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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ANISSA A DAVIS
03/15/2016

Davis, Anissa

From: Davis, Anissa
Sent: Monday, February 29, 2016 6:27 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Labeling Negotiations

Hello Allison:

We have reviewed the Prescribing Information (PI) and Container Labels submitted for NDA 207999 Ocaliva (obeticholic acid) application review and made comments/edits. Please review below. Please ensure all edits made by you are kept in track change format and do not accept the edits. If you are in agreement with the FDA revisions, accept the track changes (additions and/or deletions). Please submit your response officially to your application by Wednesday, March 9, 2016.

PI



CONTAINER LABELS

1. As currently presented, the product code in the NDC number for 5 mg strength is the same as the product code in the NDC number for 10 mg strength. This can lead to wrong strength errors because barcode scanners may only read the first 10 digits of the NDC codes and pharmacists may rely on the middle portion as a manual check. Therefore, revise the product code in the NDC numbers to ensure that the middle digits are different between strengths.
2. Please clarify if the barcode in the upper-right corner of the proposed containers labels is, in fact, the proposed barcode. If this is an accurate representation of the proposed barcode placement, we recommend reorienting the barcode to a vertical position to improve the barcode's ability to be scanned.
3. We recommend increasing the prominence of the established name (using bold font), to ensure that it is commensurate in prominence with the proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). Additionally, we recommend submitting the revised container labels with the approved proprietary name.
4. We recommend removing the bold font from "Intercept" to decrease the prominence of the company name on the PDP. As currently presented, "Intercept" competes in prominence with the product strength and established name, which are considered essential information on the container labeling.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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ANISSA A DAVIS
02/29/2016

From: Cherry-France, Cheronda
To: ["Linda Robertson"](#)
Cc: [Davis, Anissa](#)
Subject: NDA 207999: STATS/CLINICAL IR Due before COB 2.23.2016
Date: Monday, February 22, 2016 10:01:00 AM

Hi Linda:

Please provide the response to this IR in next 2 business days (before close of business on 2-23-2016).

1. "Transient glucose elevations" were observed during trial 747-301 in some patients as described in Section 12.4.3.3. Please provide details these of glucose elevations, the laboratory values and any treatment required.
2. You have reported changes in total and conjugated bilirubin as small as 1.5 $\mu\text{mol/L}$ to 2 $\mu\text{mol/L}$ (0.02 mg/dL to 0.04 mg/dL). Please clarify the sensitivity, reliability and accuracy of repeat measures of the method used for measuring conjugated bilirubin and total bilirubin.

Thanks,

Roni

Cheronda Cherry-France, RN BSN MHA
LCDR, U.S. Public Health Service Commissioned Corps
Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

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/s/

CHERONDA L CHERRY-FRANCE
02/22/2016

Davis, Anissa

From: Davis, Anissa
Sent: Friday, January 29, 2016 4:23 PM
To: b.hansen@erasmusmc.nl
Cc: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 obeticholic acid (DMF (b) (4)): Statistical Information Request

Importance: High

Hello Bettina and Linda:

We are reviewing your application, NDA 207999 Ocaliva (obeticholic acid) and have the following Statistical information request:

We plan to perform the following analyses by sub-setting Global PBC data based on patients in the early stage (SG_DSRDAM=1) with UDCA use and ALP at baseline >1.67xULN. Some of these analyses will be included in our AC presentation. We would like to share with you our plan in order for you to conduct the same analyses independently.

1. Please fill out the values in the table attached in this email (in the table ALP12 represents the different cutoffs as mentioned below).
2. For ALP at 12 months, cutoffs as 1.0xULN, 1.67xULN, 2.0xULN and 3.0xULN, for percentage change from baseline for ALP at 12 months, cutoffs as 15%, 30%, 40% and 50% reduction.
3. For composite cutoffs Alp12 as 1.67xULN+15% reduction, 1.67xULN+40% reduction, 2.0xULN+15% reduction and 2.0xULN+40% reduction.
4. Subgroup analyses also need to be conducted for region (i.e., North America vs. Europe), age (i.e., <65 & >=65) and baseline ALP (i.e., upper >465.5 U/L, mid >277.5 to <=465.5 U/L and lower <=277.5 U/L).
5. In addition, please generate similar tables for Youden's index and AUCROCs accordingly.

Except for subgroup analyses, please perform similar analyses using five-fold cross-validation (see the following paragraph for details) for item 3. Please submit your analyses results and the table to FDA by 2/18/2016.

K-fold cross-validation: The data set is divided into k subsets, and the holdout method is repeated k times. Each time, one of the k subsets is used as the test set and the other k-1 subsets are put together to form a training set. Then the average error across all k trials is computed. The advantage of this method is that it matters less how the data gets divided. Every data point gets to be in a test set exactly once, and gets to be in a training set k-1 times. Please use k=5.



Blank Jan 29 AM ...

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Please submit your response officially to the DMF by February 18, 2016!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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Senior Regulatory Project Manager

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Table 1: Performance of Different ALP at 1-year Follow-up for Prediction of Liver Transplantation or Death (C-Statistics, Hazard Ratios and Their 95% CIs)

ALP at 12 months (cutoff as 1.0xULN)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+Diag_yr			
ALP12+Age			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age			
ALP12+Diag_yr+Age+ALP0			
ALP at 12 months (cutoff as 1.67xULN)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+Diag_yr			
ALP12+Age			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age			
ALP12+Diag_yr+Age+ALP0			
ALP at 12 months (cutoff as 2.0xULN)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			

ALP12+ALP0			
ALP12+Diag_yr			
ALP12+Age			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age			
ALP12+Diag_yr+Age+ALP0			
ALP at 12 months (cutoff as 3.0xULN)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+Diag_yr			
ALP12+Age			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age			
ALP12+Diag_yr+Age+ALP0			

Percentage Change from Baseline for ALP at 12 months (cutoff as 15%)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			
Percentage Change from Baseline for ALP at 12 months (cutoff as 30%)			

Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			
Percentage Change from Baseline for ALP at 12 months (cutoff as 40%)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			
Percentage Change from Baseline for ALP at 12 months (cutoff as 50%)			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			
ALP12 cutoff as 1.67xULN and Percentage Change from Baseline for ALP at 12 months cutoff as 15%			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			

ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			
ALP12 cutoff as 1.67xULN and Percentage Change from Baseline for ALP at 12 months cutoff as 40%			
Model	C-statistics (95% CIs)	HR (95% CIs)	P-values
ALP12			
ALP12+ALP0			
ALP12+ALP0+Age			
ALP12+ALP0+Diag_yr			
ALP12+Diag_yr+Age+ALP0			

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/s/

ANISSA A DAVIS
01/29/2016

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, January 27, 2016 3:35 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Clinical Information Request

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ocaliva (obeticholic acid).

We are reviewing your application and have the following clinical information requests/comments:

1. Secondary to the fact that ALP in humans comes from several sources (i.e., liver, bone, kidney and intestines) and that patients > 60 years have higher ALP values (up to 1.5 times normal) than young adults¹, ALP may be elevated due to osteogenesis in PBC patients, and that FXR is expressed in bone and has been shown to positively regulate bone osteogenesis in mice, We are concerned that total ALP reduction might be confounded by the reduction in bone isoform predominately, with contribution from liver ALP we are concerned that some of the decrease in ALP seen in your clinical trials could be secondary to OCA's effect on bone. Therefore please respond to the follow questions:
 - a. Have you fractionated any samples for assessing the liver-specific isoform of alkaline phosphatase versus the bone specific isoform of ALP, at baseline and at end of treatment (12 month) in trial 747-301?
 - b. If you have not previously fractionated the liver and bone isoforms, then are there any blood samples stored that you can now analyze to assess the effect of OCA on liver-specific isoform of alkaline phosphatase and bone-specific isoform of alkaline phosphatase?
 - c. We recommend you conduct a liver and bone ALP isoform analyses at baseline and end of treatment for patients in all three groups of patients (placebo, OCA 5 mg titration arm and, OCA 10 mg arm) on the samples that are available.
2. For clinical trial 747-201, provide the liver biochemical parameters that were temporally related with serious adverse events (SAE) within 1 month prior to and after the event.
3. Provide liver biochemical parameters for Subject 23-004-802, who was enrolled in the OCA 50 mg treatment group who had a deviation on Day 57 (conjugated bilirubin level was 2x ULN), which should have resulted in a mandatory discontinuation; however, a waiver was granted for this deviation.

¹ Poupon R. Liver alkaline phosphatase: a missing link between cholestasis and biliary inflammation. *Hepatology*. 2015 Jun;61(6):2080-90.

Please submit your response officially to your application by February 9, 2016.

Thanks



Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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Anissa.Davis@fda.hhs.gov

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¹ Poupon R. Liver alkaline phosphatase: a missing link between cholerisis and biliary inflammation. Hepatology. 2015 Jun;61(6):2080-90.

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/s/

ANISSA A DAVIS
01/27/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, January 07, 2016 12:08 PM
To: b.hansen@erasmusmc.nl
Cc: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Clinical PBC Study Group Information Request

Importance: High

Hello Bettina and Linda:

We are currently reviewing the PBC Study Group dataset that is being utilized to support NDA 207999 OCALIVA (obeticholic acid) and have the following clinical information requests:

1. Death/Liver Transplantation Date

Although death date and liver transplantation date are unable to be submitted, please clarify whether the 'FUlast_yr' variable value signifies death year or transplant year for subjects experiencing death or transplant, respectively.

2. Labs

This is to further clarify our previous information request for lab data. We would like the following data to be additionally submitted for each lab analyte at each time-point up to month 60:

- a) The lab date
- b) The raw lab value in standard units*
- c) The specific corresponding standard units* themselves
- d) The corresponding normal range values in standard units*

*Standards units should be in US Conventional units if possible

3. We are aware that the reference range for the upper limit of normal for alkaline phosphatase may have been higher in the past than is currently accepted. Please clarify if this potential change in reference range impacted your data and how you handled this change in upper limit of normal in your analysis of alkaline phosphatase levels.

Please submit your response officially to the DMF (as before) by January 21, 2016.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
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/s/

ANISSA A DAVIS
01/07/2016

Davis, Anissa

From: Davis, Anissa
Sent: Monday, January 04, 2016 8:17 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCALIVA (obeticholic acid): Clinical Pharmacology Information Request
Importance: High

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999 is currently under review and we have the following clinical pharmacology information requests (IR):

1. In your Response to IR #2 of December 29, 2015, Serial 0043, you stated that:

a. "The initial ALP [redacted] (b) (4)
[redacted] (b) (4)
[redacted] (b) (4). Please clarify what
you referred to as [redacted] (b) (4)

b. "The subsequent [redacted] (b) (4)
[redacted] (b) (4)

2. Based upon your Response to IR of December 26, 2015, Serial 0042, we have additional IR in regard to the correction [redacted] (b) (4) requiring your further clarification.

[redacted] (b) (4)

[redacted] (b) (4)

3. We are unable to find the concentrations

(b) (4)

Please submit your response officially to your application by close of business January 8, 2016.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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/s/

ANISSA A DAVIS
01/04/2016

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, December 31, 2015 8:28 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Request

Hello Linda:

Regarding your application, NDA 207999 OCALIVA (obeticholic acid), submitted on June 27, 2015, we have the following clinical information request:

1. Clarify how DXA scan results were analyzed. Was interpretation performed locally or by a central reader?
2. What measures were taken to harmonize DXA acquisition among centers?

Please submit your response officially to your application by January 15, 2016.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

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/s/

ANISSA A DAVIS
12/31/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 30, 2015

Application Number: NDA 207999

Product Name: obeticholic acid

Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Subject: Discussion Regarding the Statistical Information Request Dated November 19, 2015

FDA Participants :

Julie Beitz, M.D., Director, Office of Drug Evaluation III

Amy Egan, M.D., Associate Director, Office of Drug Evaluation III

Dragos Roman, M.D., Acting Associate Director Division of Gastroenterology and Inborn Errors Products
(DGIEP)

Stephanie Omokaro, Acting Cross Discipline Team Lead, DGIEP

Lara Dimick, M.D., Medical Reviewer, DGIEP

Ruby Mehta, M.D., Medical Officer, DGIEP

Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)

Sue Jane Wang, Ph.D., Associate Director, Office of Biostatistics

Min Min, Ph.D., Statistical Reviewer, DBIII

Benjamin P. Vali, M.S., Statistical Reviewer, DBIII

Brian Strongin, R Ph., M.B.A., Chief, Project Management Staff, DGIEP

Intercept Participants :

Linda Robertson Ph.D., VP, Regulatory Affairs and Quality Assurance

Bettina Hansen, Ph.D., Co-Principal Investigator and Biostatistician, Global PBC Study Group

1.0 BACKGROUND:

On June 27, 2015, Intercept Pharmaceuticals, Inc (Intercept) submitted a New Drug Application (NDA), NDA 207999, for the treatment of treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UCDA. While reviewing the application, the FDA has requested for Intercept to provide data from the PBC Study Group in order to continue reviewing the application. The data was submitted to a **Drug Master File number** ((b) (4)) on October 29, 2015. Upon review of the information, a Statistical Information Request requesting additional information was sent to the applicant and Bettina on November 19, 2015. A meeting was scheduled for November 25, 2015 to discuss the Statistical Information Request.

2.0 DISCUSSION:

Discussion began at 3:00 p.m. (EST).

The FDA clarified the information stated in the IR that is due December 15, 2015. Bettina and Linda from Intercept agreed to provide the FDA with the laboratory sites' upper limits of normal data and possibly the region (e.g., France, Europe, and Canada) by December 15, 2015. Currently, the PBD study group cannot provide the FDA with the date of birth (DOB) for any of the patients and/or the date of diagnosis because this is considered privileged information.

PBC study group will attempt to provide the raw data sets by January 8, 2016.

Called ended at 3:45 p.m. (EST).

3.0 ACTION ITEMS:

Intercept to submit requested data to the FDA by December 15, 2015.

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/s/

CHERONDA L CHERRY-FRANCE
12/28/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: November 25, 2015

Application Number: NDA 207999

Product Name: obeticholic acid

Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Subject: Discussion Regarding the Statistical Information Request Dated November 19, 2015

FDA Participants :

Julie Beitz, M.D., Director, Office of Drug Evaluation III

Amy Egan, M.D., Associate Director, Office of Drug Evaluation III

Dragos Roman, M.D., Acting Associate Director Division of Gastroenterology and Inborn Errors Products (DGIEP)

Stephanie Omokaro, Acting Cross Discipline Team Lead, DGIEP

Lara Dimick, M.D., Medical Reviewer, DGIEP

Ruby Mehta, M.D., Medical Officer, DGIEP

Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)

Sue Jane Wang, Ph.D., Associate Director, Office of Biostatistics

Min Min, Ph.D., Statistical Reviewer, DBIII

Benjamin P. Vali, M.S., Statistical Reviewer, DBIII

Brian Strongin, R Ph., M.B.A., Chief, Project Management Staff, DGIEP

Intercept Participants :

Linda Robertson Ph.D., VP, Regulatory Affairs and Quality Assurance

Leigh McConnell, Ph.D., VP, Clinical Development

Tonya Marmon, Ph.D., Sr. Director, Biostatistics and Data Management

(b) (4), M.D., Regulatory Consultant

Bettina Hansen, Ph.D., Co-Principal Investigator and Biostatistician, Global PBC Study Group

1.0 BACKGROUND:

On June 27, 2015, Intercept Pharmaceuticals, Inc (Intercept) submitted a New Drug Application (NDA), NDA 207999, for the treatment of treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UCDA. While reviewing the application, the FDA has requested for Intercept to provide data from the PBC Study Group in order to continue reviewing the application. The data was submitted to a **Drug Master File number** ((b) (4)) on October 29, 2015. Upon review of the information, a Statistical Information Request requesting

additional information was sent to the applicant and Bettina on November 19, 2015. A meeting was scheduled for November 25, 2015 to discuss the Statistical Information Request.

2.0 DISCUSSION:

Discussion began at 3:00 p.m. (EST).

The FDA clarified the information stated in the IR that is due December 15, 2015. Intercept understood and noted that a follow-up meeting is necessary with Bettina to clarify the outstanding concerns about date and year time frames needed to assist the statisticians with validation of data supported in the PBC study group. Benitta has limited availability, but will attempt to discuss on Monday, November 30, 2015, after 3:00PM.

Called ended at 4.15 p.m. (EST).

3.0 ACTION ITEMS:

Intercept to submit requested data to the FDA by December 15, 2015.

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/s/

CHERONDA L CHERRY-FRANCE
12/28/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, December 24, 2015 11:48 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: RE: NDA 207999 (obeticholic acid): Clinical Pharmacology Information Requests

Hello Linda:

I incorrectly placed the wrong due date for item #3 below. **The due date is January 7, 2016.**

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

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Food and Drug Administration

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From: Davis, Anissa
Sent: Thursday, December 24, 2015 11:38 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Pharmacology Information Requests
Importance: High

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999 is currently under review and we have the following clinical pharmacology information request (IR):

- 1. In the document titled, “747-301 CHSA Comparative Analyses Requested Info”, submitted on 12/15/2015 to Module 5.3.5.1, it stated that “reference method analyses not**

available at this time for ALP” on page 1 of 3 of the document. However, reference method values were provided for total bilirubin (Page 2 of 3) and direct bilirubin (Page 3 of 3). Please provide an explanation.

2. In the dataset BASEEVAL.xpt submitted on 12/15/2015 (Serial 0036), there are blank cells in Column REFVAL for ALP. Please provide data for REFVAL and rest of the cells in Columns REFVALU, BIAS, BIASPCT, BIASMEAN, BIASMNPT, HSLOPERV, HNTRCPRV, HRSQRRV, HMEANRV. If it is not available, please state so and give an explanation.

Please submit your response, to items #1 and #2, officially to your application by 5pm (EST) Wednesday, December 30, 2015.

3. Provide a full English translation of the (b) (4) laboratory QC reports submitted on 12/18/2015 and 12/23/2015 which are in Polish.

Please submit your response, to item #3, officially to your application by January 7, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

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/s/

ANISSA A DAVIS
12/24/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, December 24, 2015 11:20 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Pharmacology Information Request

Importance: High

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999 is currently under review and we have the following clinical pharmacology information request (IR):

In your updated ADLBCHEM.xpt submitted on 12/18/2015 (Serial 0036), the Agency found the relationship between the values in Columns AVALORIG and AVALCORR for total bilirubin did not follow the correction equations in Column HRMEQAT. For example, patient's (ID 101002) original total bilirubin at visit Day 0 was 6.669. Based upon the correction equation applied to (b) (4) i.e. original value = 1.0111*corrected value (in mg/dL) + 0.3344, the corrected value = (original value-0.3344)/1.0111. The calculated corrected value is NOT 1.539 reported in AVALCORR. Provide an explanation. For total bilirubin, what are the units for the values in AVALORIG and AVALCORR?

Please provide your response officially to your application by Monday, December 28, 2015 or sooner. If you have a response to this IR now, but cannot upload the response officially via Gateway until Monday, please send me a courtesy "true and exact" copy of the response to me via email while the Gateway submission is forthcoming.

Thanks and contact me as needed.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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/s/

ANISSA A DAVIS
12/24/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, December 24, 2015 11:38 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Pharmacology Information Requests

Importance: High

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999 is currently under review and we have the following clinical pharmacology information request (IR):

1. In the document titled, “747-301 CHSA Comparative Analyses Requested Info”, submitted on 12/15/2015 to Module 5.3.5.1, it stated that “reference method analyses not available at this time for ALP” on page 1 of 3 of the document. However, reference method values were provided for total bilirubin (Page 2 of 3) and direct bilirubin (Page 3 of 3). Please provide an explanation.
2. In the dataset BASEEVAL.xpt submitted on 12/15/2015 (Serial 0036), there are blank cells in Column REFVAL for ALP. Please provide data for REFVAL and rest of the cells in Columns REFVALU, BIAS, BIASPCT, BIASMEAN, BIASMNPT, HSLOPERV, HNTRCPRV, HRSQRRV, HMEANRV. If it is not available, please state so and give an explanation.

Please submit your response, to items #1 and #2, officially to your application by 5pm (EST) Wednesday, December 30, 2015.

3. Provide a full English translation of the (b) (4) laboratory QC reports submitted on 12/18/2015 and 12/23/2015 which are in Polish.

Please submit your response, to item #3, officially to your application by January 7, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
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/s/

ANISSA A DAVIS
12/24/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, December 18, 2015 12:01 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Clinical Information Request

Hello Linda:

We are currently reviewing your application, NDA 207999 Ocaliva (obeticholic acid) and have the following clinical information request:

Regarding your November 20, 2015 submission to your application, you provided Cumulative Distribution Function (CDF) curves for the baseline time point only. In the CDF curves, the cumulative percentage of subjects needs to be plotted on the Y-axis and change score from baseline to primary time point on the X-axis. For the primary time point, we would like for you to use 6 and 12 months (i.e., one set of graphs showing change score from baseline to 6 months and another set of graphs showing change score from baseline to 12 months). Within each graph, there should be one curve for each study arm i.e. placebo, Obeticholic acid [OCA] 5 mg titration arm and OCA 10 mg arm. Additionally, provide CDF curves for patients who were on 5mg and did not titrate to the 10 mg dose in a separate graph. These analyses should be completed for 5D- Pruritus Scale, and Pruritus Visual Analog Scale (VAS).

Please submit your response officially to your application by January 4, 2016.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

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ANISSA A DAVIS
12/18/2015



NDA 207999

**REVIEW EXTENSION –
MAJOR AMENDMENT**

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) dated June 27, 2015, received June 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ocaliva (obeticholic acid) tablets, 5 mg and 10 mg.

On October 27, 2015, we received your October 27, 2015, major amendment to this application. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is May 29, 2016.

We are establishing a new timeline for communicating labeling changes and/or postmarketing requirements/commitments in accordance with “PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017.” If major deficiencies are not identified during our review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 29, 2016.

Additionally, the planned date for the Late Cycle meeting discussion has been changed to March 16, 2016. Please note that we have also changed the date of the Gastrointestinal Drugs Advisory Committee meeting that will discuss your application to April 7, 2016.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Dragos Roman, M.D.
Acting Associate Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

DRAGOS G ROMAN
12/17/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, December 16, 2015 4:53 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Pharmacology Information Request

Importance: High

Hi Linda:

In regards to NDA 207999 Ocaliva (obeticholic acid), we have the following clinical pharmacology information requests:

Please provide the following:

With the physiological PK model, simulate the following scenarios for a duration of 6 months:

A) In normal subjects and subjects with mild hepatic impairment:

- 5 mg QD dosing for 6 months
- 5 mg QD dosing for 3 months followed by 10 mg QD for 3 months

B) In subjects with moderate and severe hepatic impairment:

1. 5 mg QW for 2 weeks followed by 5 mg twice a week for the rest of the duration (5.5 months)
2. 5 mg QW for 2 weeks followed by 5 mg every 2 days for the rest of the duration (5.5 months)
3. 5 mg QW for 2 weeks followed by 5 mg twice a week for 2 weeks followed by 10 mg twice a week for the rest of the duration (5 months)
4. 5 mg QW for 2 weeks followed by 10 mg QW for the rest of the duration (5.5 months)
5. 5 mg QW for 2 weeks followed by 10 mg QW for 2 weeks followed by 10 mg twice a week for the rest of the duration (5 months)

-Provide concentration-time plots for comparison of these scenarios along with tables for comparison of steady state exposure parameters (AUC, C_{max}, C_{trough}, C_{avg} etc.) for OCA, its conjugates and total OCA at 6 months.

-Provide the analysis codes and input and output datasets in order to be able to review and recreate the above results.

Please refer to the following pharmacometric data and models submission guidelines for your submission:

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>)

We request this information to be submitted officially to your application by December 22, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
12/16/2015

Davis, Anissa

From: Davis, Anissa
Sent: Monday, December 14, 2015 1:04 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Clinical Pharmacology Information Request

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999, is currently under review and we have the following clinical pharmacology information requests (IR):

1. Provide documentations from each of three labs, (b) (4) [redacted], to demonstrate that equipment used for assaying ALP and total bilirubin were operating according to manufacture standards in regard to daily calibration, validation, etc., during the time frame when samples of ALP and total bilirubin from Study 747-301 were assayed.
2. Indicate if the same assay kits for ALP and total bilirubin were used throughout the whole study at each of the three centralized laboratories, i.e., (b) (4) [redacted]

Submit your responses by December 17, 2015. All the responses will have to be submitted officially to the NDA application.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
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/s/

ANISSA A DAVIS
12/14/2015

From: Davis, Anissa
To: [Linda Robertson \(LRobertson@interceptpharma.com\)](mailto:LRobertson@interceptpharma.com)
Subject: NDA 207999 Ocaliva (obeticholic acid): Clinical Pharmacology Information Request
Date: Thursday, December 10, 2015 11:51:00 AM

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999 is currently under review, and we have the following clinical pharmacology information requests (IR):

In your response on September 25, 2015 to FDA Request for Information about analytical methods used for ALP, direct bilirubin and total bilirubin in Study 747-301, you stated that correction equations were generated from the baseline assessment data where (b) (4)

a. Provide the original data which formed the “baseline assessment” so that the Agency may verify your correction equations for each analyte and each site ((b) (4)). Provide summary statistical data and a brief description to support your statement that (b) (4) demonstrated better precision when compared to (b) (4) . The dataset should be in .xpt format with a data definition file.

b. The Agency found that the relationship between (b) (4) in (b) (4) (b) (4) Provide an explanation.

c. (b) (4) A data definition file should also be submitted.

d. Provide an explanation as to why (b) (4) did not have corrected values in the dataset (b) (4) submitted on 9/25/2015.

e. Submit the cited book chapter in regard to the basis of biological variation: Biological Variation- From Principles to Practice – Callum G. Fraser, AACC Press (2001).

Please submit the datasets and your response within three business days (by December 15, 2015). All the responses will have to be submitted officially to the NDA.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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/s/

ANISSA A DAVIS
12/10/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, November 19, 2015 7:31 PM
To: Linda Robertson (LRobertson@interceptpharma.com); 'b.hansen@erasmusmc.nl'
Subject: NDA 207999 obeticholic acid: Statistical Information Requests

Importance: High

Hello Linda and Bettina:

We are reviewing the Global PBC Study datasets that were submitted the FDA on October 29, 2015 in support of NDA 207999 (obeticholic acid) and have the following comments and information requests:

The Global PBC study dataset (i.e., the GPBC_FDA SAS dataset) that you submitted is not complete. Firstly, there are many variable name/label discrepancies between the submitted GPBC_FDA.sas7bdat and GPBC_FDA.xpt files. The XPT file appears to have truncated the sas.sas7bdat file contained within it, and consequently this file was deemed unreliable for review. Hence all comments below reflect our review of the GPBC_FDA.sas7bdat file alone unless stated otherwise.

Based on your submitted SAS programs, there are some variables that are missing (i.e., have not been included in the dataset). Therefore, we cannot confirm your analysis results by using your SAS programs. Please provide **all** of the variables that are shown in your submitted SAS programs with a **clear description** of these variables. We also observed that some variable names are not consistent between the dataset and the SAS programs. Please re-submit your dataset and the SAS programs with consistent variable names, and check carefully whether there are any more discrepancies between the SAS dataset files themselves (i.e., between the GPBC_FDA.sas7bdat file and the GPBC_FDA.xpt file) and between the data and the SAS programs. We have identified the following issues that need your clarification, and additional requests that need to be addressed.

I. Data Fields on the Global PBC Study Case Report Form (CRF) that were not included within the GPBC_FDA SAS Dataset

- a. *Top of the CRF:*
 - Date of first visit (baseline)

- b. *'Baseline patient information' section:*
 - i. *'General patient information at baseline' subsection:*
 - Date of birth
 - Ethnicity
 - Pregnancy
 - Alcohol (including the "if yes" field)
 - Smoking
 - UDCA Dose (mg/kg)
 - UCDA Date of start therapy

 - ii. *'Information about PBC at baseline' subsection:*
 - Date of diagnosis PBC
 - Initial diagnostic liver biopsy (yes/no) (including the Date field)
 - Mayo Risk Score
 - Child-Pugh Score
 - Auto-immune-overlap syndrome

Other (than PBC) major diseases affecting 5-years life expectancy
Co-existing other liver diseases (like alcoholic liver disease and Hepatitis B or C virus)

- c. *'Follow up periode' section:*
Dates for all lab time points
End of follow up Date
- d. *'Clinical events during follow up' section:*
Death Date
Liver Transplantation Date
HCC Date
Other (yes/no)
Cirrhosis (yes/no)
Decompensation (yes/no) what: _____

II. Additional Requests

- a. It appears that the GPBC_FDA SAS dataset variables 'FU_yr' and 'FU_mnth' represent the raw "time-to-event from baseline" data in years and months, respectively. For subjects experiencing the event of interest (i.e., death or liver transplant), please confirm that these variables represent the time to death or liver transplant, in years and months respectively, for these subjects. Similarly, for subjects not experiencing the event of interest (i.e., death or liver transplant), please confirm that these variables represent the time to point of last contact, in years and months respectively, for these subjects. Additionally, and for clarification purposes, how were these variables derived without the aforementioned missing Date of first visit (baseline) and clinical event dates (i.e., dates for death, liver transplantation, and/or HCC)?
- b. Please additionally submit lab units corresponding to all lab values already submitted within the GPBC_FDA SAS dataset.
- c. In your GPBC_FDA.xpt data file, please clarify your definitions of SG2 through SG10 and INTERCEP, INTERCEO through INTERCE9 since there are some discrepancies between your dataset and Descriptive GPBC_FDA.pdf. For example, SG5 in the dataset was defined as "bilirubin>ULN but <=2xULN and ALP>" and in the .pdf it's defined as "bilirubin >ULN but <=2xULN and ALP>=1.67xULN but <3xULN". In addition, there are many mismatches in variable names between your dataset and Descriptive_GPBC_FDA.pdf (i.e., PARISI12 through PARISI60).
- d. Please provide the coding details for variables 'Region_ID' and 'AMA'; AMA values of "9" specifically need disambiguation. Also in order to match the Global PBC study data with the 747-301 trial data, we need more information about AMA and UDCA as stated in the inclusion criteria for the 747-301 trial:
- Positive AMA titer or if AMA negative or in low titer (<1:80) PBC specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, 2-oxo-glutaric acid dehydrogenase complex)
 - Taking UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 0, or unable to tolerate UDCA (no UDCA for ≥3 months) prior to Day 0.
- e. Please additionally submit an annotated Case Report Form (aCRF) that presents the dataset variable name (as included within the GPBC_FDA SAS dataset) next to each CRF field.
- f. Regarding the *'Clinical events during follow up'* section of the CRF, please provide dates for Other, Cirrhosis, and Decompensation?

- g. Please provide the SAS analysis program that can be used with the GPBC_FDA SAS dataset to reproduce the results presented within the 2014 Lammers journal article published in 'Gastroenterology' if available.
- h. There were variables contained within the two SAS analysis programs of the Global PBC study group data sent by Intercept on October 29, 2015 (eCTD sequence 0033) that are not included within the GPBC_FDA SAS dataset. They are as follows:
 - i. yi-roc.sas: 'alp12_20' and 'bili12_10'
 - ii. cstat-phreg.sas: 'bili12_10' and 'ln_alp12'

Please explain what these variables are and how they were derived.

Please submit your response officially to the DMF by December 15th 2015 or notify us about the timeline by which you can respond to these requests as soon as possible. If there are items you cannot provide, please state which ones.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

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Senior Regulatory Project Manager

Food and Drug Administration

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ANISSA A DAVIS
11/19/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, November 03, 2015 1:08 PM
To: 'Linda Robertson'
Cc: Janine Segich
Subject: RE: NDA 207999 (obeticholic acid): Clinical Information Request

Hello Linda:

Here is our response to your question below- **“We need to understand the effect of OCA on the safety and efficacy in patients with fibrosis and cirrhosis. Please provide both a list of the patients with their stage of fibrosis and also an analysis of the response to treatment and safety by fibrosis stage”.**

The new due date for you to respond to the information request in question is November 20, 2015.

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
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From: Linda Robertson [mailto:lrobertson@interceptpharma.com]
Sent: Monday, November 02, 2015 4:57 PM
To: Davis, Anissa
Cc: Janine Segich
Subject: RE: NDA 207999 (obeticholic acid): Clinical Information Request

Hi Anissa,

As discussed, we are in the process of preparing a response to the clinical information request below will provide the information requested. However, to facilitate your review, and ensure we provide a useful response, would you and your team please provide context to your request as follows:

Is the question underlying the request for the number of patients with biopsy samples regarding 1) the effect of OCA on biochemical response in patients with fibrosis and cirrhosis or 2) the effect of OCA on fibrosis in PBC patients.

Thanks much for your assistance,

Best regards,

Linda

Linda Robertson, Ph.D.
VP, Regulatory Affairs and Quality Assurance
Intercept Pharmaceuticals
4760 Eastgate Mall
San Diego, CA 92121

Office 858-652-6805

Cell (b) (6)

From: Davis, Anissa [<mailto:Anissa.Davis@fda.hhs.gov>]
Sent: Wednesday, October 28, 2015 10:55 AM
To: Linda Robertson <lrobertson@interceptpharma.com>
Subject: NDA 207999 (obeticholic acid): Clinical Information Request

Hi Linda:

We are reviewing your application, NDA 207999 (obeticholic acid) and have the following clinical information requests:

1. We note that the majority of patients had liver biopsy at some time point for diagnosis, as seen in the 747-301 clinical study report. Clarify, how many patients had stage 1, 2, 3 and 4 fibrosis and cirrhosis, and the timing of obtaining these biopsy samples.
2. For Study 747-301, please provide cumulative distribution function (CDF) curves, one curve for each study arm (placebo, Obeticholic acid [OCA] 5 mg titration arm and OCA 10 mg arm) for the following PRO assessments: PBC-40 Itching and Fatigue subscales, PBC-40 Question 14, 5D- Pruritus Scale, and Pruritus Visual Analog Scale (VAS).
3. Please also provide a copy of the Pruritus VAS.

Please submit your request officially to your application by November 11, 2015.

Thank you!



Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration

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/s/

ANISSA A DAVIS
11/03/2015



NDA 207999

MID-CYCLE COMMUNICATION

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for INT-747 (obeticholic acid) tablets, 5 mg and 10 mg..

We also refer to the teleconference between representatives of your firm and the FDA on October 27, 2015. 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 me at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
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 27, 2015, 9:30 AM – 10:30 AM (EST)

Application Number: NDA 207999

Product Name: obeticholic acid

Indication: **treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA**

Applicant Name: Intercept Pharmaceuticals, Inc.

Meeting Chair: Dr. Lara Dimick-Santos

Meeting Recorder: CDR Anissa Davis-Williams

FDA ATTENDEES

Donna Griebel, M.D., Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, DGIEP

Dragos Roman, M.D., Acting Associate Director, DGIEP

Amy Egan, M.D., Associate Director, Office of Drug Evaluation III

Stephanie Omokaro, Acting Cross Discipline Team Lead, DGIEP

Lara Dimick, M.D., Medical Reviewer, DGIEP

Ruby Mehta, M.D., Medical Officer, DGIEP

Sue-Chih Lee, PhD, Team Leader, Division of Clinical Pharmacology III (DCPIII)

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, DCPIII

Shen Li, Ph.D., Clinical Pharmacology Reviewer, DCPIII

Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)

Min Min, Ph.D., Statistical Reviewer, DBIII

Benjamin P. Vali, M.S., Statistical Reviewer, DBIII

Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP

Tracy Behrsing, Ph.D., Pharmacology Reviewer, DGIEP

Benjamin Stevens, Ph. D., M.P.H., Chemistry Drug Substance Reviewer, New Drug API Branch II

Nitin Mehrotra, Ph.D., Pharmacometrics Team Leader, Division of Pharmacometrics, Office of Clinical Pharmacology (OCP)

Dhanajay Marathe, Ph.D., Pharmacometrics Reviewer, OCP

Hitesh Shroff, Ph.D., CMC Reviewer, Division of Biopharmaceutics, Office of Pharmaceutical Quality (OPQ)

Christos Mastroyannis, M.D., Medical Officer, Division of Pediatric and Maternal Health

Kimberley Swank, Pharm.D., Division of Pharmacovigilance I

Kira Leishear, Ph.D., M.S., Epidemiologist Reviewer, Division of Epidemiology 1 (DEPI-1)
Sukhminder Sandhu, Ph.D., M.P.H., M.S., Epidemiology Team Leader, DEPI-1
Maria Walsh, R.N., M.S., Associate Director for Regulatory Affairs, Office of Drug Evaluation III
LCDR Richard Ishihara, Regulatory Scientist, Office of Drug Evaluation III
Joette Meyer, Pharm.D., Associate Director for Labeling, DGIEP
Selena Daniels, Pharm.D., M.S., Clinical Outcome Assessment Staff, Endpoints Reviewer
LCDR Cheronda Cherry-France, RN, B.S.N., M.H.A., Regulatory Project Manager, DGIEP
CDR Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M., Senior Regulatory Project Manager, DGIEP
Pegghah Khorrami, Independent Assessor, Eastern Research Group

APPLICANT ATTENDEES

Linda Robertson, Ph.D., VP, Regulatory Affairs and Quality Assurance
David Shapiro, M.D., Chief Medical Officer
Leigh McConnell, Ph.D., VP, Clinical Development
Jeffrey Edwards, Ph.D., Sr. Dir, Clinical Pharmacology
Mark Young, Ph.D., VP, Non-Clinical Development
Maeve McDonnell, Ph.D., Director, Regulatory
Melissa Rewolinski, Ph.D., VP, Product Development
(b) (4) M.D., Regulatory Consultant
Roya Hooshmand-Rad, M.D., Exec. Dir., Clinical Safety
Tonya Marmon, Ph.D., Senior Director, Biostats and Data Management
Kyle Fraher, Sr. Dir, Project Management

1.0 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.

2.0 SIGNIFICANT ISSUES

Clinical/Statistics:

We are concerned that the majority of patients (92%) in the clinical trial 747-301 had normal bilirubin levels at trial entry and therefore the effects on the composite endpoint of reduction in bilirubin and alkaline phosphatase (ALP) are not likely to predict benefits

in these patients. For these patients a reduction in ALP alone will be the only measurable efficacy assessment. You have not provided sufficient evidence that a reduction in ALP in isolation has been shown to be reasonably likely to predict clinical benefit in patients with primary biliary cirrhosis (PBC); therefore, a reanalysis of the PBC study group data focusing on a population that matches the baseline characteristics of patients enrolled in clinical trial 747-301 will be necessary to support your claim that a reduction in ALP to less than 1.67 X ULN and greater than or equal to 15% from baseline is reasonably likely to predict clinical benefit.

We are concerned that the population enrolled in the clinical trial 747-301 is not representative of the broader population of patients with PBC. The trial population represents only patients with early stage disease and therefore the results of the trial will represent efficacy and safety only in this population. The safety, efficacy and optimal dosing of obeticholic acid (OCA) in patients with moderately advanced or advanced stage of disease cannot be established. This may be reflected in the labeled indication.

We are concerned that there are very little data to support that monotherapy is effective in patients who are intolerant to ursodeoxycholic acid (UDCA).

Meeting Discussion on October 27, 2015:

Intercept noted that in patients with normal bilirubin that a decrease in bilirubin level was predictive of clinical benefit in the PBC study group data and that in the clinical trial, placebo patients had an increase in bilirubin and treated patients' bilirubin remained stable.

The FDA stated that more safety and efficacy information on patients with moderately advanced, advanced stage disease, monotherapy treatment, and treatment in patients with cirrhosis may be necessary.

Nonclinical:

We do not have any concerns at this time.

Clinical Pharmacology:

In the absence of any dose adjustment for subjects with moderate to severe hepatic impairment, there could be safety/tolerability issues due to very high drug/conjugate exposures. We acknowledge your detailed response to our information request and we are exploring alternative dosing recommendations.

We have the following additional concerns:

- a) in lieu of formal cross-validation, you used existing lab harmonization program to establish correction factors across labs assaying ALP and bilirubin (direct and total);
- b) nine patients on placebo in the pivotal phase 3 study 301 had measurable trough concentrations of OCA and its conjugates and an adverse event of

pruritus requiring treatment within two months of initiating therapy was seen in one of these patients. Elevation of total and direct bilirubin was seen in two additional placebo patients, and a decline was seen in high density lipoproteins-cholesterol (HDL-c) levels in at least two other patients.

We acknowledge your responses to the Agency's information request in regard to these two issues. Your responses are under review.

Chemistry/ Biopharmaceutics:

We do not have any concerns at this time.

3.0 INFORMATION REQUEST

Here are the outstanding IRs for your application at the time of this meeting:

- Chemistry IR dated 10/14/15, due 10/28/15
- Clinical Pharmacology IR dated 10/20/15, due 10/28/15

4.0 MAJOR SAFETY CONCERNS/RISK MANAGEMENT

We are still in the process of reviewing the safety data from this application. We note that there were fractures in 6 patients in the treatment arm and 3 patients in the placebo arm. In addition, HDL-c was noted to be lower in the patients treated with OCA than in placebo patients.

5.0 ADVISORY COMMITTEE MEETING

The advisory committee has been scheduled for January 13, 2016; however, if a major amendment is issued, this date will change. We will notify you, should this change occur.

6.0 LATE-CYCLE MEETING /OTHER PROJECTED MILESTONES

The proposed date for the late cycle meeting (LCM) is January 5, 2016. In addition, please note the following projected milestone dates. However, these dates may change. You will be notified accordingly:

Labeling, PMR/PMC to Applicant:	November 30, 2015
LCM Background Package:	December 20, 2015
PDUFA Action:	February 29, 2016

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/s/

ANISSA A DAVIS
10/28/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, October 28, 2015 1:55 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Request

Hi Linda:

We are reviewing your application, NDA 207999 (obeticholic acid) and have the following clinical information requests:

1. We note that the majority of patients had liver biopsy at some time point for diagnosis, as seen in the 747-301 clinical study report. Clarify, how many patients had stage 1, 2, 3 and 4 fibrosis and cirrhosis, and the timing of obtaining these biopsy samples.
2. For Study 747-301, please provide cumulative distribution function (CDF) curves, one curve for each study arm (placebo, Obeticholic acid [OCA] 5 mg titration arm and OCA 10 mg arm) for the following PRO assessments: PBC-40 Itching and Fatigue subscales, PBC-40 Question 14, 5D- Pruritus Scale, and Pruritus Visual Analog Scale (VAS).
3. Please also provide a copy of the Pruritus VAS.

Please submit your request officially to your application by November 11, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
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(301) 796-9904 (fax)
[**Anissa.Davis@fda.hhs.gov**](mailto:Anissa.Davis@fda.hhs.gov)

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/s/

ANISSA A DAVIS
10/28/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 207999

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Intercept Pharmaceuticals, Inc.
4760 Eastgate Mall
San Diego, CA 92121

ATTENTION: Linda Robertson, PhD
VP, Regulatory Affairs and Quality Assurance

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) dated June 27, 2015, received June 29, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Obeticholic Acid Tablets, 5 mg and 10 mg.

We also refer to your correspondence, dated and received July 31, 2015, requesting review of your proposed proprietary name, Ocaliva.

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

If any of the proposed product characteristics as stated in your July 31, 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 Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-5295. For any other information regarding this application, contact Anissa Davis, Regulatory Project Manager in the Office of New Drugs, at 301-796-5016.

Sincerely,

{See appended electronic signature page}

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

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/s/

TODD D BRIDGES
10/27/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, October 20, 2015 3:05 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCA: Clinical Pharmacology Information Request

Hello Linda:

We are reviewing your application, NDA 207999 (obeticholic acid) and have the following clinical pharmacology information requests:

- In Clinical Study 747-205, the observed Cmax values at steady state for glyco-OCA and tauro-OCA in patients with primary biliary cirrhosis were likely underestimated due to insufficient sampling scheme. The PK blood samples were collected from 0 to 6 hours postdose at Week 8, whereas the median tmax has been reported at 10 hours postdose at steady state for both glyco-OCA and tauro-OCA per Study 747-105 (healthy subjects). These Cmax values at steady state for glyco-OCA and tauro-OCA in patients with primary biliary cirrhosis are needed for the drug-drug interaction assessment. We request you estimate steady-state Cmax in patients with PBC.
- OCA and its conjugates were found to be P-gp substrates in Study Report (b) (4) 13694, but the findings were negative in another Study Report (b) (4) 14661. State whether OCA and its conjugates are P-gp substrates or not, and provide supporting data and rationale.
- Cytotoxicity was found at OCA concentrations $\geq 1 \mu\text{M}$ in Study Report 8261773 (Evaluation of Cytochrome P450 Induction Following Exposure of DSP-1747 to Primary Cultures of Human Hepatocytes). But in Study Report ICPT-1002-3 (In vitro evaluation of OCA, tauro-OCA, and glyco-OCA cytotoxicity and induction potential using B-CLEAR and transporter certified hepatocytes), cytotoxicity was not observed at OCA concentrations up to 100 μM . Clarify why there is a difference in cytotoxicity between the 2 studies and whether cytotoxicity is expected at therapeutic concentration.

Please submit your responses officially to your application by October 28, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
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/s/

ANISSA A DAVIS
10/20/2015



NDA 207999

INFORMATION REQUEST

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Obeticholic Acid Tablets, 5 mg and 10 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by October 28, 2015 in order to continue our evaluation of your NDA.

1. Any measured impurity values that are less than 1.0% should be reported out to two decimal places.
2. (b) (4) should be listed as a raw material and appropriate specifications (b) (4)
[Redacted]
3. [Redacted] (b) (4)

[Redacted] (b) (4)

F.

[Redacted]

(b) (4)

[Redacted]

(b) (4)

14. Provide any available updated drug substance stability data for the three primary and three registration batches. Submit this information as either an Excel or SAS data set using the format below:

Time	Batch	Test Parameter	Result	Unit	Acceptance Criteria

15.

[Redacted]

(b) (4)

If you have any questions, please contact Heather Strandberg, Senior Regulatory Health Project Manager, at (240) 402-9096.

Sincerely,

Heather S.
Strandberg -S

Digitally signed by Heather S. Strandberg -
S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000581961,
cn=Heather S. Strandberg -S
Date: 2015.10.14 13:03:44 -04'00'

Heather Strandberg, PharmD
Senior Regulatory Health Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, October 14, 2015 4:07 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Information Request

Hello Linda:

We are continuing our review of NDA 207999 (obeticholic acid) and have the following clinical information requests (IR):

In reference to the IR sent on 10/8/15, please provide analysis of the clinical outcomes as listed below:

- 1. In addition to deaths, liver related death and liver transplantation please provide the following:**
 - a. Liver related event: liver failure, or hepatocellular carcinoma, or death occurring within 2 months of an episode of variceal bleeding, spontaneous bacterial peritonitis, hepatorenal syndrome, or hepatic encephalopathy as an outcome**
 - b. Decompensation events: like ascites, variceal bleeding and encephalopathy**

Please submit your response officially to your application by October 23, 2015!

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
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Food and Drug Administration
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ANISSA A DAVIS
10/14/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, October 09, 2015 2:15 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (OCA): Clinical Pharmacology Information Request

Hello Linda:

Regarding NDA 207999 that was submitted on June 27, 2015 is currently under review. We have the following clinical pharmacology information requests:

- 1) We have following requests for information on Study 747-301:
 - a) In dataset ADPC.xpt submitted under Study 747-301 on June 29, 2015, we noted that nine patients in the placebo arm had detectable trough concentrations of OCA and/or its conjugates. Provide an explanation. In addition, describe assay specificity (Validation Method RPT02968) when UDCA is included in samples.
 - b) In the same dataset ADPC.xpt mentioned in a) above, flag patients in "5 mg titration to 10 mg" arm who remained on 5 mg after 6 month.
 - c) Based upon dataset ERDAT.xpt submitted on 8/19/2015, it appeared that trough concentrations of OCA and its conjugates were not determined in Month 12 for patients remained on 5 mg for a year. Clarify if this is true.

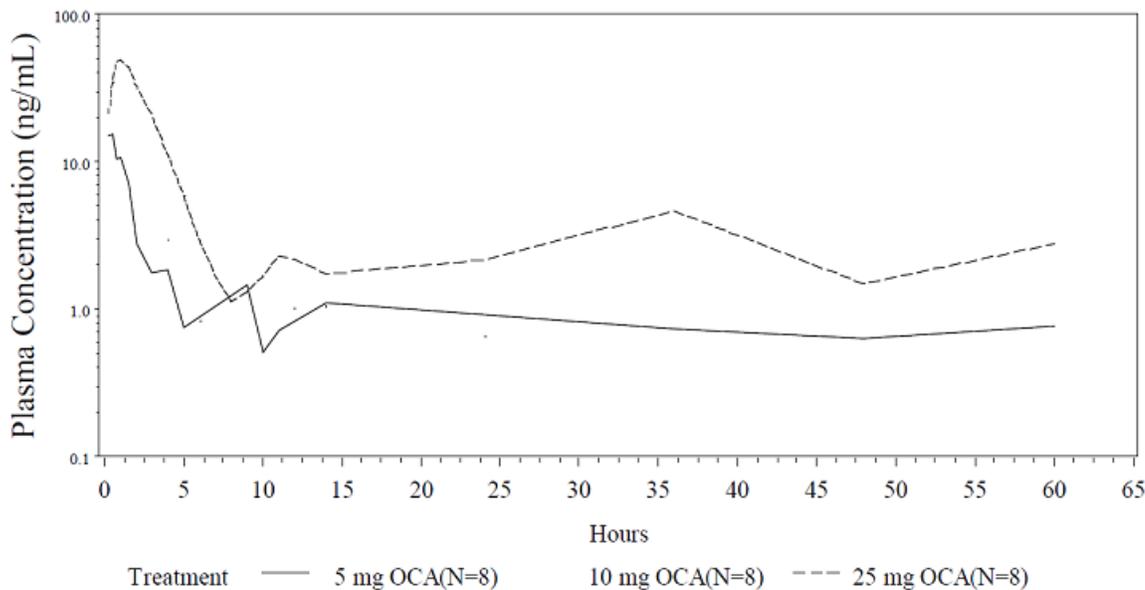
Please submit your response to the above officially to your application by October 14, 2015.

- 2) Update concentration-time profiles in Section 14.2.2 Plasma Concentration Figures of Study Report 747-105 where profiles of 10 mg did not show well. An example is shown below:

Intercept Pharmaceuticals, Inc.
Protocol 747-105

Page 1 of 1

Figure 14.2.2.3
Mean Single Dose OCA Plasma Concentration (ng/mL) Time Profiles by Dose on a Semi-Logarithmic Scale



Note: The lower limit of quantitation for plasma is 0.5 ng/mL.
values for the 10 mg and 25 mg dose are time shifted by 10 min and 20 min, respectively, to improve readability.
Program: FCONCSINGLE3.SAS (Run DateTime: 01SEP14 12:34)

Data Source: ADPC

Please submit your response officially to the above to your application by October 16, 2015.

All the responses will have to be submitted officially to the NDA as well.

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
10/09/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, October 08, 2015 3:08 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Cc: b.hansen@erasmusmc.nl
Subject: NDA 207999 obeticholic acid: Clinical Information Request

Importance: High

Hello Linda:

We are continuing our review of NDA 207999 (obeticholic acid) and have the following clinical information requests:

1. Please provide rationale and data analyses to support your selection of the cut-off for the primary surrogate endpoint, i.e., $1.67 \times \text{ULN}$ for alkaline phosphatase, from the data of the PBC study group. You should analyze data in the subpopulations noted below using several well accepted statistical methods to validate classification boundaries, such as ROC analysis, subset testing, Youden's Index and C statistic.
 - a. All Global PBC study patients
 - b. Global PBC study patients with, at enrollment, bilirubin $\leq \text{ULN}$ and ALP $\geq 1.67 \times \text{ULN}$ but $< 3 \times \text{ULN}$
 - c. Global PBC study patients with, at enrollment, bilirubin $\leq \text{ULN}$ and ALP $\geq 3 \times \text{ULN}$ but $< 5 \times \text{ULN}$
 - d. Global PBC study patients with, at enrollment, bilirubin $\leq \text{ULN}$ and ALP $\geq 5 \times \text{ULN}$
 - e. Global PBC study patients with, at enrollment, bilirubin $> \text{ULN}$ but $\leq 2 \times \text{ULN}$ and ALP $\geq 1.67 \times \text{ULN}$ but $< 3 \times \text{ULN}$
 - f. Global PBC study patients with, at enrollment, bilirubin $> \text{ULN}$ but $\leq 2 \times \text{ULN}$ and ALP $\geq 3 \times \text{ULN}$ but $< 5 \times \text{ULN}$
 - g. Global PBC study patients with, at enrollment, bilirubin $> \text{ULN}$ but $\leq 2 \times \text{ULN}$ and ALP $\geq 5 \times \text{ULN}$
 - h. Global PBC study patients with, at enrollment, ALP $> 3 \times \text{ULN}$ and/or AST $> 2 \times \text{ULN}$ and/or bilirubin $> \text{ULN}$
 - i. Global PBC study patients with, at enrollment, ALP $> 3 \times \text{ULN}$ and AST $> 2 \times \text{ULN}$ and bilirubin $> \text{ULN}$
 - j. Global PBC study patients with, at enrollment, ALP $\leq 3 \times \text{ULN}$ and/or AST $\leq 2 \times \text{ULN}$ and bilirubin $\leq \text{ULN}$

Please submit your responses officially to your application by October 23, 2015!

Thank you!



Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22 Room: 5378

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/s/

ANISSA A DAVIS
10/08/2015

Davis, Anissa

From: Davis, Anissa
Sent: Monday, October 05, 2015 11:51 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 OCA: CMC Labeling Information Request

Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are reviewing your container labels and have the following information request:

- Delete the statement [REDACTED] (b) (4)
- Display the storage conditions as shown below:
Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature]

Please submit your response (revised labels) officially to your application by October 19, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
10/05/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 21, 2015

Application Number: NDA 207999

Product Name: obeticholic acid

Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Subject: Clinical Pharmacology Information Request

FDA Participants :

Ruby Mehta, M.D., Medical Reviewer, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Lara Dimick, M.D., Medical Reviewer, DGIEP

Sue-Chih Lee, Ph.D., Team Leader, Division of Clinical Pharmacology III (DCPIII)

Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, DCPIII

Intercept Participants :

Linda Robertson, Ph.D. VP, Regulatory Affairs and Quality Assurance

David Shapiro, M.D., Chief Medical Officer

Shawn Schaffer, Ph.D., Executive Director, Quality Assurance

Jeffrey Edwards, Ph.D., Senior Director, Clinical and preclinical pharmacology and DMPK

Tonya Marmon, Ph.D., Senior Director, Biostatistics and Data Management

1.0 BACKGROUND:

On June 27, 2015, Intercept Pharmaceuticals, Inc (Intercept) submitted a New Drug Application (NDA), NDA 207999, for the treatment of treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UCDA. On September 1, 2015, the FDA sent Intercept a Clinical Pharmacology Information Request (IR). On September 4, 2015, Intercept responded. On September 10, 2015, based on the review of the responses, the FDA sent Intercept another Clinical Pharmacology IR. However, the FDA requested to speak to Intercept to further discuss the IR to ensure clarity. The meeting was scheduled to be held September 21, 2015.

Call began at 1:05 p.m.

2.0 DISCUSSION:

The FDA clarified the information stated in the IR. Intercept understood what is needed in the response to the IR and will submit their response by September 25, 2015.

Call ended at 1:22 p.m.

3.0 ACTION ITEMS:

Intercept to submit requested data to the FDA by September 25, 2015.

APPEARS THIS WAY ON ORIGINAL

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/s/

ANISSA A DAVIS
09/28/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207999

INFORMATION REQUEST

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Obeticholic Acid Tablets, 5 mg and 10 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by October 16, 2015 in order to continue our evaluation of your NDA.

- In your environmental analysis, you estimate that the expected introduction concentration (EIC) of obeticholic acid will be below 1 part per billion (ppb), and thus that a categorical exclusion from developing an environmental assessment (EA) is appropriate under 21 CFR 25.31(b). Your nonclinical overview, however, notes that the rat embryo-fetal development study reported evidence of developmental toxicity. Also, recent literature indicates a possible role of nuclear receptors such as FXR in endocrine-related environmental toxicity (e.g., OECD 2012, Detailed Review Paper on the State of the Science on Novel In Vitro and In Vivo Screening and Testing Methods and Endpoints for Evaluating Endocrine Disruptors). Since drugs with endocrine-related activity have been shown to have potential developmental or reproductive effects in aquatic organisms at environmentally relevant concentrations, we request additional information to determine whether extraordinary circumstances exist (see FDA's recent draft guidance on this subject at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf>). Furthermore, your claim for a categorical exclusion did not provide a statement of no extraordinary circumstances, as required per 21 CFR 25.15(a). Therefore, please provide supporting data for your categorical exclusion request, including a statement about extraordinary circumstances, by October 16, 2015. If the statement of no extraordinary circumstances cannot be supported, an EA will be required.

If you have any questions, please contact Heather Strandberg, Senior Regulatory Health Project Manager, at (240) 402-9096.

Sincerely,

Heather S.
Strandberg -S

Digitally signed by Heather S.
Strandberg -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=2000581961
, cn=Heather S. Strandberg -S
Date: 2015.09.24 09:02:35 -04'00'

Heather Strandberg, PharmD
Senior Regulatory Health Project Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, September 10, 2015 8:08 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Information Request

Hello Linda:

NDA 207,999 as submitted on June 27, 2015 is currently under review. Specifically, we have reviewed your 9/4/2015 submission, which was in response to a previous Information Request, and have the following further requests:

1. For each analyte (i.e, ALP, total bilirubin and direct bilirubin), provide a summary table comparing the assay methods used in selected laboratories ((b) (4)). You may consider presenting in a format as shown below.

Laboratory	(b) (4)	(b) (4)	(b) (4)
A. Methodology (a brief description, including system, internal standard, etc. used for assay)			
B. Distinct features of methodology (i.e., how the method differs from the other two)			
C. Performance as claimed in the commercial kit: Accuracy, Precision And so on ...			
D. Sponsor's assay validation results: Accuracy precision and so on ...			

2. Regarding Study 747-301, provide individual listing of laboratory values of ALP, total bilirubin, and direct bilirubin from all patients measured at various time points (Days or Weeks) including the baseline values. Both the original values and the revised values after applying a correction factor should be

presented. If a value was never revised, indicate NA in the corresponding cells for corrected value and correction factor. You may consider presenting the dataset in the following presentation. Provide the listing in .xpt format.

Subject ID	Treatment	Analyte	Time of the sample drawn (Week)	Original value	Corrected value	Correction factor	Lab

3. Provide your rationale for selecting (b) (4) as the reference lab.
4. Regarding the correction equations, indicate for each analyte per lab what data were used to generate the correction equation and how the equations were developed.

Because of the complexity of the matter, the Agency will schedule a teleconference with you to discuss the details of these requests before you issue a formal Response preferably for the week of September 20, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
 CDR, United States Public Health Service (USPHS)
 Senior Regulatory Project Manager
 Food and Drug Administration
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/s/

ANISSA A DAVIS
09/21/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, September 18, 2015 2:01 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 obeticholic acid: Mid-Cycle Communication Meeting

Hello Linda:

We had to make some adjustments to the Mid-Cycle Internal meeting date. This has caused a delay for the Mid-Cycle Communication Meeting with your team. Below is the new meeting time to discuss the application with Intercept.

Application: NDA 207999

Date: October 27, 2015

Time: 9:30 a.m. – 10:30 a.m. (EST)

Teleconference Information:

To start this meeting

-
1. Go to [REDACTED] (b) (4)
 2. If you are not logged in, log in to your account.

Teleconference information

1. Provide your number when you join the meeting to receive a call back. Alternatively, you can call one of the following numbers:

Local: [REDACTED] (b) (4)
toll free: [REDACTED] (b) (4)

2. Follow the instructions that you hear on the phone.

Cisco Unified MeetingPlace meeting ID: [REDACTED] (b) (4)

Thanks and reach out to me if you have any questions or concerns. Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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ANISSA A DAVIS
09/21/2015

MEMORANDUM OF TELECONFERENCE

Teleconference Date: September 11, 2015

Application Number: NDA 207999

Product Name: obeticholic acid

Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Subject: Obtaining the PBC Study Group Data

FDA Participants :

Amy Egan, M.D., Assistant Director, Office of Drug Evaluation III

Dragos Roman, M.D., Associate Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)

Lara Dimick, M.D., Medical Reviewer, DGIEP

Min Min, Ph.D., Statistical Reviewer, Division of Biometrics III (DBIII)

Benjamin P. Vali, M.S., Statistical Reviewer, DBIII

Nitin Mehrotra, Ph.D., Pharmacometrics Team Leader, Division of Pharmacometrics, Office of Clinical Pharmacology (OCP)

Dhanajay Marathe, Ph.D., Pharmacometrics Reviewer (OCP)

Jayne Peterson, R.Ph., J.D., Director Division of Advisory Committee and Consultant Management (DACCM)

LT Cindy Hong, Pharm.D., Staff member, DACCM

Yvette Waples

Intercept Participants :

Linda Robertson Ph.D., VP, Regulatory Affairs and Quality Assurance

Leigh McConnell, Ph.D., VP, Clinical Development

Tonya Marmon, Ph.D., Sr. Director, Biostatistics and Data Management

(b) (4), M.D., Regulatory Consultant

Bettina Hansen, Ph.D., Co-Principal Investigator and Biostatistician, Global PBC Study Group

1.0 BACKGROUND:

On June 27, 2015, Intercept Pharmaceuticals, Inc (Intercept) submitted a New Drug Application (NDA), NDA 207999, for the treatment of treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UCDA. While reviewing the application, the FDA has requested for Intercept to provide data from the PBC Study Group in order to continue reviewing the application. A meeting was scheduled for September 11, 2015 to discuss how Intercept will be able to obtain the data in order for FDA to continue review of the application.

2.0 DISCUSSION:

Discussion began at 12:05 p.m. (EST). After introductions of both FDA and Intercept participants, FDA stated that the PBC study group paper submitted to the NDA did not present similar population that was enrolled in the trial for the application. Intercept first commented about the difficulties of obtaining the data from the PBC Study Group in that the consents for obtaining data prohibited that data being released to third parties. Intercept then offered several solutions to obtain the information needed.

FDA stated the need for the analysis and database information that is being requested should be from a group that matched the baseline characteristics of the patient population in the phase 3 trial. FDA requested at least 200 of these cases should be submitted for review.

The PBC Group representative, Bettina Hansen, listed a plan for Intercept as it relates to sending them the data, and Intercept stated that they will try to have the requested data to us before FDA's Mid-Cycle meeting scheduled for the end of September.

Initially, Dr Hansen will send output results from a similar group that matches the enrollment criteria for the patients in the phase 3 trial. She will then attempt to obtain consent from some of the major centers ethics review committees to send patient level data from the PBC study group.

FDA noted that the review of this data and the timing of its submission could require the need for an extension of the review clock.

Called ended at 12:50 p.m. (EST).

3.0 ACTION ITEMS:

Intercept to submit requested data to the FDA by the end of September.

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/s/

ANISSA A DAVIS
09/21/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, September 16, 2015 3:37 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Nonclinical Information Request

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a review of your application and have the following nonclinical information request:

- Your Toxicology Written Summary (2.6.6; p. 43) states that small amounts of glyco-OCA were formed in the rat general toxicity studies and were qualified at a maximum level of 170 ng·h/mL and 325 ng·h/mL in males and females, respectively (0.10- and 0.19-fold, respectively, human glycine exposure of 1755 ng·h/mL at a 10 mg dose). Please identify the nonclinical study report(s) referred to in this statement.

Please submit your response officially to your application by September 23, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
09/16/2015



**METHODS VALIDATION
MATERIALS RECEIVED**

NDA 207999

September 15, 2015

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92121

Dear Linda Robertson, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Obeticholic Acid Tablets, 5 mg and 10 mg and to our August 12, 2015, letter requesting sample materials for methods validation testing.

We acknowledge receipt on September 11, 2015, 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 (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, 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/

LAURA POGUE
09/15/2015

Davis, Anissa

From: Davis, Anissa
Sent: Monday, September 14, 2015 2:33 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Requests

Importance: High

Hello Linda:

We are reviewing your application, NDA 207999 (obeticholic acid) and have the following clinical information requests:

Global PBC Study Group data Information Requests:

1. Please reconduct the analysis (as was presented in Figure 10 on page 46 of the Global PBC study report) of Liver Transplant or Death outcome data from the Global PBC Study Group for the following groups of Global PBC patients. Each of these following Global PBC patient analysis groups should match the baseline characteristics of all corresponding patients enrolled in study 747-301. The baseline characteristics used for this matching criterion should be as follows: age, gender, duration of diagnosis and concomitant ursodeoxycholic acid (UDCA) use. For each analysis group, please additionally present the percentage of patients who reached a clinical outcome of Liver Transplant or Death.
 - a. All Global PBC study patients
 - b. Global PBC study patients with, at enrollment, bilirubin \leq ULN and ALP $\geq 1.67 \times$ ULN but $< 3 \times$ ULN
 - c. Global PBC study patients with, at enrollment, bilirubin \leq ULN and ALP $\geq 3 \times$ ULN but $< 5 \times$ ULN
 - d. Global PBC study patients with, at enrollment, bilirubin \leq ULN and ALP $\geq 5 \times$ ULN
 - e. Global PBC study patients with, at enrollment, bilirubin $>$ ULN but $\leq 2 \times$ ULN and ALP $\geq 1.67 \times$ ULN but $< 3 \times$ ULN
 - f. Global PBC study patients with, at enrollment, bilirubin $>$ ULN but $\leq 2 \times$ ULN and ALP $\geq 3 \times$ ULN but $< 5 \times$ ULN
 - g. Global PBC study patients with, at enrollment, bilirubin $>$ ULN but $\leq 2 \times$ ULN and ALP $\geq 5 \times$ ULN
 - h. Global PBC study patients with, at enrollment, ALP $> 3 \times$ ULN and/or AST $> 2 \times$ ULN and/or bilirubin $>$ ULN
 - i. Global PBC study patients with, at enrollment, ALP $\leq 3 \times$ ULN and AST $\leq 2 \times$ ULN and bilirubin \leq ULN
2. Repeat all analyses from information request #1 above using the Global PBC study subgroup of patients who had concomitant UDCA usage.
3. Repeat all analyses from information request #1 above using the Global PBC study subgroup of patients who did not have concomitant UDCA usage (i.e., were intolerant to UDCA).

4. Please submit all patient-level datasets from the Global PBC Study and obtain the appropriate consents to obtain this data.

Please submit your responses officially to your application by September 25, 2015.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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ANISSA A DAVIS
09/14/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, September 11, 2015 4:24 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 (obeticholic acid): Clinical Information Request

Hello Linda:

We are reviewing your application, NDA 207999 (obeticholic acid) and have the following clinical information requests:

Please submit the following or identify where it is located in the NDA:

1. Analyze the data for the OCA titration arm separately for patients who remained at OCA 5 mg arm and for patients who were titrated to OCA 10 mg arm. Present these data in graphical depiction and/or figures and include on the graphs/figures the outcomes for patients started on OCA 10 mg at baseline for the following:
 - a. Primary endpoint/key secondary endpoint and Other Secondary endpoints
 - b. Percentage of subjects with a decrease in ALP of $\geq 20\%$, and $\geq 40\%$ from Baseline
 - c. Percentage of subjects achieving the biochemical treatment response criteria as defined by different responder criteria:
 - a. ALP $\leq 3 \times$ ULN and AST $\leq 2 \times$ ULN and bilirubin \leq ULN ((Corpechot 2008); Paris I)
 - b. ALP $\leq 1.5 \times$ ULN and AST $\leq 1.5 \times$ ULN and bilirubin \leq ULN ((Corpechot 2011), Paris II)
 - c. ALP $\leq 1.67 \times$ ULN and bilirubin \leq ULN ((Momah 2012), Mayo II)
 - d. ALP $\leq 1.76 \times$ ULN ((Kumagi 2010b), Toronto II)
2. Of the 5 patients in the titration arm who had Total bilirubin $>$ ULN at baseline how many achieved normal bilirubin (values \leq ULN) and/or normal albumin (values \geq lower limit of normal [LLN]); (Kuiper 2009) [Rotterdam criteria]).
4. In the titration group, of the 36 patients who remained on OCA 5 mg after 6 months, you have provided reasons for 21 (reached primary endpoint) and 8 (pruritus) however, have not provided a reason for 7 patients who remained on 5 mg OCA at 6 months. Provide the reason why these 7 patients were not titrated to OCA 10 mg at 6 months.
5. The key pertinent inclusion criteria for enrollment of patients in the clinical trial 747-301 included patients diagnosed with Primary biliary cirrhosis (PBC) as demonstrated by ≥ 2 of the 3 diagnostic factors. These included
 - a. elevated alkaline phosphatase for at least 6 months
 - b. Positive anti-mitochondrial antibody/specific antibodies for PBC
 - c. Liver biopsy consistent with PBC.

6. Clarify how many patients in the clinical trial enrolled in the treatment groups were diagnosed with Primary Biliary Cirrhosis (PBC) using
 1. All three criteria
 2. Two of the three criteria.
 3. One criterion only. Clarify if there were any protocol violations that included patients meeting only one or none of the 3 criteria.

Please submit your response officially to your application by September 25, 2015.

Thanks

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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ANISSA A DAVIS
09/11/2015

Executive CAC

Date of Meeting: September 8, 2015

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Tim McGovern, Ph.D., ONDIO, Member
Sushanta Chakder, Ph.D., DGIEP, Pharm Tox Supervisor
Tracy Behrsing, Ph.D., DGIEP, Presenting Reviewer

Author of Draft: Tracy Behrsing, Ph.D.

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

NDA # 207999

Drug Name: INT-747

Sponsor: Intercept Pharmaceuticals, Inc.

Background

INT-747 is a modified bile acid and farnesoid X receptor (FXR) agonist under development for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Rat Carcinogenicity Study

In the 24-month carcinogenicity study, Crl:CD(SD) rats (65/sex/group) were administered INT-747 by oral gavage at dose levels of 0, 2, 7, or 20 mg/kg/day. Animals in dual control groups received vehicle only [0.5% carboxymethylcellulose (CMC) in deionized water]. Dose selection was based on the maximum tolerated dose (MTD) as per the ECAC recommendations.

In males, there were no treatment-related effects on survival. However, due to the reduced group size in high dose males, all surviving males were terminated during Week 100/101. In females, pairwise comparisons showed statistically significant decreases in survival rates in the mid-dose group compared to pooled controls and control group 2.

No drug-related neoplastic findings were observed in male rats. In females, there was a statistically significant increase in the incidence of benign ovarian granulosa cell tumors at the high dose (3/65), as compared to the pooled control groups (0/130; $p=0.0309$). The incidence of this rare tumor type in the ovaries at the high dose (4.6%) exceeded the (b) (4) historical control range (up to 1.67%). In the cervix, vagina, and cervix and vagina combined, there was a statistically significant increase in the incidence of benign granular cell tumors at the high dose (5/65, 3/65, and 8/65, respectively), as compared to the pooled control groups (0/130; $p=0.0030$, $p=0.0309$, and $p<0.001$, respectively). The combined incidence of granular cell tumors in the cervix and vagina at the high dose (12.3%) approached the maximum (b) (4) historical control incidence for granular

cell lesions in the cervix and vagina combined (14.0%). Furthermore, trend analysis and pairwise comparison (high dose versus pooled controls) of granular cell tumors in the cervix and vagina combined showed this finding to be highly significant ($p < 0.001$).

Mouse Carcinogenicity Study

In the 24-month carcinogenicity study, Crl:CD-1 mice (65/sex/group) were administered INT-747 by oral gavage at dose levels of 0, 4, 10, or 25 mg/kg/day. Mice in dual control groups received vehicle only (0.5% CMC in deionized water). Dose selection was based on the MTD as per the ECAC recommendations.

There were no treatment-related effects on survival in males. There was a statistically significant increase in the survival rate of high dose females, compared to pooled controls and control group 2.

There were no drug-related neoplastic findings in male or female mice.

Executive CAC Recommendations and Conclusions

Rat:

- The Committee concurred that the study was acceptable, noting prior concurrence with the protocol.
- The Committee concurred that benign granulosa cell tumors in the ovaries, and benign granular cell tumors in the cervix and vagina of females were drug related.

Mouse:

- The Committee concurred that the study was acceptable, noting prior concurrence with the protocol.
- The Committee concurred that there were no drug-related neoplasms in male or female mice.

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

cc:\

/Division File, DGIEP
/Sushanta Chakder, DGIEP
/Tracy Behrsing, DGIEP
/Anissa Davis, DGIEP
/ASeifried, OND IO

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/s/

ADELE S SEIFRIED
09/10/2015

ABIGAIL C JACOBS
09/10/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, September 09, 2015 10:04 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Information Requests

Hello Linda:

Your submission dated June 27, 2015 to NDA 207,999, is currently under review and we have the following clinical pharmacology requests for information:

1. In regard to your PBPK report “Modeling and simulations to support liver safety of obeticholic acid” (report):
 - a. Clarify if you reproduced Molino’s 1986 results using the model you constructed in Phoenix.
 - b. Compare in detail ADME properties of OCA and CDCA, and their respective conjugates. Such details include quantitative, protein level activities of drug metabolism, diffusion, and transport in each system/space.
 - c. Introduction of the report (page 7) summarized fold-increase values of bile acids in serum and liver in patients with cirrhosis or PBC/PSC versus healthy subjects. You also stated that taurine conjugation of CDCA may be greater in hepatic impaired subjects (page 27). For these conditions, adjust your physiology model by considering known physiology changes and simulate plasma and liver levels of respective bile acids. Estimates of the effect of hepatic impairment on OCA hepatic uptake and taurine conjugation (Table 7.10) can be referenced/modified in the model for the new simulations. Compare simulated plasma and liver bile acid levels with observed data mentioned above.
 - d. Figure 4.3 of the report shows ER relationship using predicted liver total OCA levels. These liver levels are indirectly calculated using model predicted plasma/liver Cmax ratios. Justify the adequacy of this calculation.
 - e. Overlay 90% CI of both predicted and observed data on the same plot for figures 7.13 and 7.14.
2. In regard to Study 747-115 and Study 747-116:
 - a. Conduct additional bioequivalence testing on PK parameter Cmax and AUC₀₋₁₆₈ of tauro-OCA and glycol-OCA and provide analysis datasets in .xpt format and results to the Agency.
3. In the population PK/PD and Simulation Report, there seems to be a mismatch in the calculated/simulated exposures for subjects with hepatic impairment when comparing Figure 8.4 (Forest plot on pg. 42: shows 3-fold exposures of total OCA in severe hepatic impairment compared to normal), with Table 9.1 and Table 9.2 (pg. 44-45: both showing around > 8-fold exposures of total OCA in moderate / severe hepatic impairment compared to normal subjects).

4. Provide the following figures with overlay of observed and Population PK estimated concentration-time profiles of OCA, its conjugates and total OCA for normal and mild, moderate, and severe hepatic impairment subjects in the hepatic impairment study (Study 747-103):
 - a. Population level comparison (mean/median) of observed and predicted data grouped by hepatic function category
 - b. Subject level comparison of observed and predicted data
5. With the population PK model, simulate the scenarios with 5 mg QD dosing in normal subjects and alternative dosing regimen (e.g. 5 mg Q2D, QW etc.) in subjects with mild/moderate/severe hepatic impairment. Provide concentration-time plots for comparison of these scenarios along with tables for comparison of single dose and steady state exposure parameters (AUC, Cmax, Ctough, Cavg etc.) for OCA, its conjugates and total OCA. With these simulations, identify a dosing schedule that can match the steady state plasma exposures in hepatic impairment subjects with 5 mg QD dosing in normal subjects.
6. Provide the analysis codes and input and output datasets in order to be able to review and recreate the above two results (point #4 and #5).

Please submit above requested information officially to your application for review by close of business, Sep 17, 2015.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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ANISSA A DAVIS
09/09/2015

Davis, Anissa

From: Davis, Anissa
Sent: Friday, September 04, 2015 9:39 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: AC Meeting for NDA 207999

Hello Linda:

I want to remind you that the Advisory Committee (AC) Meeting for NDA 207999 (obeticholic acid) has been scheduled January 13, 2016. Your team will be allowed 90 minutes to present, and the agency would like a copy of your agenda when finalized. I will inform you of a deadline date for this agenda at a later date.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
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/s/

ANISSA A DAVIS
09/04/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, September 01, 2015 11:47 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Information Request

Your submission dated June 27, 2015 to NDA 207,999, is currently under review and we have the following clinical pharmacology requests for information:

1. Provide full validation reports, including cross-validation reports, for assay methodologies for ALP and direct bilirubin and total bilirubin used in Study 747-301. Indicate how many labs were involved and how many assay methods were used. List all the samples to which a correction factor was applied, the value of the correction factor, and the procedures involved to derive the correction factor.
2. Provide concentrations of glycol- and tauro-OCA following IV dose of OCA from Study 747-113 and calculate the absolute bioavailability for total OCA. If such data are not available, please state so.
3. Clarify the discrepancy in FXR EC50 values:

In your Figure 2 of the Clinical Overview, it appears that EC50 for CDCA is 8.66 uM while UDCA has no activity. However, EC50 for UDCA is given as 8.66 uM in your Table 1 of Summary of Clinical Efficacy.

Figure 2: Structural Activities of OCA, CDCA and UDCA

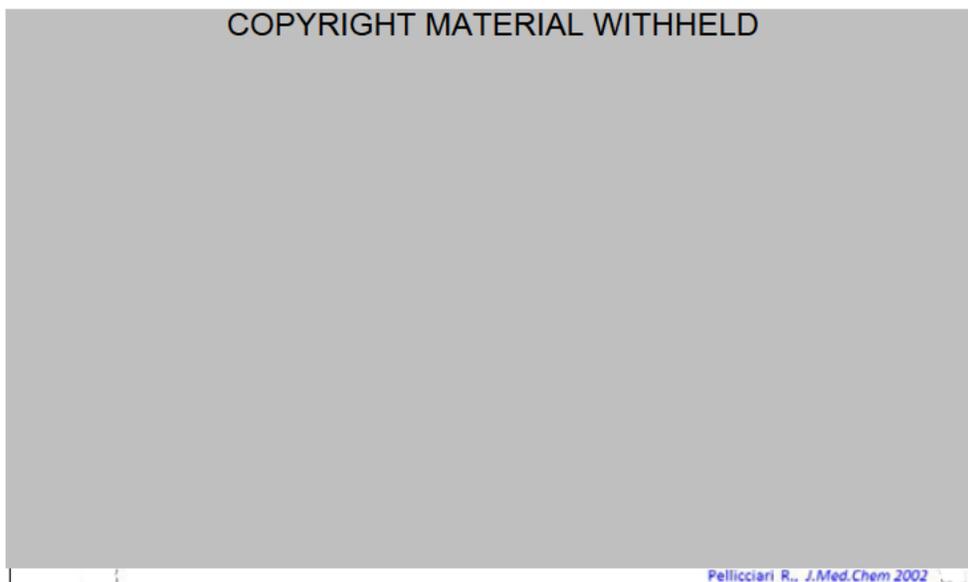


Table 1: Comparison of Key Mechanisms of OCA and UDCA

	OCA	UDCA	Comment
<i>Structure</i>			<ul style="list-style-type: none"> Both molecules are derived from CDCA OCA contains a 6α-ethyl moiety UDCA is a 7β isomer of CDCA
<i>Approval Status</i>	<ul style="list-style-type: none"> Submitted 	<ul style="list-style-type: none"> Approved (Ursodiol, Actigall, URSO 250, URSO Forte) 	<ul style="list-style-type: none"> OCA is indicated as an add-on therapy for patients with PBC with an inadequate response to UDCA
<i>Dosage</i>	<ul style="list-style-type: none"> 5 mg/day to 10 mg/day Dosed ~100x lower than UDCA 	<ul style="list-style-type: none"> 13 mg/kg/day to 15 mg/kg/day 	<ul style="list-style-type: none"> UDCA displaces endogenous BA pool After administration, OCA and its conjugates comprises only a fraction of total bile acid pool
<i>FXR Activation (EC₅₀)</i>	<ul style="list-style-type: none"> 0.09 μM 	<ul style="list-style-type: none"> 8.6 μM 	<ul style="list-style-type: none"> UDCA does not have meaningful FXR activity Addition of 6α-ethyl moiety enhanced OCA FXR activity by ~100-fold relative to the endogenous bile acid CDCA
<i>Key Mechanisms of action</i>	<ul style="list-style-type: none"> Regulates bile acid synthesis Cytoprotective via modulation of multiple bile acid transporters Increase biliary bicarbonate "umbrella" Promotes choleresis Direct anti-inflammatory effects Decrease/reverse fibrosis Immunomodulatory 	<ul style="list-style-type: none"> Increases hydrophilicity of endogenous BA pool Stimulation of hepatocellular ductal secretion Increase biliary bicarbonate "umbrella" Cytoprotective (via dilution of bile acid pool) Immunomodulatory/anti-inflammatory effects 	<ul style="list-style-type: none"> UDCA MOA likely post-translational and indirect due to dilution of endogenous BA pool (hence high dosage requirement) OCA activity predominantly due to activation of hepatic and intestinal nuclear FXR transcription of downstream genes and stimulation of FGF-19 secretion

Please submit the requested information for review by close of business Sep 4, 2015. All the responses will have to be submitted officially to the NDA as well.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

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(301) 796-5016 (office)

(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
09/01/2015

Davis, Anissa

From: Davis, Anissa
Sent: Monday, August 31, 2015 11:26 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Statistical Information Request

Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

In regards to your response dated August 20, 2015 to our information request dated August 11, 2015, we have the following statistical information request follow-up:

- **Provide your datasets (raw and derived) of the meta-analyses for the Global PBC Study for our review. In addition to the datasets, please submit your analysis programs, either by R or SAS, along with a thorough data definition file(s).**

Please submit your response officially to your application by September 19, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
08/31/2015

Davis, Anissa

From: Davis, Anissa
Sent: Monday, August 31, 2015 11:22 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Statistical Information Request

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a review of your submitted statistical data and have the following statistical information request:

1. For all patients randomized in the 747-301 study that also rolled over into the ongoing long-term safety extension period, provide a separate line graph for each of the following items. For each line graph, time should range from the beginning of the 747-301 study (i.e., randomization day) through the time point with the latest available data from the ongoing long-term safety extension period. Patients should be presented within their originally randomized treatment groups.
 - a. Plot the mean (\pm standard deviation) alkaline phosphatase concentration in units per liter (U/L) for all patients.
 - b. Plot the mean (\pm standard deviation) alkaline phosphatase concentration in U/L for all patients with ursodeoxycholic acid (UDCA) use at baseline.
 - c. Plot the median (\pm one tertile) alkaline phosphatase concentration in U/L for all patients without UDCA use at baseline.
 - d. Plot the mean (\pm standard deviation) total bilirubin concentration in micromoles per liter ($\mu\text{mol/L}$) for all patients.
 - e. Plot the mean (\pm standard deviation) total bilirubin concentration in $\mu\text{mol/L}$ for all patients with UDCA use at baseline.
 - f. Plot the median (\pm one tertile) total bilirubin concentration in $\mu\text{mol/L}$ for all patients without UDCA use at baseline.

2. For all patients randomized to placebo or 10mg OCA in the 747-201 study that also rolled over into the ongoing long-term safety extension period, provide a separate line graph for each of the following items. For each line graph, time should range from the beginning of the 747-201 study (i.e., randomization day) through the time point with the latest available data from the ongoing long-term safety extension period. Patients should be presented within their originally randomized treatment groups.
 - a. Plot the median (\pm one tertile) alkaline phosphatase concentration in U/L.
 - b. Plot the median (\pm one tertile) total bilirubin concentration in $\mu\text{mol/L}$.

Please submit your response officially to your application by September 25, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
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ANISSA A DAVIS
08/31/2015



NDA 207999

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92121

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) dated June 27, 2015, received June 29, 2015 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for obeticholic acid tablets, 5 mg and 10 mg.

We also refer to your amendments dated July 31, 2015 and August 20, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is February 29, 2016. 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>).

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 requirement/commitment requests by November 30, 2015.

In addition, the planned date for our internal mid-cycle review meeting is September 29, 2015. 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:**

Clinical Pharmacology

1. The dedicated hepatic impairment study shows that the exposure to total obeticholic acid (OCA) in subjects with moderate and severe hepatic impairment is 4 and 17 times higher than that observed in subjects with normal hepatic function. The recommendation of whether OCA should be used in subjects with moderate and severe hepatic impairment will be a review issue.

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

We request that you submit the following information by September 4, 2015:

1. Provide the following information for the 7% of patients who were not on ursodeoxycholic acid (UDCA) at baseline:
 - a. Alkaline phosphatase, total bilirubin, aminotransferases, gamma-glutamyl transferase and albumin levels prior to enrollment (specifically: before starting UDCA, during UDCA and after stopping UDCA therapy prior to trial entry).
 - b. Duration of UDCA therapy these patients received prior to discontinuation of UDCA.
 - c. Reason for discontinuation of UDCA.
2. Please provide all the narratives for the patients who had significant increases in MELD score during the trial. Some of these data are presented in the “Clinical outcomes-All cause mortality and clinical complications: safety population” in the clinical study report for trial 747-301. The subject numbers are 134001, 174001 in the placebo arm and 153003, 180310, 129002 in the OCA arm.
3. Provide the narrative for subject number 139003 who experienced hepatic encephalopathy and was on OCA 5mg. These data were presented in the “Clinical outcomes-All cause mortality and clinical complications: safety population” in the clinical study report for trial 747-301.
4. Please clarify if the alkaline phosphatase, total and direct bilirubin measures are performed with CLIA certified methods in a central lab, and provide a summary of the methodology used including the variability of the assay results (i.e., precision and accuracy).

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances, and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified format items from the SRPI checklist and have additional high-level labeling comments and requests for additional information for you to consider (see attached PI).

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by September 18, 2015. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

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

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

PROMOTIONAL MATERIAL

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-

up form with annotated references, and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

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

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

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

REQUIRED PEDIATRIC ASSESSMENTS

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

Because none of these criteria apply to your application, you are exempt from this requirement.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director

Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

13 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

DRAGOS G ROMAN

08/28/2015

Signing on behalf of Dr. Donna Griebel

Davis, Anissa

From: Davis, Anissa
Sent: Friday, August 28, 2015 9:38 AM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Comments and Requests

Importance: High

Hello Linda:

We have the following clinical pharmacology correspondence regarding your response dated 8/25/15 to the clinical pharmacology information request dated 8/20/15:

When you submit the requested dataset for study 115 and 116, please indicate clearly whether a subject's AUC_∞ for each analyte (OCA, glycol-OCA, tauro-OCA, and total OCA) was calculated by using the subject's individual terminal elimination rate constant ($\lambda_{z,i}$) or the mean of the subjects with a definable terminal elimination rate constant ($\lambda_{z,pop}$). Please provide a summary on how many subjects have a definable terminal phase for each analyte in every study period (Period 1 and Period 2).

Thank you.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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Anissa.Davis@fda.hhs.gov

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ANISSA A DAVIS
08/28/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, August 25, 2015 10:40 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Response and Information Request

Importance: High

Hello Linda:

With reference to your responses on 19 August 2015 to our request for information dated 12 August 2015 regarding clinical pharmacology for NDA 207999, we have the following comment to facilitate completion of our data request from you:

- In your response to #3, you have proposed a way to calculate TSLD based on lab draw time from lab dataset. Please generate the TSLD as per your proposal and submit it as an update to the exposure-response dataset.

Please submit your response officially to your application by August 31, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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/s/

ANISSA A DAVIS
08/25/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, August 20, 2015 2:29 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 obeticholic acid: Clinical Pharmacology Information Request

Hello Linda:

Your submission dated June 29, 2015 to NDA 207999 is currently under review, and we have the following clinical pharmacology information requests:

1. Please submit the following data files within 3 business days (August 25, 2015):

- a. In your pp.xpt files for Studies 747-115 and 747-116, you did not include parameters for glycol-OCA and tauro-OCA. Please submit a new pp.xpt file for each of the two studies including the associated PK listing of these two metabolites. The listing should include R squared and R squared adjusted.
- b. Please also submit a new ADPP.xpt file for each of the studies (115 and 116) including glycol-OCA and tauro-OCA.
- c. Please provide a description on how the AUC_{∞} is derived for OCA and its conjugated metabolites. Are there any criteria used to determine whether the AUC_{∞} is estimable or not?

Please submit your responses officially to your application.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

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/s/

ANISSA A DAVIS
08/20/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, August 18, 2015 12:16 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Information Regarding Financial Disclosures

Importance: High

Hello Linda:

Regarding the email that you sent to me on August 18, 2015 concerning financial disclosure for NDA 207999 INT-747 (obeticholic acid), the clinical reviewer has the following response:

We refer you to your financial disclosure (Module 1.3.4) submission pages 84 and 85 of 89, where you stated you will be collecting and reporting the financial disclosures for the sub-investigators for trial 747-202 and 747-301. We want to assure the trial conduct was not affected by the financial interest of these investigators. **Please submit these disclosures ASAP before 8-21-2015, failure to submit these financial disclosure is a refuse to file issue.**

Please submit your response officially to your application.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR, United States Public Health Service (USPHS)
Senior Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22 Room: 5378
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/s/

ANISSA A DAVIS
08/18/2015

From: Nkah, Shila
To: [Davis, Anissa](#)
Subject: BE Sites to be Inspected - NDA-207999
Date: Monday, August 17, 2015 1:18:00 PM
Attachments: [NDA 207999-OSIS Bioequivalence Audit Request.pdf](#)

From: Nkah, Shila
Sent: Monday, August 17, 2015 1:06 PM
To: Davis, Anissa
Subject: BE Sites to be inspected - NDA-207999

Dear Anissa,
This email is to notify you that the sites listed on the table below will be inspected.

App. Type	App. #	Facility Name	Facility Address	Facility Type	Assessment Outcome
NDA	207999		(b) (4)	Analytical	Inspect
		Orlando Clinical Research Center	5055 S. Orange Avenue, Orlando, FL	Clinical	Inspect

A decline to inspect memo for the clinical site (Clinical Pharmacology of Miami, Inc.) will be submitted in Darrts. Feel free to contact me if you have any questions.

Thanks,

Shila Nkah, M.S.
Project Manager
Office of Study Integrity & Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food & Drug Administration
White oak Bldg. 51, Rm. 5318
Phone: (301)-796-8347
Email: shila.nkah@fda.hhs.gov
Please consider the environment before printing this e-mail.

From: Nkah, Shila
Sent: Thursday, August 06, 2015 10:42 AM
To: Davis, Anissa
Subject: Acknowledgment of Receipt of Bioequivalence Audit Request Consult - NDA-207999

Dear Anissa,

This email acknowledges receipt of the Bioequivalence Audit Request Consult for NDA 207999 submitted on August 5, 2015. I am the OSIS PM assigned to this NDA.
The consult has been sent for assessment. I will be updating you on the site inspection decision as soon as the information is available.

Note: The OSIS Review Requested by Date is not listed on the consult, please provide date.
Feel free to contact me if you have any questions.
Thank you.

Shila Nkah, M.S.
Project Manager
Office of Study Integrity & Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food & Drug Administration
White oak Bldg. 51, Rm. 5318
Phone: (301)-796-8347
Email: shila.nkah@fda.hhs.gov
Please consider the environment before printing this e-mail.

From: osafda@fda.gov [<mailto:osafda@fda.gov>]
Sent: Wednesday, August 05, 2015 1:50 PM
To: Shang, Elizabeth; Wilkins Parker, Jamie; Davis, Anissa; Leishear, Kira; Winiarski, Aleksander; CDER OSI; Shroff, Hitesh; Duan, Peng; Behrsing, Tracy; Vall, Benjamin P; ct.viswanathan@fda.hhs.gov; Lee, Sue Chih H; CDER OSIS BEQ; Chen, Tien Mien; Barlow, Matthew; Hachey, Erin; Swank, Kimberley; Bashaw, Edward D; ddrds@cdcr.fda.gov; Mehta, Ruby; Strandberg, Heather

Subject: Finalized - NDA-207999 Biopharmaceutical Inspections Request (FRM-CONSULT-09)



[Proceed to DARRTS Welcome Screen](#)

Finalized - Biopharmaceutical Inspections Request (FRM-CONSULT-09)

The following communication has been signed and finalized.

Functions

Communication	Communication Group	Communication Name
FRM-CONSULT-09	CONSULT	Biopharmaceutical Inspections Request

Linked Supporting Documents

Application Type and Number	Sponsor	Product Name (Preferred)	Submission Type and Number	Group ID	Supporting Document Number	Category/Subcategory	Submit Date	Receive Date
NDA-207999	INTERCEPT PHARMACEUTICALS INC	OBETICHOLIC ACID	ORIG-1		2	Form 3674	06/27/2015	06/29/2015

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Number	Submission Classification	Group ID
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Signers

Signer	Proxy Signer	Signed Status	Signed Date
SHANG, ELIZABETH Y.		signed	07/31/2015
DAVIS, ANISSA A.		signed	07/31/2015
BASHAW, EDWARD D.		signed	08/05/2015

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/s/

SHILA S NKAH
08/17/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 8/17/2015

TO: Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: NDA 207999

The Division of New Drug Bioequivalence Evaluation (DNDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Requested Site Inspection

Facility Type	Facility Name	Facility Address
Clinical	Clinical Pharmacology of Miami, Inc.	550 West 84th Street, Miami, FL 33014

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/s/

SHILA S NKAH
08/17/2015

Davis, Anissa

From: Davis, Anissa
Sent: Thursday, August 13, 2015 4:28 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: QT-IRT Information Request

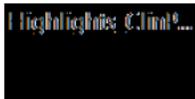
Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We have the following information request:

1. Complete and update the attached ClinPharm and Cardiac Safety Table



APPEARS THIS WAY ON ORIGINAL

2. Submit all ECG waveforms related to study report 747-108 to the ECG warehouse at www.ecgwarehouse.com and inform me via email when this has been done.

Please submit your response to #1 officially to your application and complete #2 as soon as possible.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

Use zip code **20903** if shipping via United States Postal Service (USPS)

(301) 796-5016 (office)

(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

Therapeutic dose	Include maximum proposed clinical dosing regimen	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC
	Multiple Dose	Mean (%CV) Cmax and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent • Median (range) for metabolites
Distribution	Vd/F or Vd	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent • Mean (%CV) for metabolites
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC
	Sex	Specify mean changes in Cmax and AUC
	Race	Specify mean changes in Cmax and AUC
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in Cmax and AUC
	Food Effects	Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.	
Preclinical Cardiac Safety	Summarize <i>in vitro</i> and <i>in vivo</i> results per S7B guidance.	
Clinical Cardiac Safety	Describe total number of clinical trials and number of subjects at different drug exposure levels. Summarize cardiac safety events per ICH E14 guidance (e.g., QT prolongation, syncope, seizures, ventricular arrhythmias, ventricular tachycardia, ventricular fibrillation, flutter, torsade de pointes, or sudden deaths).	

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/s/

ANISSA A DAVIS
08/13/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, August 12, 2015 9:25 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Pharmacology Information Request

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a preliminary review of the pharmacology section and have the following clinical pharmacology information requests:

With reference to the submitted NDA material, please provide the following:

1. Justification of why Phase 3 data was not used for population PK modeling to quantify the impact of covariates and to estimate individual predicted exposures for exposure-response analyses.
2. Submit the analysis codes along with output to reproduce the results of exploratory PK-PD and Exposure-response analyses submitted as a part of "POPULATION PK/PD AND SIMULATION REPORT".
3. Please modify the exposure-response dataset with a column for 'time since last dose' for the measurements of PK concentrations for each individual in Phase 3, if the information is available.

Please refer to the following pharmacometric data and models submission guidelines for your submission: (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>)

We request this information to be submitted by August 19, 2015.

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

Use zip code **20903** if shipping via United States Postal Service (USPS)

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(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
08/12/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, August 12, 2015 3:42 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999 obeticholic acid: Nonclinical Information Request

Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a preliminary review of the nonclinical section and have the following nonclinical information requests:

1. Impurity [REDACTED] (b) (4) impurity of obeticholic acid (OCA), is a degradation product of OCA tablets. Section 3.2.P.5.5. (Characterization of Impurities) states that Impurity (b) (4) is not considered to be mutagenic based on computational evaluation by Derek Nexus and Leadscope Model Applier. Please submit full reports of your computational assessment for this impurity.
2. Section 2.6.6 (Toxicology Written Summary) states that a genotoxicity risk assessment was completed for the primary ingredients of OCA synthesis using DEREK and MultiCASE, or literature evaluations. According to your submission, structural alerts for mutagenicity were identified for [REDACTED] (b) (4). However, the genotoxic impurity assessment in Section 3.2.S.3.2 (Impurities) does not include an assessment of [REDACTED] (b) (4). Please provide a safety assessment of [REDACTED] (b) (4) as a potential genotoxic impurity per the ICH M7 guidance.

Please submit your response officially to your application by August 26, 2015.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
08/12/2015



**REQUEST FOR METHODS
VALIDATION MATERIALS**

NDA 207999

August 12, 2015

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92121

Dear Linda Robertson, Ph.D.:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Obeticholic Acid Tablets, 5 mg and 10 mg.

We will be performing methods validation studies on Obeticholic Acid Tablets, 5 mg and 10 mg, as described in NDA 207999.

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

Method, current version

- 1) (b) (4) : Related substances Impurities (b) (4) (RI-detection)
- 2) (b) (4) : Related substances Impurity (b) (4) (RI-detection)
- 3) (b) (4) : Assay and Identification (HPLC-RI-detection)
- 4) QCM888: HPLC method for the Identification, Assay, and Content Uniformity of INT-747 in INT-747 Film Coated Tablets 5mg, 10 mg, and 25 mg
- 5) 11M017: HPLC Assay method for INT-747 in uniformity of Dosage Units and Content of INT-747 film coated tablets 5 mg, 10 mg, and 25 mg Coated Tablets 5mg, 10 mg, and 25 mg
- 6) QCM857: The HPLC method for the Determination of Impurity (b) (4) in INT-747 Film Coated Tablets 5 mg, 10 mg and 25 mg
- 7) 11M020: The HPLC assay method for determining impurity (b) (4) in int-747 film coated tablets, 5 mg, 10 mg and 25 mg
- 8) 14M019: The HPLC Assay Method for Determining Impurity (b) (4) and Unspecified Impurities in Obeticholic Acid (OCA) tablets, 5 mg, 10 mg AND 25 mg
- 9) QCM1069: The HPLC Method for the Determination of Impurity (b) (4) and Unspecified Impurities in OCA Film Coated Tablets 5 mg, 10 mg and 25 mg

Samples and Reference Standards

(b) (4)
(b) (4) Reference Standard (C020)
(b) (4) mg INT-747 Reference Standard
(b) (4) mg OCA Reference Standard
(b) (4) Drug Substance
(b) (4) mg Impurity (b) (4) reference substance (B078, (b) (4))
(b) (4) mg Impurity (b) (4) reference substance (C030)
(b) (4) mg Impurity (b) (4) reference substance
Placebo Tablets
(b) (4) Obeticholic Acid Tablets, 5 mg
(b) (4) Obeticholic Acid Tablets, 10 mg

Equipment

(b) (4)

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 email. You may contact me by telephone (314-539-2155), FAX (314-539-2113), or email (Laura.Pogue@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Laura C. Pogue, 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/

LAURA POGUE
08/12/2015

Davis, Anissa

From: Davis, Anissa
Sent: Tuesday, August 11, 2015 2:28 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Clinical Information Request

Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a preliminary review of the clinical section and have the following clinical information request:

1. You must provide financial disclosures for the investigators and sub-investigators involved in clinical trials 747-201, 747-202, and 747-301. If they are not submitted by 8-20-2015, this will be cause for refusing to file the application.
2. Provide your data (raw and derived) of the meta-analyses for the Global PBC Study for our review. In addition to the data, please submit your analysis programs, either by R or SAS, along with a thorough data definition file. For this submission, we recommend you comply with the latest CDISC standard. You should also include any communications with the FDA related to biomarker analyses. These should be submitted prior to 8-20-2015.

Please submit an official copy to your application by August 20, 2015 or sooner.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

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Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
08/11/2015

From: [Nkah, Shila](#)
To: [Davis, Anissa](#)
Subject: Acknowledgment of Receipt of Bioequivalence Audit Request Consult - NDA-207999
Date: Thursday, August 06, 2015 10:42:00 AM
Attachments: [NDA 207999-OSIS Bioequivalence Audit Request ES.pdf](#)

Dear Anissa,

This email acknowledges receipt of the Bioequivalence Audit Request Consult for NDA 207999 submitted on August 5, 2015. I am the OSIS PM assigned to this NDA. The consult has been sent for assessment. I will be updating you on the site inspection decision as soon as the information is available.

Note: The **OSIS Review Requested by Date** is not listed on the consult, please provide date.

Feel free to contact me if you have any questions.

Thanks

Shila Nkah, M.S.
 Project Manager
 Office of Study Integrity & Surveillance
 Office of Translational Sciences
 Center for Drug Evaluation and Research
 Food & Drug Administration
 White oak Bldg. 51, Rm. 5318
 Phone: (301)- 796- 8347
 Email: shila.nkah@fda.hhs.gov

Please consider the environment before printing this e-mail.

From: oasfda@fda.gov [mailto:oasfda@fda.gov]
Sent: Wednesday, August 05, 2015 1:50 PM
To: Shang, Elizabeth; Wilkins Parker, Jamie; Davis, Anissa; Leishear, Kira; Winiarski, Aleksander; CDER OSI; Shroff, Hitesh; Duan, Peng; Behrsing, Tracy; Vali, Benjamin P; ct.viswanathan@fda.hhs.gov; Lee, Sue Chih H; CDER OSIS BEQ; Chen, Tien Mien; Barlow, Matthew; Hachey, Erin; Swank, Kimberley; Bashaw, Edward D; ddrdsi@cderr.fda.gov; Mehta, Ruby; Strandberg, Heather
Subject: Finalized - NDA-207999 Biopharmaceutical Inspections Request (FRM-CONSULT-09)



[Proceed to DARRTS Welcome Screen](#)

Finalized - Biopharmaceutical Inspections Request (FRM-CONSULT-09)

The following communication has been signed and finalized.

Functions	Communication Group	Communication Name
Communication FRM-CONSULT-09	CONSULT	Biopharmaceutical Inspections Request

Linked Supporting Documents

Application Type and Number	Sponsor	Product Name (Preferred)	Submission Type and Number	Group ID	Supporting Document Number	Category/Subcategory	Submit Date	Receive Date
NDA-207999	INTERCEPT PHARMACEUTICALS INC	OBETICHOLIC ACID	ORIG-1		2	Form 3674	06/27/2015	06/29/2015

Linked Submissions

Application Type and Number	Sponsor	Preferred Product Name	Submission Type and Number	Submission Classification	Group ID
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Signers Signer	Proxy Signer	Signed Status	Signed Date
SHANG, ELIZABETH Y.		signed	07/31/2015
DAVIS, ANISSA A.		signed	07/31/2015
BASHAW, EDWARD D.		signed	08/05/2015

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SHILA S NKAH
08/06/2015

Davis, Anissa

From: Davis, Anissa
Sent: Wednesday, July 29, 2015 5:07 PM
To: Linda Robertson (LRobertson@interceptpharma.com)
Subject: NDA 207999: Labeling Information Request

Importance: High

Hello Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for INT-747 (obeticholic acid).

We are conducting a preliminary review of your submitted label and have the following information request:

Request for Pregnancy and Lactation Labeling Rule (PLLR) Information

On December 4, 2014, the Food and Drug Administration published the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,” also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR went into effect on June 30, 2015. According to PLLR, Risk Summary statements for sections 8.1 (Pregnancy), 8.2 (Lactation), and 8.3 (Females and Males of Reproductive Potential) must be based on available human and nonclinical data. The Risk Summary must also state when there are no human data or when available human data do not establish the presence or absence of drug-associated risk (21 CFR 201.57(c)(9)(i)(B)(1)).

Together with submission of the proposed labeling for PLLR compliance, you should provide the following information to support the labeling content: a review and summary of the relevant published literature, summary of cases reported in the pharmacovigilance database, interim ongoing or final report on a closed pregnancy registry (if applicable).

During our preliminary review of your submitted labeling, you did not provide a review and summary of the available literature to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. Thus, your proposed PLLR labeling changes cannot be agreed upon until the information request is fulfilled.

However, because the application was submitted prior to the PLLR effective date of June 30, 2015, you have the option to fully comply with PLLR requirements during this review cycle or fully comply before June 30, 2019. If you choose to voluntarily comply with PLLR in full during this review cycle, **we request that you officially submit the following information on obeticholic acid use in pregnant and lactating women no later than October 1, 2015:**

- review and summary of all available published literature regarding obeticholic acid
- review and summary from your pharmacovigilance database,
- revised labeling incorporating the above information (in Microsoft Word) that complies with PLLR.

Alternatively, if you choose to wait until June 30, 2019 to comply, then the pregnancy category must be retained in labeling. No partial PLLR conversions may be made.

Refer to the Guidance for Industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>). Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

Thank you!

Anissa

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.

CDR, United States Public Health Service (USPHS)

Senior Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

White Oak Building 22 Room: 5378

10903 New Hampshire Avenue

Silver Spring, Maryland

*Use zip code **20903** if shipping via United States Postal Service (USPS)*

(301) 796-5016 (office)

(301) 796-9904 (fax)

Anissa.Davis@fda.hhs.gov

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/s/

ANISSA A DAVIS
07/29/2015



NDA 207999

INFORMATION REQUEST

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Obeticholic Acid Tablets, 5 mg and 10 mg.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a written response by July 31, 2015 in order to continue our evaluation of your NDA.

Biopharmaceutics Comments

The clinically tested 10 mg [REDACTED] ^{(b) (4)} tablet formulation is bridged to 10 mg commercial image yellow tablet formulation through a BE study 747-115.

If a biowaiver is planned for the proposed 5 mg tablet strength, submit the biowaiver request with supportive dissolution profile data and appropriate justifications (e.g. for the difference observed in dissolution profile comparison).

If you have any questions, please contact Heather Strandberg, Senior Regulatory Health Project Manager, at (240) 402-7999.

Sincerely,

Moojhong Rhee -S

Digitally signed by Moojhong Rhee -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, cn=Moojhong Rhee -S,
0.9.2342.19200300.100.1.1=1300041261
Date: 2015.07.24 13:20:34 -04'00'

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

From: [Brancazio, Matthew \(FDA\)](#)
To: lrobertson@interceptpharma.com
Cc: [Brancazio, Matthew \(FDA\)](#)
Subject: NDA 207999 INT-747 (obeticholic acid) - Clinical Information Request (IR)
Date: Thursday, July 16, 2015 12:53:52 PM
Importance: High

Dr. Robertson,

We have identified the need for a clinical information request for your recent NDA 207999 submission dated June 27, 2015, received June 29, 2015, for INT-747 (obeticholic acid).

Provide either a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine OR direct the medical reviewer as to where the explanation can be located in the current submission.

Please verify receipt of this information request and respond by **July 22, 2015**.

Respectfully,

Matt Brancazio, Pharm.D., MBA
CDR, U.S. Public Health Service Commissioned Corps
Senior Regulatory Health Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
CDER/FDA

(301) 796-5343 (office)
(301) 796-9904 (fax)
matthew.brancazio@fda.hhs.gov

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/s/

MATTHEW B BRANCAZIO
07/16/2015



NDA 207999

NDA ACKNOWLEDGMENT

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

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: obeticholic acid tablets, 5 mg and 10 mg

Date of Application: June 27, 2015

Date of Receipt: June 29, 2015

Our Reference Number: NDA 207999

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 August 28, 2015, 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 Gastroenterology and Inborn Errors Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
07/16/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 063307

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

Intercept Pharmaceuticals, Inc.
4350 La Jolla Village Drive, Suite 960
San Diego, CA 92122

ATTENTION: Linda Robertson
VP, Regulatory Affairs and Quality Assurance

Dear Dr. Robertson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Obeticholic Acid Tablets, 5 mg and 10 mg.

We also refer to your correspondence, dated and received August 18, 2014, requesting review of your proposed proprietary name, (b) (4)

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

(b) (4)

A large rectangular area of the document is completely redacted with a solid grey fill, obscuring the reasons for the name being unacceptable.

¹ Institute for Safe Medication Practices. Follow ISMP Guidelines to safeguard the design and use of automated dispensing cabinets (ADCs). ISMP Med Saf Alert Acute Care. 2009; 14(3): 1-4

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.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

² <http://dij.sagepub.com/com/content/early/2012/08/21/0092861512456282>

³ Institute for Safe Medication Practices. Follow ISMP Guidelines to safeguard the design and use of automated dispensing cabinets (ADCs). ISMP Med Saf Alert Acute Care. 2009; 14(3): 1-4

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf>)
- 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 Aleksander Winiarski, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5295. For any other information regarding this application, contact Anissa Davis, Regulatory Project Manager in the Office of New Drugs, at (301) 796-5016.

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/

KELLIE A TAYLOR on behalf of TODD D BRIDGES
02/12/2015



NDA 207999

ACKNOWLEDGE NDA PRESUBMISSION

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, PhD
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: INT-747 (obeticholic acid)

Date of Submission: DECEMBER 19, 2014

Date of Receipt: DECEMBER 19, 2014

Our Reference Number: NDA 207999

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA listed above at the top of the first page of any communications concerning this supplemental application. Unless you are using the FDA Electronic Submissions Gateway (ESG), send all submissions by overnight mail or courier to the following address:

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

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) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H.,
C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANISSA A DAVIS
01/05/2015



IND 063307

MEETING MINUTES

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, PhD
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INT 747 (obeticholic acid).

We also refer to the meeting between representatives of your firm and the FDA on November 18, 2014. The purpose of the meeting was to discuss the content and format of the planned NDA submission for INT-747 (obeticholic acid) for the treatment of primary biliary cirrhosis (PBC) for patients with inadequate response to or unable to tolerate ursodeoxycholic acid.

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 me at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
RESPONSE TO FDA PRELIMINARY COMMENTS DATED 14NOV2014
IND 066307/ NDA 207999



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 18, 2014, 9:00 a.m. - 10:00 a.m.
Meeting Location: FDA White Oak, Bldg 22

Application Number: IND 063307
Product Name: INT-747 (obeticholic acid)
Indication: **treatment of patients with primary biliary cirrhosis**
Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Meeting Chair: Dr. Lara Dimick-Santos
Meeting Recorder: CDR Anissa Davis-Williams

FDA ATTENDEES

Julie Beitz, M.D., Director, Office of Drug Evaluation III
Donna Griebel, M.D., Director, DGIEP
Lara Dimick, M.D., F.A.C.S., Medical Team Leader, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Ruby Mehta, M.D., Medical Officer, DGIEP
Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M., Senior Regulatory Project Manager, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Dinesh Gautam, Ph.D., Pharmacology Reviewer, DGIEP
Yeh-Fong Chen, Ph.D., Statistical Reviewer, DBIII
Benjamin P. Vali, M.S., Statistical Reviewer, DBIII
Sue-Chih Lee, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology 3, OCP
Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, Division of Clinical Pharmacology 3, OCP
Tien-Mien Chen, Ph.D., Biopharmaceutic reviewer, Division of Biopharmaceutics, ONDP, OPQ
Menfo Imoisili, M.D., medical officer, Office of Orphan Product Development
Nyedra Booker, Pharm. D., M.P.H., Risk Management Analyst, Division of Risk Management (DRISK)

EASTERN RESEARCH GROUP ATTENDEES

Patrick Zhou, Independent Assessor
Chris Sese, Independent Assessor

SPONSOR ATTENDEES

INTERCEPT PHARMACEUTICALS, INC

Linda Robertson, Ph.D., Vice President, Regulatory Affairs and Quality Assurance

David Shapiro, M.D., F.R.C.P., Chief Medical Officer

Leigh MacConell, Ph.D., Vice President, Clinical Development

Mark Young, Ph.D., Vice President, Nonclinical Development

Melissa Rewolinski, Ph.D., Vice President, Product Development

Maeve McDonnell, Ph.D., Director, Regulatory Affairs

Jeffrey Edwards, Ph.D., Director of Clinical Pharmacology and DPMK

Roya Hooshmand-Rad, M.D., Ph.D., Exec. Director Clinical Research

Tonya K. Marmon, Dr.P.H., Director, Biostatistics and Data Management

(b) (4), M.D., Regulatory Consultant

1.0 BACKGROUND

Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist being developed in the United States (US) and Europe for the treatment of patients with primary biliary cirrhosis (PBC) and other chronic liver diseases. OCA has been granted Orphan Drug Designation in the US (09 Apr 2008) and Orphan Medicinal Product Designation in the European Union (EU) (27 Jul 2010) for the treatment of PBC. This IND was also granted Fast Track on May 27, 2014.

On September 11, 2014, Intercept Pharmaceuticals, Inc. requested a Pre-NDA meeting to discuss the content and format of the planned NDA submission for INT-747 (obeticholic acid) for the treatment of primary biliary cirrhosis (PBC) for patients with inadequate response to or unable to tolerate ursodeoxycholic acid (URSO, UDCA). NDA number has already been assigned, NDA 207999.

On October 2, 2014, the meeting was granted and scheduled to occur on November 18, 2014, via face-to-face meeting at the Silver Spring, MD location of the Food and Drug Administration.

2. DISCUSSION

Questions provided by Intercept Pharmaceuticals, Inc. (Intercept) are in plain text. Responses provided by the FDA on November 14, 2014 are in **bold text**. Comments provided by Intercept on November 17, 2014 are in *italics*. Meeting Discussion on November 18, 2014 is in ***bold italics***.

2.1. Questions and Responses

Question 1: Does the Division agree with the overall format and content of the filing dossier (ie, nonclinical, pharmaceutical development, and clinical development) to support the planned NDA for accelerated approval of OCA in the treatment of PBC?

FDA Response to Question 1:

No, we do not agree. In your NDA, you will need to submit validation reports for the analytical methods used for measuring OCA and its conjugates in humans, as well as in-study bioanalytical reports for each of the clinical studies. It does not appear that you listed these sections in Table A1: eCTD Table of Contents for OCA in the Treatment of PBC.

The listed nonclinical studies and clinical content appear to be adequate to support the NDA application.

Also see and address Biopharmaceutics and Clinical Pharmacology comments in “Additional Comments”, Section 2.2. Additional Comments are not refuse to file issues; however, they will need to be addressed eventually (if not in the NDA submission, then as post approval studies/trials).

Intercept comments dated November 17, 2014:

Thank you very much for your comments regarding the adequacy of the filing dossier to support submission of an NDA for accelerated approval of OCA in the treatment of patients with PBC. As advised, we will submit validation reports for the measurement of OCA and its conjugates in humans as well as bioanalytical reports for each of the relevant clinical studies in the NDA. Their omission in Table A1 was an oversight. Our responses to Biopharmaceutics and Clinical Pharmacology comments are detailed below.

Additional Discussion:

Intercept will submit validation and in-study bioanalytical reports as suggested. FDA stated that the content appears to be adequate for submission.

Question 2: Does the Division concur with the planned statistical analyses proposed for the ISE as described in the SAP (see Appendix F) including the study grouping, side-by-side comparisons of the individual safety and efficacy studies supported by the pooling approach, the handling of treatment groups in the LTSE phases to address the variable dosing regimens allowed in the LTSEs, and the proposed statistical analyses of the primary and secondary efficacy variables?

FDA Response to Question 2:

Your analysis approach appears reasonable.

Additional Discussion:

No additional discussion needed

Question 3: Does the Division concur with the planned statistical analyses proposed for the ISS as described in the SAP (see Appendix F) including the study grouping as described below, the pooling approach, the handling of treatment groups in the LTSE phases to address the variable dosing regimens allowed in the LTSEs, and the adverse events of special interest?

FDA Response to Question 3:
Your analysis approach appears reasonable.

Additional Discussion:
No additional discussion needed

Question 4: Does the Agency agree with our proposal to initiate a rolling submission in Q42014 comprised of Module 4 and the supporting nonclinical written and tabulated summaries of Module 2 (2.6.1 – 2.6.7)?

FDA Response to Question 4:
Yes, this is acceptable.

Additional Discussion:
Intercept stated that the remaining modules will be submitted to the NDA in approximately June 2015.

Post Meeting Addendum:
FDA utilized the rolling submission proposal in the briefing package as an official rolling submission request and issued a formal granted letter on November 18, 2014.

Intercept should supply the list of the clinical and manufacturing sites in module 1.6.2., with a clear module section title so reviewers can easily identify the document. This should contain a list of the sites, with the address and name(s) of the investigator for each site. Please refer to section 6.0 for additional information.

Question 5: Does the Division concur that the proposed scope of post-marketing pharmacovigilance activities is appropriate to ensure patient safety in the commercial setting?

FDA Response to Question 5:
We are unable to provide an answer at this time. This will be a review issue. However, given the increase in cholesterol and LDLs you have observed in your clinical trials, in the trial you propose to conduct to verify clinical benefit, you should perform a systematic assessment for cardiovascular outcomes of non-fatal stroke, non-fatal myocardial infarction and cardiovascular death.

Intercept comments dated November 17, 2014:
Thank you very much for your feedback. We are fully committed to providing appropriate patient safety oversight in the commercial setting. To ensure appropriate post-marketing pharmacovigilance in patients treated with OCA, the proposed prescribing information will advise healthcare providers to regularly monitor patient serum lipid levels (in conjunction with routine monitoring of liver tests). In addition, and consistent with the above

recommendation, we will be performing a careful assessment of cardiovascular outcomes as a part of the confirmatory clinical outcomes trial, Study 747-302. In this large Phase 3b study, cardiovascular events will be prospectively and independently adjudicated, and the cardiovascular safety of OCA will be further evaluated based on the incidence of important cardiovascular events (major adverse cardiovascular events [MACE]) including oversight by an independent Data and Safety Monitoring Committee (DSMC).

It should be noted that hypercholesterolemia, often involving an increase in HDL cholesterol, is a common feature in PBC patients^{1,2}. In clinical trials of OCA in the treatment of PBC patients, mean baseline HDLc levels were somewhat elevated. Although a decrease was observed, mean HDLc levels remained above the lower limit of normal in OCA treated subjects. The reduction was evident by 2 weeks after starting OCA and remained stable for the duration of the trials. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in subjects with PBC, while low density lipoprotein cholesterol (LDLc) and triglyceride concentrations remained in general comparable to baseline and placebo throughout much of the treatment period. The clinical relevance of the decrease in HDLc is unknown, especially for subjects with PBC given their relative high baseline HDLc.

Additional Discussion:

Intercept will submit a detailed plan for adjudication of cardiovascular events for the FDA to review. FDA and Intercept agreed that the trial may proceed as planned in parallel with FDA review of the adjudication plan.

2.2. ADDITIONAL FDA COMMENTS

Biopharmaceutics Comments:

- 1. Dissolution Testing: Include the dissolution method report supporting the selection of the proposed test. This report should include the following information:**
 - a. Solubility data for the drug substance as a function of pH range;**
 - b. Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least $\frac{(b)}{(4)}$ % of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;**

¹ Longo et al Gut 2002 51:265-9

² Sorokin et al Atherosclerosis 2007 194:293-9

- c. **Provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative drug release with time; and**
 - d. **Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).**
2. **Dissolution Acceptance Criteria: Provide the complete dissolution profile data (i.e., 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, and 12) from the clinical and stability registration batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the drug dissolution acceptance criteria, the following points should be considered:**
- a. **The in vitro dissolution specifications should encompass the timeframe over which at least $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.**
 - b. **Data from the lots used in the clinical trials and primary stability studies must be used.**
 - c. **The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.**

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the provided data.

Intercept comments dated November 17, 2014:

Thank you very much for your feedback. As agreed during the CMC Type C meeting held on 14 Nov 2013 and described above, we will include a detailed dissolution method report supporting selection of the proposed test and the release criteria in the NDA.

Additional Discussion:

Intercept will submit a meeting request to the IND for written responses only, for discussion of the dissolution method development. This will be submitted after the first rolling submission to the NDA. Intercept may request a follow up teleconference, if needed, after review of the FDA's responses.

Clinical Pharmacology Comments:

- a. Please refer to the Written Response sent to you on February 5, 2014. We again recommend that you address the effect of gastric-acid reducing agents (e.g., Proton Pump Inhibitors, H2-blockers and antacids) on the absorption of the drug from your proposed product, and the consequent changes in the systemic exposure of OCA and its conjugates. It does not appear that you have done so based upon the List of Clinical Pharmacology Studies submitted in this meeting package.
- b. You also need to refer to the comments from the February 5th, 2014 written responses regarding renal impairment study and effect of OCA and its conjugates on the PK of Bupropion and Repaglinide.

Intercept comments dated November 17, 2014:

Thank you very much for your feedback. Consistent with comments from the 5 February 2014 written responses, we are addressing the potential effect of gastric-acid reducing agents on the pharmacokinetics of OCA as a part of our clinical program. Study 747-112 will specifically assess the effect of omeprazole, a proton pump inhibitor, on the steady-state plasma PK of OCA in healthy adult subjects. In addition, the ISE will include integrated assessments of the effect of concomitant use of gastric-acid reducing agents on efficacy parameters, and pharmacometric modeling and simulation approaches will be taken to characterize the effect of potential covariates, including gastric-acid reducing agents, on plasma OCA concentrations and PK model parameters. In addition, the ISE will include integrated assessments of the effect of concomitant use of gastric-acid reducing agents on efficacy parameters and pharmacometric modeling and simulation approaches will be taken to characterize the effect of potential covariates, including gastric-acid reducing agents, on plasma OCA exposure. In addition, [REDACTED] (b) (4) [REDACTED]. We are further assessing the need for additional post-approval DDI studies, including bupropion and repaglanide, based on ongoing in vitro studies using a different and more physiologically appropriate in vitro hepatocyte preparation (sandwich culture system).

Additional Discussion:

Intercept will also submit the data to the NDA for pH solubility and buffer solubility in support of the gastric-acid reducing effects.

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Please see above responses, comments, additional discussions and post meeting addendums for details.
- 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 at this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components. However, in addition, we note that a chemistry pre-submission meeting was held on November 13, 2013. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

4.0 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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change

5.0 PRESCRIBING INFORMATION

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

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

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

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under PDUFA V. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

6.0 Office of Scientific Investigations (OSI) Requests

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

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

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

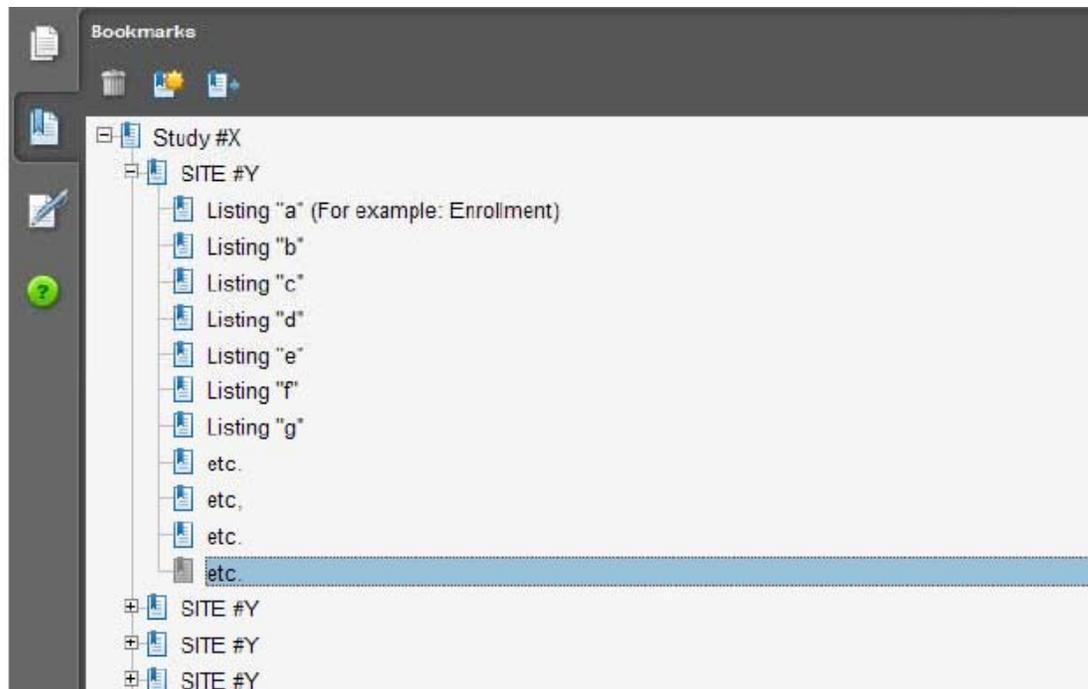
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.

- c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft “Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ³	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.

³ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

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

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

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

7.0 ISSUES REQUIRING FURTHER DISCUSSION

None at this time.

8.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit Type C “Written Response Only” meeting request regarding dissolution method development.	Intercept	TBD; however, after the initiation of the rolling review to NDA.

9.0 ATTACHMENTS AND HANDOUTS

Intercept responses dated November 17, 2014, to the FDA’s preliminary comments dated November 14, 2014.

**RESPONSE TO FDA PRELIMINARY COMMENTS DATED 14NOV2014
IND 066307/ NDA 207999**

Questions from Intercept Pharmaceuticals, Inc. (Intercept) are in plain text. The preliminary FDA responses sent to Intercept on Nov 14, 2014 are in *italics*. The Intercept comments are in **bold**.

Question 1. Does the Division agree with the overall format and content of the filing dossier (ie, nonclinical, pharmaceutical development, and clinical development) to support the planned NDA for accelerated approval of OCA in the treatment of PBC?

FDA Response:

No, we do not agree. In your NDA, you will need to submit validation reports for the analytical methods used for measuring OCA and its conjugates in humans, as well as in-study bioanalytical reports for each of the clinical studies. It does not appear that you listed these sections in Table A1: eCTD Table of Contents for OCA in the Treatment of PBC.

The listed nonclinical studies and clinical content appear to be adequate to support the NDA application.

Also see and address Biopharmaceutics and Clinical Pharmacology comments in “Additional Comments”, Section 2.2. Additional Comments are not refusal to file issues; however, they will need to be addressed eventually (if not in the NDA submission, then as post approval studies/trials).

Intercept comments:

Thank you very much for your comments regarding the adequacy of the filing dossier to support submission of an NDA for accelerated approval of OCA in the treatment of patients with PBC. As advised, we will submit validation reports for the measurement of OCA and its conjugates in humans as well as bioanalytical reports for each of the relevant clinical studies in the NDA. Their omission in Table A1 was an oversight. Our responses to Biopharmaceutics and Clinical Pharmacology comments are detailed below.

Question 2: Does the Division concur with the planned statistical analyses proposed for the ISE as described in the SAP (see Appendix F) including the study grouping, side-by-side comparisons of the individual safety and efficacy studies supported by the pooling approach, the handling of treatment groups in the LTSE phases to address the variable dosing regimens allowed in the LTSEs, and the proposed statistical analyses of the primary and secondary efficacy variables?

FDA Response:

Your analysis approach appears reasonable.

Intercept comments:

Thank you very much for your feedback. No further discussion is required.

Question 3: Does the Division concur with the planned statistical analyses proposed for the ISS as described in the SAP (see Appendix F) including the study grouping as described below, the pooling approach, the handling of treatment groups in the LTSE phases to address the variable dosing regimens allowed in the LTSEs, and the adverse events of special interest?

FDA Response:

Your analysis approach appears reasonable.

Intercept comments:

Thank you very much for your feedback. No further discussion is required.

Question 4: Does the Agency agree with our proposal to initiate a rolling submission in Q42014 comprised of Module 4 and the supporting nonclinical written and tabulated summaries of Module 2 (2.6.1 – 2.6.7)?

FDA Response :

Yes, this is acceptable.

Intercept comments:

Thank you very much for your feedback. No further discussion is required.

Question 5: Does the Division concur that the proposed scope of post-marketing pharmacovigilance activities is appropriate to ensure patient safety in the commercial setting?

FDA Response:

We are unable to provide an answer at this time. This will be a review issue. However, given the increase in cholesterol and LDLs you have observed in your clinical trials, in the trial you propose to conduct to verify clinical benefit, you should perform a systematic assessment for cardiovascular outcomes of non-fatal stroke, non-fatal myocardial infarction and cardiovascular death.

Intercept comments:

Thank you very much for your feedback. We are fully committed to providing appropriate patient safety oversight in the commercial setting. To ensure appropriate post-marketing pharmacovigilance in patients treated with OCA, the proposed prescribing information will advise healthcare providers to regularly monitor patient serum lipid levels (in conjunction with routine monitoring of liver tests). In addition, and consistent with the above recommendation, we will be performing a careful assessment of cardiovascular outcomes as a part of the confirmatory clinical outcomes trial, Study 747-302. In this large Phase 3b study, cardiovascular events will be prospectively and independently adjudicated, and the cardiovascular safety of OCA will be further evaluated based on the incidence of important cardiovascular events (major adverse cardiovascular events [MACE]) including oversight by an independent Data and Safety Monitoring Committee (DSMC).

It should be noted that hypercholesterolemia, often involving an increase in HDL cholesterol, is a common feature in PBC patients^{1,2}. In clinical trials of OCA in the treatment of PBC patients, mean baseline HDLc levels were somewhat elevated. Although a decrease was observed, mean HDLc levels remained above the lower limit of normal in OCA treated subjects. The reduction was evident by 2 weeks after starting OCA and remained stable for the duration of the trials. Commensurate with decreases in HDLc, decreases in total cholesterol were observed in subjects with PBC, while low density lipoprotein cholesterol (LDLc) and triglyceride concentrations remained in general comparable to baseline and placebo throughout much of the treatment period. The clinical relevance of the decrease in HDLc is unknown, especially for subjects with PBC given their relative high baseline HDLc.

¹ Longo et al Gut 2002 51:265-9

² Sorokin et al Atherosclerosis 2007 194:293-9

ADDITIONAL FDA COMMENTS

Biopharmaceutics Comments:

- 1. Dissolution Testing: Include the dissolution method report supporting the selection of the proposed test. This report should include the following information:*
 - a. Solubility data for the drug substance as a function of pH range;*
 - b. Detailed description of the dissolution method being proposed for the evaluation of your product and the developmental parameters (i.e., selection of the equipment/apparatus, dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.). If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. If possible, the dissolution profile should be complete and cover at least (b)(4)% of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend use of at least twelve samples per testing variable;*
 - c. Provide the complete dissolution profile data (individual, mean, SD, profiles) for your product. The dissolution data should be reported as the cumulative drug release with time; and*
 - d. Include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).*
- 2. Dissolution Acceptance Criteria: Provide the complete dissolution profile data (i.e., 10, 20, and 30 minutes; 1, 2, 4, 6, 8, 10, and 12) from the clinical and stability registration batches supporting the selection of the dissolution acceptance criteria (i.e., specification-sampling time points and specification values). For the setting of the drug dissolution acceptance criteria, the following points should be considered:*
 - a. The in vitro dissolution specifications should encompass the timeframe over which at least (b)(4)% of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.*
 - b. Data from the lots used in the clinical trials and primary stability studies must be used.*
 - c. The dissolution acceptance criteria should be set in a way to ensure consistent performance from lot to lot and these criteria should not allow the release of any lots with dissolution profiles outside those that were tested clinically.*

Note that the final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA. However, the acceptability of the proposed dissolution acceptance criteria for your product will be made during the NDA review process based on the totality of the provided data.

Intercept comments:

Thank you very much for your feedback. As agreed during the CMC Type C meeting held on 14 Nov 2013 and described above, we will include a detailed dissolution method report supporting selection of the proposed test and the release criteria in the NDA.

Clinical Pharmacology Comments:

1. Please refer to the Written Response sent to you on February 5, 2014. We again recommend that you address the effect of gastric-acid reducing agents (e.g., Proton Pump Inhibitors, H₂-blockers and antacids) on the absorption of the drug from your proposed product, and the consequent changes in the systemic exposure of OCA and its conjugates. It does not appear that you have done so based upon the List of Clinical Pharmacology Studies submitted in this meeting package.

2. You also need to refer to the comments from the February 5th, 2014 written responses regarding renal impairment study and effect of OCA and its conjugates on the PK of Bupropion and Repaglinide.

Intercept comments:

Thank you very much for your feedback. Consistent with comments from the 5 February 2014 written responses, we are addressing the potential effect of gastric-acid reducing agents on the pharmacokinetics of OCA as a part of our clinical program. Study 747-112 will specifically assess the effect of omeprazole, a proton pump inhibitor, on the steady-state plasma PK of OCA in healthy adult subjects. In addition, the ISE will include integrated assessments of the effect of concomitant use of gastric-acid reducing agents on efficacy parameters, and pharmacometric modeling and simulation approaches will be taken to characterize the effect of potential covariates, including gastric-acid reducing agents, on plasma OCA concentrations and PK model parameters. In addition, the ISE will include integrated assessments of the effect of concomitant use of gastric-acid reducing agents on efficacy parameters and pharmacometric modeling and simulation approaches will be taken to characterize the effect of potential covariates, including gastric-acid reducing agents, on plasma OCA exposure. In addition, (b) (4)

We are further assessing the need for additional post-approval DDI studies, including bupropion and repaglanide, based on ongoing in vitro studies using a different and more physiologically appropriate in vitro hepatocyte preparation (sandwich culture system).

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/s/

ANISSA A DAVIS
11/24/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063307

GRANT ROLLING REVIEW

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, PhD
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INT-747 (obeticholic acid).

We also refer to your October 20, 2014, request for rolling submission and review of portions for review of your planned New Drug Application (NDA) for INT-747 (obeticholic acid), which was designated Fast Track for the treatment of primary biliary cirrhosis.

We have reviewed and accept your request and plan for submitting portions of the proposed application.

If the Fast Track designation for INT-747 (obeticholic acid) for primary biliary cirrhosis is rescinded, submission of portions of the NDA will not be permitted under this program.

For further information regarding Fast Track designation, please refer to the FDA *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*¹.

If you have any questions, contact CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

IND 063307
Page 2

Center for Drug Evaluation and Research

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/s/

DONNA J GRIEBEL
11/18/2014



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063307

GRANT FAST TRACK

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4350 La Jolla Village Drive
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INT-747 (obeticholic acid).

We also refer to your April 4, 2014, request for Fast Track designation. We have reviewed your request and concluded that it meets the criteria for the Fast Track designation. Therefore, we are designating as a Fast Track development program the investigation of INT-747 (obeticholic acid) for treatment of patients with primary biliary cirrhosis. Please note that if the clinical development program you pursue does not continue to meet the criteria for Fast Track designation, the application will not be reviewed under the Fast Track program.

For further information regarding Fast Track Drug Development Programs, please refer to the FDA document "Guidance for Industry on Fast Track Drug Development Programs: Designation, Development, and Application Review". This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079736.pdf> or may be requested from the Office of Communications, Division of Drug Information at 301-796-3400 or 1-888-463-6332.

If you have any questions, contact CDR Anissa Davis-Williams, Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I.
Deputy Director
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

ANDREW E MULBERG
05/27/2014

Executive CAC

Date of Meeting: October 4, 2011

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair
Paul Brown, Ph.D., OND IO, Member
Aisar Atrakchi, Ph.D., DPP, Alternate Member
Sushanta Chakder, Ph.D., DGIEP, Supervisor
Charles Wu, Ph.D., DGIEP Presenting Reviewer

Author of Minutes: Charles Wu, Ph.D.

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

The committee did not address the sponsor's proposed statistical evaluation for the carcinogen bioassays, as this does not affect the sponsor's ability to initiate the bioassays. The sponsor may seek guidance on the statistical evaluation of bioassay results from agency staff separately. Data files should be submitted electronically following the CDER/CBER Guidance for Industry, Providing Regulatory Submission in Electronic Format- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008) and the associated Study Data Specifications document.

IND #: 63307

Submit date: August 29, 2011

Drug Name: INT-747

Sponsor: Intercept Pharmaceuticals

Background

INT-747, a modified bile acid and a farnesoid X receptor (FXR) agonist, is being developed for the treatment of primary biliary cirrhosis. The anticipated therapeutic dose of INT-747 for this indication is ≤ 25 mg/day. The sponsor submitted the rationale for the dose selection for a proposed 2-year oral gavage carcinogenicity study in SD rats and a 2-year oral gavage carcinogenicity study in CD-1 mice.

Rat Carcinogenicity Study Protocol and Dose Selection

The sponsor proposed to conduct a 2-year oral (gavage, 10 mL/kg) carcinogenicity study of INT-747 at 0 (vehicle), 0 (vehicle), 6, 15, and 25 mg/kg/day in Sprague-Dawley rats (n = 65/sex/dose). INT-747 will be administered once daily by gavage, in 0.5% (w/v) carboxymethylcellulose as the vehicle. A complete necropsy will be conducted on all animals (found dead, euthanized *in extremis*, and at scheduled necropsy) and a standard battery of tissues/organs will be processed for histopathological examinations with a peer review.

Based on deaths at the 60 mg/kg/day dose in both males and females in the 26-week studies in rats, the 25 mg/kg/day dose was proposed as the high dose for the 2-year rat carcinogenicity studies.

Mouse Carcinogenicity Study Protocol and Dose Selection

The sponsor proposed to conduct a 2-year oral (gavage, 10 mL/kg) carcinogenicity study of INT-747 at 0 (vehicle), 0 (vehicle), 10, 20, and 30 mg/kg/day in CD-1 mice (n = 65/sex/dose). INT-747 will be administered by oral gavage once daily, in 0.5% (w/v) carboxymethylcellulose as the vehicle. A complete necropsy will be conducted on all animals (found dead, euthanized *in extremis*, and at scheduled necropsy) and a standard battery of tissues/organs will be processed for histopathological examinations with a peer review.

In the 13-week oral repeat dose toxicity study in CD-1 mice, groups of animals were treated with 4, 12, 40 and 120 mg/kg/day. Due to extreme clinical signs observed at the 120 mg/kg/day dose, this dose was reduced to 80 mg/kg/day on Day 8 after a drug holiday from Day 2 through Day 7. There were deaths of male and female animals at the 120/80 mg/kg/day dose. Based on deaths in this dose group, 30 mg/kg/day was proposed as the high dose for the 2-year mouse carcinogenicity study.

Executive CAC Recommendations and Conclusions:

Rat:

- The Committee recommended doses of 2, 7, and 20 mg/kg/day by oral gavage for both males and females, based on deaths observed at 60 mg/kg/day in the 26-week toxicity study.

Mouse:

- The Committee recommended doses of 4, 10, and 25 mg/kg/day by oral gavage for both male and female mice, based on deaths observed at 80 mg/kg/day in the 13-week toxicity study.

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

cc:\

/Division File, DGIEP
/S. Chakder, Ph.D., Supervisor, DGIEP
/C. Wu, Ph.D., Primary Reviewer, DGIEP
/J. Benjamin, Project Manager, DGIEP
/A. Seifried, OND IO

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/s/

ABIGAIL C JACOBS
10/06/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063307

MEETING MINUTES

Intercept Pharmaceuticals, Inc
Attention: Pia Lindström, Dr PH
VP, Regulatory Affairs and Quality Assurance
4370 La Jolla Village Drive, Suite 1050
San Diego, CA, 92122

Dear Dr. Lindström:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INT-747 (obeticholic acid) (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on August 5, 2010. The purpose of the meeting was to discuss your clinical development plan.

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 me at (301) 796-4147.

Sincerely,

{See appended electronic signature page}

Hee (Sheila) Lianos, RPh., PharmD.
Regulatory Project Manager
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

FDA 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: August 5, 2010
1:30 to 2:30 p.m. (EST/DST)

Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: 063307
Product Name: INT -747 (obeticholic acid; 6-ECDCA; 6 α -ethylchenodeoxycholic acid) (b) (4)

Indication: Primary Biliary Cirrhosis
Sponsor/Applicant Name: Intercept Pharmaceuticals, Inc.

Meeting Chair: Hugo Gallo-Torres and Hee (Sheila) Lianos
Meeting Recorder: Hee (Sheila) Lianos

FDA ATTENDEES

Nayyar Anil, M.D.	Medical Officer, Division of Gastroenterology Products (DGP)
Hugo Gallo-Torres, M.D.	Medical Team Lead, DGP
Donna Griebel, M.D.	Division Director, DGP
Andrew Mulberg, M.D.	Deputy Division Director, DGP
Charles Wu, PhD	Non-clinical Reviewer, DGP
Sushanta Chakder, PhD	Non-clinical Supervisor, DGP
Hee (Sheila) Lianos, PharmD	Project Manager, DGP
Marie Kowblansky, PhD	Pharmaceutical Assessment Lead
Wen Jen Chen, PhD	Biostatistician
Jane Bai, PhD	Clinical Pharmacology Reviewer
John Senior, M.D.	Associate Director, Office of Surveillance and Epidemiology
Leonard Seeff, M.D.	Contractor, Business Process Improvement Staff

SPONSOR ATTENDEES

Pia Lindström, Dr PH	Regulatory Affairs
Mark Pruzanski, MD	Founder and CEO
Melissa Rewolinski, PhD	Product Development
David Shapiro, MD	Chief Medical Officer

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

Lorenzo Tallarigo, MD
Intercept Consultants

(b) (4), MD
(b) (4), MSc
(b) (4), MD
(b) (4), MD

Chairman

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

1.0 BACKGROUND

May 24, 2010	The Agency received and granted a May 21, 2010, meeting request from Intercept Pharmaceuticals for the purpose of discussing their end of phase 2 data.
February 1, 2007	A meeting was scheduled between Intercept Pharmaceuticals and the FDA to discuss the end of phase 1 (EOP1) studies for INT-747. In the subsequent meeting minutes, the Agency stated that the usefulness of serum alkaline phosphatase (ALP), as a primary efficacy endpoint in patients with primary biliary cirrhosis (PBC), can only be discussed after the appropriate phase 2 studies have been conducted and the FDA has reviewed the resulting data.
January 30, 2006	Original Investigational New Drug application (IND) 063307 for INT-747 was received by the FDA.
October 27, 2004	<p>A meeting between Intercept Pharmaceuticals and the FDA was scheduled to discuss the clinical evaluation of INT-747. The Agency provided preliminary responses to Intercept on October 21, 2004. Intercept decided to accept the Agency's preliminary responses in lieu of the October 27, 2004, meeting.</p> <p>Questions in Intercept's background materials, dated September 24, 2004, were in regard to their non-clinical plan, proposed phase 1 clinical study design and quality control measures that should be taken for the manufacture and use of INT-747 at the phase 1 stage. The Agency provided items to consider for the safety and tolerability of INT-747 in patients with liver fibrosis and Hepatitis C. It was also conveyed to the Sponsor that although serum biomarkers of liver fibrosis may be acceptable for exploratory studies, phase 3 studies should have primary endpoints that are clinically meaningful.</p>

Following introductions, Intercept's questions, from the July 1, 2010, background information package, were used as the basis for further discussion regarding their clinical study and other supportive data (as submitted).

The format of these minutes provides for Intercept's questions in regular typeface, followed by the Agency's responses in **bolded print**, followed by the August 5, 2010, meeting discussion in *italic and bolded print*.

2. DISCUSSION

Intercept Pharmaceuticals agreed with the Agency's preliminary responses to the following questions 5, 8,10,12,18 and 19.

2.1. Overall Program and Primary Endpoint

Intercept, as discussed in earlier regulatory meetings, proposes to use plasma alkaline phosphatase (ALP), specifically relative ALP fall, as the primary efficacy endpoint.

***Question 1** Does the Division agree that if both efficacy and appropriate safety are demonstrated, the proposed studies will provide sufficient data for approval?*

FDA Response:

We are concerned about the proposed primary endpoint of relative decrease in alkaline phosphatase (ALP) as a surrogate for clinical outcome, in patients with primary biliary cirrhosis (PBC), for the phase-3 trials. Please see our response to question 2 regarding primary efficacy assessments.

***Question 2** Does the Division agree that, in the context of the proposed program, ALP is an appropriate endpoint to demonstrate efficacy in support of approval?*

FDA Response:

No, we do not agree. As conveyed to you during your February 1, 2007, and October 6, 2009, meetings with the FDA, we do not agree that the proposed surrogate endpoint, % change in ALP, is an appropriate primary endpoint to evaluate the efficacy of INT-747 in patients with PBC. We do not believe that ALP, as stand alone, can be accepted as the primary endpoint at the current time. We have the following comments and recommendations:

- i. We are not opposed to the use of surrogate endpoints to support an accelerated approval for INT-747 for the treatment of PBC. However, the information you have provided in the briefing package does not provide enough evidence to justify the use of ALP as a surrogate endpoint.**
- ii. You should propose responder definition criteria that are based on multiple levels of ALP reduction, with or without a composite endpoint with multiple biochemical tests, which can reasonably predict benefit in some of the clinically meaningful outcomes during the disease progression (e.g., portal**

hypertension, ascites, and pruritus). You may use information from your portal hypertension (PHT) trial (if successful) to propose reduction in hepatic venous pressure gradient (HVPG) as one of the interim efficacy measures.

- iii. PBC is a slowly progressive condition. It may not be possible to demonstrate clinical benefit, in patients with early and stable disease, with short duration trials. We recommend you to enroll patients with moderate and severe disease so that clinical outcome may be measured during your trials.
- iv. In addition, you should propose a trial or an approach for continued monitoring of efficacy and safety in patients enrolled in your phase 3 trials. This may include continuing the use of obeticholic acid (OCA) in order to demonstrate benefit in overall survival, need for liver transplantation, or time to transplant.
- v. Most of the data and justification for your proposed surrogate (i.e., ALP) are related to the prognosis in patients with PBC who are still taking UDCA. OCA is a new molecular entity (NME). Therefore, OCA may have other effects (favorable or adverse) on liver function/histology that may impact its efficacy and safety profile which is not yet available. Since pruritus is an unfortunate symptom in PBC patients, we are also concerned about a dose-related increase in incidence of pruritus from your phase 1 and phase 2 trials. Therefore, additional information on efficacy and safety will be useful in determining the net benefit.

Additional Comments:

You propose a duration of (b) (4) for your phase 3 trials. This may not be adequate to demonstrate clinically meaningful benefit. We encourage you to consider a longer duration of treatment so that interpretable data can be generated from your trials.

Meeting Discussion:

The Division did not agree that ALP alone would be considered an appropriate endpoint to demonstrate efficacy and that it was an applicant's responsibility to show that the proposed surrogate endpoint is reasonably associated with clinical benefit when requesting approval under the Subpart H program . The Division encouraged Intercept to maintain a dialog for their clinical program as they work to find a viable surrogate endpoint.

2.2. RECRUITMENT

Although the Sponsor plans to recruit a new group of patients into the phase 3 studies, the Sponsor would like to re-enroll the patients from the phase 2 program if recruitment proves to be difficult. In either case, the Sponsor believes that patients who received placebo in the double blind (DB) phases of either Study 747-202 or Study 747-201, but did not participate in the long

term safety extension (LTSE), would be eligible. Eligible patients will have been off obeticholic acid (OCA; INT-747) treatment for at least 6 months before being enrolled in a phase 3 study.

Question 3 *Does the Division agree that this enrollment plan is acceptable?*

FDA Response:

Patients that received placebo in the double-blind phases of either study 747-202 or 747-201 may be enrolled in a randomized fashion.

- **Please clarify the statement that eligible patients will have been off OCA treatment for at least 6 months before enrollment.**

2.3. STRATIFICATION

In Studies 747-301 and 747-302, the Sponsor proposes to stratify patients according to the following criteria:

- Disease prognostic risk and prior response to UDCA therapy – (“Paris criteria”)
[Corpechot 2008]: ALP > 3 x upper limit of normal (ULN) or aspartate aminotransferase (AST) > 2 x ULN or bilirubin > 1.0 mg/dL (17 mmol/L) 1 year post UDCA

These patients have worse survival and increased liver transplant risk. The proportion of patients who change from a positive to negative Paris criteria will be assessed as a secondary endpoint.

- Monotherapy

In addition, in Study 747-302, patients not on UDCA therapy will be stratified separately.

Question 4 *Does the Division agree that these are appropriate stratification criteria for the phase 3 protocols?*

FDA Response:

Stratification of PBC patients is important due to small size of the trials. There are several confounding variables that may affect the endpoints of the trials. Therefore balanced representation between the treatment groups through adequate stratification is crucial. We recommend that stratification be done at enrollment based on published guidelines by the AASLD¹ and patients with features of overlap syndrome and autoimmune hepatitis be excluded.

Additional Comments:

INT-747, a farnesoid X receptor (FXR) agonist, is a NME and has a different mechanism of action from UDCA, which is approved for the treatment of PBC. Therefore, additional information effects of INT-747 on liver histology will be important. We recommend that all enrolled patients have baseline liver biopsy and a follow up liver biopsy (performed at the end of the trial in a subset of patients) for evaluation of improvement, deterioration or no deterioration in selected markers of liver injury on histology. The patient subset should include an adequate number of patients from each category: with or without biochemical, and clinical improvement.

¹ Silveira MG et al. American Association for the Study of Liver Diseases endpoints conference: Design and Endpoints for clinical Trials In Primary Biliary Cirrhosis. Hepatology 2010, 52 (1): 349-59.

2.4. ENHANCED LIVER FIBROSIS MARKERS AND TRANSIENT ELASTOGRAPHY

The Sponsor plans to use both the non-invasive enhanced liver fibrosis (ELF) blood markers and transient elastography (TE) as exploratory secondary endpoints to assess fibrosis. Neither of these tests is currently FDA approved.

Question 5 Does the Division agree that the use of these tests in the phase 3 studies is appropriate?

FDA Response:

Yes, we agree. These non- invasive enhanced liver fibrosis (ELF) blood markers and transient elastography (TE) may be used as exploratory secondary endpoints to assess fibrosis.

2.5. DURATION AND PATIENT EXPOSURE

The Sponsor plans to have evaluated nearly 600 patients in the clinical trials, approximately 500 of whom will have received drug by mid 2013 when the New Drug Application (NDA) is planned. By then, almost 450 patients will have participated in the PBC studies, over 375 randomized to receive OCA in the DB phase. In addition, approximately 280 patients will have been studied in the National Institute of Health (NIH) nonalcoholic steatohepatitis (NASH) Clinical Research Network's FLINT study (although data will not likely be available until mid 2014); of these 140 will receive OCA for 18 months. It is therefore estimated that there will be nearly 475 patient years of experience by the time the NDA/Marketing Authorization Application (MAA) is filed. This will rise to approximately 600 patient years at the time of a Safety Update Report 6 months after the projected NDA/MAA filing.

Question 6 Does the Division agree that the program patient numbers are sufficient to obtain marketing approval for PBC?

FDA Response:

INT-747 is intended for the long-term treatment of PBC. It is your responsibility, as a sponsor, to carry out the adequate safety evaluation during clinical drug development based on the occurrence and detection of adverse events (AE profile). (Please refer to the International Conference on Harmonisation (ICH) Guideline E1: *The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions.*)

2.6. OTHER PHARAMCOLOGY STUDIES

Liver impairment – portal hypertension

Obeticholic acid has been shown to reduce portal pressure in 2 preclinical models and the Sponsor is now planning to conduct a study in patients with portal hypertension. The study, which will not be blinded, will be conducted in 2 'steps' for each dose.

- An evaluation of safety, followed by direct portal catheterization
- Assessment of portal circulation hemodynamics

This study will provide some data on plasma drug concentrations in cirrhotic patients (Child Pugh scores 7 to 12). It is not anticipated that the absorption or conjugation of the drug will

differ greatly compared with non cirrhotic subjects. In addition, the study will provide some pilot efficacy data about drug effects in portal hypertension (neutral, adverse, or beneficial) .

Question 7 *Does the Division agree that a study in patients with portal hypertension will provide the appropriate data for OCA in populations with cirrhosis?*

FDA Response:

In order to understand the pharmacokinetic (PK) characteristics in patients with severe liver impairment, we recommend that you measure the plasma levels of both liver enzymes and bilirubin in your safety monitoring. You should include an adequate number of patients to allow for statistically meaningful calculations of PK parameters in Study 747-204 (your PK study in patients with portal hypertension).

Renal Disease

Bile acids are excreted almost exclusively via the fecal route in healthy individuals, and the data for OCA are consistent with this. In the multiple dose normal volunteer study (747-102) < 0.25% of the drug was excreted via the urine (mainly as the glycine conjugate). There were no clinically meaningful changes in renal biochemistry seen in either the diabetes/nonalcoholic fatty liver disease (NAFLD) study (747-203) or the PBC study (747-202) and renal adverse events (AEs) were not seen with increased frequency in the OCA treated patients in either study. The effects of OCA therapy on renal function and AEs will be assessed in each study and across the entire program. Patients with hepatorenal syndrome will be excluded from the phase 3 studies.

The Sponsor does not believe that a study in renally impaired patients is warranted and considers that dose modification should not be necessary in patients with concomitant renal disease.

Question 8 *Does the Division agree that a study in renally impaired patients is not warranted?*

FDA Response:

Based on your submitted data, we agree.

Cardiac Conduction

PBC is not associated with cardiac conduction defects or arrhythmias and bile acids are not known to prolong cardiac ventricular repolarization. The electrocardiographic (ECG) data, read by a single reader, to date have not shown a signal of concern. The Sponsor plans to collect digital ECGs in the phase 3 program. The Sponsor believes that the risk of torsade de pointes is far exceeded by the potential benefit of treatment. Accordingly, (b) (4)

(b) (4) orphan-designated program.

Question 9 *Does the Division agree (b) (4)*

FDA Response:

(b) (4) **You are required to perform a TQT study.**

Drug and Food Interaction

The Sponsor considers that the in vitro CYP450 isoenzyme inhibition and induction data indicate that it is unlikely that OCA will cause meaningful drug interactions. There were no meaningful changes in ursodeoxycholic acid (UDCA) blood levels in Study 747-202 and this will continue to be assessed in phase 3 in all relevant patients. The Sponsor does not believe that conducting clinical studies to evaluate specific drug-drug interactions due to CYP isoenzymes is warranted.

Question 10 Does the Division agree that the ongoing evaluation of UDCA and OCA plasma levels, together with the in vitro CYP450 studies, conducted and planned, are adequate to allow appropriate drug interaction and dosing recommendations in the product label?

FDA Response:

Please provide your rationale(s) for the irregularities seen in the area under the curve (AUC) accumulation index for obeticholic acid (OCA) and its conjugate metabolites on Day 12 over the dose range studied. The decrease in AUC accumulation index with dose for tauro-OCA, for example, may imply some drug effects on the disposition of OCA. Since OCA is a bile salt analogue, we recommend that you conduct in-vitro studies to understand the interaction between OCA and bile salt export pump (BSEP) activity (i.e., drug-bile interaction). Inhibition of BSEP may cause liver injury. Depending on the in-vitro results of your induction study, with respect to CYP2B6 (as compared to phenobarbital and rifampicin), and your drug-bile interaction study with respect to BSEP, drug-drug interaction (DDI) and drug-bile interaction studies may be needed to show clinical relevance. (Please see below for the reference to our Guidance document on drug interaction studies below.)

Bioequivalence

Given the data seen in the normal volunteers, the Sponsor is not planning to conduct additional food interaction studies which show considerable enterohepatic recirculation of OCA. Similarly, assuming that the in vitro properties of the tablet dosage form is similar to that of the capsules used in the phase 2 studies, the properties of OCA with its extensive enterohepatic recirculation suggest that conducting a human bioequivalence study is not necessary. (The primary need for capsule: tablet proof of equivalence is to support the monotherapy claim based on Study 747-201).

Question 11 Does the Division agree with the Sponsor's plan not to conduct additional clinical pharmacology studies (except blood sampling in the portal hypertension study) in parallel with the phase 3 program?

FDA Response:

See our responses to Questions 9 and 10 above. In addition, if the formulation used in your clinical studies is different from the formulation which will eventually be marketed, a bridging study may be needed. (Please see below for the reference to our Guidance document for general considerations on bioavailability and bioequivalence studies for orally administered drug products).

* *Guidance for Industry: Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling (September 2006)*
(<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>)

* *Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs (Oct 2005)*

* *Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products — General Considerations (March, 2003).*

* *Guidance for Industry: Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation*

2.7. CHEMISTRY, MANUFACTURING AND CONTROLS DATA

This Briefing Document reviews the drug substance (DS) and drug product (DP) manufacturers and release specifications for the phase 3 clinical trial materials. The selection of the Good Manufacturing Practice (GMP) active pharmaceutical ingredient (API) starting material and its release specifications is also discussed. Finally, (b) (4) (b) (4) is discussed.

Proposed Concurrent Validation Plan

The Sponsor proposes to perform concurrent validations of the DS and DP processes, starting with a single production scale batch submitted as a part of the NDA.

Question 12 *Does the Division agree with the plans for NDA filing batch sizes and for concurrent validations of manufacturing processes of drug substance and drug product?*

FDA Response:

When you submit your NDA, it will be acceptable for you to submit information for the drug substance batch sizes ((b) (4) kg and (b) (4) kg) and drug product batch sizes ((b) (4) kg and (b) (4) kg) that you propose. However, you will need to discuss your plans for validating the manufacturing process with the Division of Manufacturing and Product Quality within the Office of Compliance.

Qualified Impurity

The Sponsor proposes to identify (b) (4) Impurity (b) (4) as a Qualified Impurity based on 1) it is a (b) (4), 2) there is significant information available on its commercial use and safety, and 3) the clinical experience with INT-747 drug products containing (b) (4) in the phase 1 and 2 studies.

Question 13 *Does the Division agree with the designation of (b) (4) as a Qualified Impurity and the proposed specifications for (b) (4) (not more than (b) (4)%) in the drug substance and drug product?*

FDA Response:

Since [REDACTED] ^{(b) (4)}, it is considered to be qualified impurity and the proposed ^{(b) (4)}% limit is acceptable.

2.8. NONCLINICAL TOPICS

This Briefing Document summarizes the studies that have been completed to date within the nonclinical safety program (Table 2). Currently, dose range finding studies in mice are ongoing in preparation for rodent carcinogenicity studies. In addition, a pre/postnatal developmental toxicity study in rats is planned to complete the nonclinical safety testing with INT-747.

***Question 14** Does the Division agree with the overall completeness of the nonclinical safety testing program?*

FDA Response:

Yes, we agree.

2.9. REGULATORY TOPICS

Accelerated Approval of New Drugs for Serious or Life Threatening Illnesses.

The Sponsor will seek Accelerated Approval for OCA under the Code of Federal Regulations (CFR) 21, Subpart H, § 314.510 (Approval based on a surrogate endpoint). The Sponsor believes that OCA qualifies as a drug product that has an effect on a surrogate endpoint (ALP) that predicts clinical benefit. The Sponsor also believes that OCA provides meaningful therapeutic benefit to patients as add-on to UDCA treatment.

The official FDA meeting minutes from the End of Phase 1 meeting and the Type C meeting teleconference (Statistical Analysis Plan, Study 202), support this conclusion:

End of Phase 1 meeting minutes, 01 MAR 2007

- “There can be agreement on the potential for [alkaline phosphatase (AP)] AP to serve as a primary endpoint after the appropriate phase 2 studies have been conducted and reviewed. It is apparent at this time that AP would be viewed as a surrogate endpoint from a regulatory perspective and appropriate for a subpart H submission.”

Type C meeting teleconference (Statistical Analysis Plan, Study 202), 06 NOV 2009

- “The Agency refers to the application’s 2007 End of Phase (EOP) 1 meeting where it was indicated that AP would be appropriate for a surrogate to support a subpart H submission. The Agency is evaluating new literature¹⁻² to determine if certain composite markers that have been shown to predict or demonstrate relevance to clinical outcome would be more appropriate surrogate markers compared to AP alone, to evaluate the efficacy. Keeping in view of this recent scientific information AP may not be adequate as a stand alone surrogate to support a future subpart H submission.”

In the phase 3 program, the Sponsor plans to evaluate the treatment response using the Rotterdam and Paris criteria (references 1 and 2, respectively, cited by FDA in the above meeting minutes) to assess composite markers in addition to other solo ALP algorithms developed by Parés 2006 (Barcelona) and Kumagi 2010 (Toronto). The evaluation of these recently developed criteria will address the FDA’s request to evaluate other (than ALP alone) composite markers in these PBC patients, although both of these composite markers are only applicable to a small proportion of PBC patients with inadequate response to UDCA. The Sponsor therefore proposes using these as secondary study endpoints.

The Sponsor believes that the PBC studies are both adequate and well controlled studies. To further support a Subpart H submission, the Sponsor is planning to conduct post marketing phase 4 confirmatory studies to verify the anticipated clinical benefit from OCA. The Sponsor proposes to further discuss these post marketing commitments at the time of the pre NDA meeting.

Question 15 *Does the Division agree that OCA qualifies for an accelerated approval with a post marketing commitment to further study OCA in PBC patients?*

FDA Response:

Please see our responses to questions 2 and 4.

Orphan Designation and Protocol Review.

OCA (INT-747) was granted orphan drug designation for the indication of PBC on 09 APR 2008 by FDA and on 08 APR 2010 by the European Medicines Agency (EMA). The Sponsor understands that orphan product sponsors receive protocol assistance for clinical protocols. As the Sponsor develops the protocols for phase 3 the Sponsor would like to request review and comments from the Division.

Question 16 *Does the Division foresee this as a feasible option, or will Special Protocol Assessment(s) be required?*

FDA Response:

Please refer to our response to question 2. We encourage you to continue discussions with the division to address these issues and reach an agreement before you submit a Special Protocol Assessment (SPA).

Pediatric Waiver and/or Exclusivity.

Since OCA has orphan drug designation for the treatment of PBC, the Sponsor understands that it should be exempt from the requirement to conduct pediatric clinical trials. Pediatric PBC is extremely rare and a literature search revealed only a few reported patients [Dahlan 2003]. It is therefore, essentially unfeasible to conduct studies in pediatric PBC patients. The Pediatric Research Equity Act states:

“Thus, submission of a pediatric assessment is not required for an application to market a product for an orphan-designated indication, and waivers are not needed at this time. However, if only one indication for a product has orphan designation, a pediatric assessment may still be required for any applications to market that same product for the non-orphan indication(s)”.

Thus, the Sponsor concludes that a waiver for a pediatric assessment is not required for OCA in the indication of PBC.

Question 17 *Does the Division agree that OCA in the treatment of PBC would qualify for pediatric exclusivity?*

FDA Response:

(We acknowledge your request to strike out this question per your correspondence (email) dated July 26, 2010)

Monotherapy Claim.

Study 747-201 (monotherapy) involves the once daily administration of OCA at 10 or 50 mg, or placebo as monotherapy for 12 weeks (DB phase) and it is still ongoing. The primary endpoints are change in ALP and safety. An open label LTSE phase is being conducted to allow patients to receive OCA, at least until OCA receives regulatory approval.

The data in this study will be analyzed in a similar manner to that of Study 747-202. The intent to treat (ITT) population will be used for the primary analysis.

Question 18 Does the Division agree that the data from this monotherapy study, if positive, will support a monotherapy claim?

FDA Response:

Please refer to our concern regarding efficacy endpoint phase-3 trials. The claim for monotherapy needs to be supported by well controlled, phase-3 trials assessing efficacy and safety in the target population.

2.10. CARCINOGENICITY STUDIES

Currently, dose range finding studies in mice are ongoing in preparation for rodent carcinogenicity studies. At the time of the anticipated NDA filing (Q2/Q3, 2013), it is possible that the clinical and CMC modules will be completed prior to the final histopathology data analysis from the carcinogenicity studies are available. The Sponsor proposes to submit the NDA with all modules (including Module 4) with the exception of the final histopathology data from the carcinogenicity study. These data would be submitted during the NDA review time.

Question 19 Does the Division agree with the approach to submit the final carcinogenicity data during the NDA review time?

FDA Response:

No, we do not agree. Final study reports of the carcinogenicity studies should be submitted with your New Drug Application (NDA) at the time of submission.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

The Agency will send the Sponsor a separate advice letter to provide further guidance on their clinical plan.

4.0 ACTION ITEMS

There were no action items.

5.0 ATTACHMENTS AND HANDOUTS

There was no formal presentation or delivery of extra materials during the meeting.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-63307

GI-1

INTERCEPT
PHARMACEUTICA
LS INC

INT-747

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

/s/

HEE K LIANOS
09/01/2010

LATE-CYCLE COMMUNICATION
DOCUMENTS



NDA 207999

LATE-CYCLE MEETING MINUTES

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) dated June 27, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for OCALIVA (obeticholic acid) tablets, 5 mg and 10 mg.

We also refer to the Late-Cycle Meeting (LCM) between representatives of your firm and the FDA on March 22, 2016.

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 CDR Anissa Davis-Williams, Senior Regulatory Project Manager at (301) 796-5016

Sincerely,

{See appended electronic signature page}

Lara Dimick-Santos, M.D.
Cross Discipline Team Leader, Medical Reviewer
Division of Gastroenterology and Inborn Errors
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: March 22, 2016; 11:00 a.m. – 12:30 p.m. (EST)
Meeting Location: FDA White Oak; Bldg. 22, Room 1421

Application Number: 207999
Product Name: OCALIVA (obeticholic acid)
Applicant Name: Intercept Pharmaceuticals, Inc.

Meeting Chair: Lara Dimick-Santos
Meeting Recorder: Anissa Davis-Williams

FDA ATTENDEES

Office of Drug Evaluation III

Amy G. Egan, M.D., M.P.H. Deputy Director
LCDR Richard Ishihara Regulatory Scientist

Division of Gastroenterology and Inborn Errors Products

Dragos Roman, M.D. Associate Director
Lara Dimick-Santos, M.D. Cross Discipline Team Leader/Medical Reviewer
Stephanie Omokaro, M.D. Medical Team Leader
Ruby Mehta, M.D. Medical Reviewer
Joette Meyer, PharmD. Associate Director for Labeling
Sushanta Chakder, Ph.D. Pharmacology/Toxicology Team Leader
Tracy Behrsing, Ph.D. Pharmacology/Toxicology Reviewer
Anissa Davis-Williams, RN, M.P.H. Regulatory Project Manager

Office of Clinical Pharmacology

Elizabeth Shang, Ph.D. Clinical Pharmacology Reviewer
Steven Li, Ph.D. Clinical Pharmacology Reviewer
Nitin Mehrotra, Ph.D. Pharmacometrics Team Leader
Dhanajay Marathe, Ph.D. Pharmacometrics Reviewer

Division of Biometrics III

Yeh-Fong Chen, Ph.D. Statistical Team Leader
Min Min, Ph.D. Statistical Reviewer

Office of Pharmaceutical Quality

Hitesh Shroff, Ph.D. Chemistry Reviewer
Tien-Mien Chen, Ph.D. Acting Biopharmaceutics Leader

Peng Duan, Ph.D. Biopharmaceutics Reviewer

Office of Surveillance and Epidemiology

Ling-Yu Wu, Pharm.D. Safety Evaluator Team Leader, Division of Pharmacovigilance
Kimberly Swank, Pharm.D. Safety Evaluator, Division of Pharmacovigilance
Mishale Mistry, Pharm.D., M.P.H. Acting Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)

Clinical Outcome Assessment Staff

Selena Daniels, Pharm.D., M.S. Endpoints Reviewer

Office of Scientific Investigations/Division of Clinical Compliance Evaluation

Susan Leibenhaut, M.D. Medical Reviewer

Division of Advisory Committee and Consultant Management

Cindy Hong, Pharm.D. Designated Federal Officer

Rare Disease Program

Jonathan Goldsmith, M.D. Associate Director

Division of New Drug Bioequivalence

Shila Nkah, M.S. Project Manager

EASTERN RESEARCH GROUP ATTENDEES

Peggha Khorrami, Independent Assessor

APPLICANT ATTENDEES

Linda Robertson, Ph.D.	Vice President , Regulatory Affairs and Quality Assurance
David Shapiro, M.D., FRCP	Chief Medical Officer, Executive Vice President, Development
Leigh MacConell, Ph.D.	Vice President, Clinical Development
Roya Hooshmand-Rad, M.D., Ph.D.	Executive Director, Medical Safety and Pharmacovigilance
Mark Pruzanski, M.D.	Chief Executive Officer
Tonya Marmon, Ph.D.	Senior Director, Biostatistics and Data Management
Mark Young, Ph.D.	Vice President, Non-clinical
Jeffrey Edwards, Ph.D.	Senior Director, Clinical and Preclinical Pharmacology, DMPK
(b) (4), M.D., FACP	Consultant, (b) (4).
Melissa Rewolinski, Ph.D.	Vice President, Product Development

1. BACKGROUND

NDA 207999 was submitted on June 27, 2015 for OCALIVA (obeticholic acid).

Proposed indication(s): Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

PDUFA goal date: May 29, 2016

FDA issued a Background Package in preparation for this meeting on March 18, 2016.

2. **DISCUSSION** (Comments from FDA are in plain text. Responses from Intercept are in *italics*. Meeting Discussion is in ***bold italics***).

1. Introductory Comments

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues

- a. Your Phase 3 trial enrolled primarily patients with early stage disease, and provided limited data on patients with moderately severe or severe stages of PBC (Rotterdam criteria).

Intercept Pharmaceutical comments dated March 21, 2016:

We agree that based on the Rotterdam criteria, there are limited data on patients with moderately severe or severe stages of PBC.

There are other criteria commonly employed in clinical practice to categorize patients with PBC (and other chronic liver diseases) across the disease spectrum. We have employed criteria to define a subset of patients with advanced disease in the Phase 3 study, as follows:

- Baseline total bilirubin >ULN*
- Baseline ALP >5 x ULN*
- Baseline transient elastography ≥ 10.7 kPa (advanced fibrosis or cirrhosis)*
- Cirrhosis based on initial biopsy or baseline biopsy data*
- Medical history indicating events associated with clinical events of hepatic decompensation*

Based on this definition, approximately 1/3 of the Phase 3 patient population had evidence of advanced disease at baseline (30 placebo, 22 OCA titration and 20 OCA 10mg). Similar efficacy was observed in patients who met the criteria for advanced disease stage as compared to patients with non-advanced disease. Specifically, a significantly greater proportion of OCA-treated patients achieved the primary endpoint irrespective of disease stage. Further, clinically relevant and statistically significant improvements in ALP and total bilirubin were demonstrated in the advanced population. Of note, the magnitude of reduction in both ALP and total bilirubin was greater in the advanced disease population compared to those with earlier stage disease.

There was a higher incidence of hepatic-related adverse events (AEs) in patients with advanced disease; however, at the doses studied, there was no dose-dependent trend in the incidence of hepatic-related events. Given the advanced disease stage in this patient subset, these hepatic AEs were likely attributed to disease progression. We believe that although relatively limited, the data do suggest that OCA may safely be used and is efficacious in advanced stage PBC patients. The ongoing Phase 4 trial (Study 747-302) is intended to further support this observation.

Meeting Discussion:

FDA does not agree with grouping moderately advanced and advanced PBC together (as is done in Intercept's response above), and supports using the Rotterdam criteria as the basis for categorizing PBC patients as having early, moderately advanced, or advanced stage of the disease. FDA does not agree with the post-hoc use of the criteria listed above to define a subset of patients with 'advanced disease' in the Phase 3 trial; however, FDA is open to further discussion about alternative criteria for PBC staging in the context of the phase 4 confirmatory trial. FDA reiterated that there is a need to enroll patients across all stages of PBC to ensure verification of clinical benefit to all patients who are candidates for treatment with OCA.

- b. There are limited data in the NDA submission on the use of obeticholic acid as monotherapy.

Intercept Pharmaceutical comments dated March 21, 2016:

We accept that there are limited data on the use of OCA as monotherapy. Consistent with the reported low percentage of patients who are unable to tolerate UDCA based on epidemiology data, the clinical data evaluating OCA treatment as monotherapy are relatively limited. Between the Phase 2 and Phase 3 trials, a total of 47 patients received OCA as monotherapy. Please see response to Question 6b.

Meeting Discussion:

See Meeting Discussion under 6.b. below regarding enrollment of patients receiving OCA monotherapy in the phase 4 confirmatory trial.

- c. Clarify what outcome analysis you plan to conduct in patients with an inadequate response in alkaline phosphatase, in particular what will be the comparator for this analysis and justify the choice of such a comparator.

Intercept Pharmaceutical comments dated March 21, 2016:

Assuming this question pertains to the Phase 4 confirmatory trial (Study 747-302), all patients will be required to continue treatment with blinded study medication (placebo or OCA added to background UDCA in most patients) until trial completion. This is the case irrespective of biochemical response, given that the study is designed to confirm clinical benefit in terms of a time to clinical outcome event analysis. In general, patients

are encouraged to stay on treatment until trial completion. Early discontinuation of patients showing an inadequate ALP response would confound the outcomes analysis and preclude interpretation of results.

Meeting Discussion:

See Meeting Discussion under 6.c. below.

d.  (b) (4)

Intercept Pharmaceutical comments dated March 21, 2016:

 (b) (4)

Meeting Discussion:

FDA advised Intercept to  (b) (4)

e. For your phase 3 trial data, you applied correction factors to harmonize the values of ALP, total and direct bilirubin. In the original NDA submission, there was no information on the harmonization methodology and validation. During the review cycle, some of your responses to Agency's information requests related to this analytical harmonization issue were incomplete or erroneous necessitating extra review time and efforts. We would like to discuss how this could be avoided in future submissions.

Intercept Pharmaceutical comments dated March 21, 2016:

We acknowledge the issues with the data harmonization across regional central laboratories and welcome your thoughts and suggestions. We take quality issues very seriously and are committed to ensuring that this never recurs in the future. Therefore, we have implemented a comprehensive

corrective action plan that includes a careful QC of the data and additional oversight of vendors to ensure appropriate quality.

Meeting Discussion:

No additional discussion.

3. Additional Applicant Data

Intercept Pharmaceutical comments dated March 21, 2016:

Additional data regarding the advanced disease patient subset and the association of bilirubin <ULN with transplant-free survival are included in accompanying slides.

Meeting Discussion:

FDA acknowledged the information provided by Intercept.

4. Information Requests

Clinical

Information Request dated March 17, 2016 is outstanding. Response is due by March 20, 2016.

Intercept Pharmaceutical comments dated March 21, 2016:

As requested, the response to the Clinical Information Request dated March 17, 2016 was submitted on March 20, 2016.

Meeting Discussion:

Response to the Clinical Information Request was received officially on March 21, 2016 and forwarded to the review team on March 22, 2016.

5. Discussion of Upcoming Advisory Committee Meeting

Intercept will be providing an outside speaker to present in an unbiased fashion the natural history, diagnosis, and current treatment of primary biliary cirrhosis. We have allotted 20-30 minutes for this presentation. Intercept should submit the slides for this presentation to the FDA at soon as possible.

Intercept Pharmaceutical comments dated March 21, 2016:

We are working with Dr. Kris Kowdley to develop an unbiased presentation of the natural history, diagnosis and current treatment of primary biliary cirrhosis. As requested, we will submit slides to the FDA as soon as possible to ensure adequate time for review and feedback.

Meeting Discussion:

No additional discussion.

6. Postmarketing Requirements/Postmarketing Commitments

Clinical - Post Marketing Requirements (PMR)

We have identified several issues with your proposed protocol for the confirmatory phase 4 clinical trial intended to verify and describe the anticipated clinical benefit of obeticholic acid treatment. These issues are as follows:

- a. The population proposed for enrollment may not provide adequate information on the safety and efficacy (clinical benefit) across the entire spectrum of the disease, i.e., patients with early, moderately advanced and advanced stage disease.

Intercept Pharmaceutical comments dated March 21, 2016:

The design of the Phase 4 confirmatory trial (Study 747-302) was intended to confirm the safety and efficacy of OCA in patients with PBC. In order to achieve sufficient clinical outcomes in a timely fashion, it was necessary to focus on the patients with moderately advanced disease, ie, an inclusion criteria of total bilirubin > upper limit of normal (ULN) and $\leq 3x$ ULN or an ALP >5x ULN. These inclusion criteria should result in some degree of overlap with patients included in the Phase 3 trial (Study 747-301).

Meeting Discussion:

FDA recommends that Intercept stratify patients into all three PBC disease stages ensuring adequate powering for each stage of disease. This staging can be based on Rotterdam criteria or FDA is open to discussing other criteria. FDA recognizes it may be inappropriate to enroll patients with advanced cirrhosis for drug treatment.

- b. It is possible that, as designed, the confirmatory trial may not enroll a sufficient number of patients on obeticholic acid monotherapy. This issue could be addressed by specifying a sufficient number of patients on OCALIVA monotherapy in the confirmatory trial, or evaluating monotherapy treated patients in a separate trial.

Intercept Pharmaceutical comments dated March 21, 2016:

We appreciate the need for confirmation of clinical benefit when OCA is administered as monotherapy in patients unable to tolerate UDCA and, as such, plan to evaluate this as part of the ongoing Phase 4 confirmatory trial (Study 747-302), which is open to enrollment of patients not receiving UDCA. Based on the Global PBC Study Group, it is estimated that approximately 10-15% of PBC patients are not on therapy and would meet the inclusion criteria in the confirmatory trial. We will take your suggestion into consideration to require a minimum number of patients intolerant to UDCA.

Meeting Discussion:

Intercept will propose options for assessing the safety and efficacy of OCA as monotherapy for FDA consideration.

- c. The trial will not address the issue of whether there is a clinical benefit of continuing obeticholic acid treatment in patients with an inadequate response in alkaline phosphatase relative to thresholds used to define clinical response, as at this time you are continuing all patients on drug, irrespective of their response.

Intercept Pharmaceutical comments dated March 21, 2016:
Please see response to Question 2c.

Meeting Discussion:

Intercept stated that the trial design is appropriate to assess the long term clinical benefit of OCA treatment, relative to placebo, in patients who are biochemical ‘non-responders’. Intercept conveyed a willingness to consider alternative trial designs that FDA may consider appropriate. A design that discontinues patients who do not respond to OCA (i.e., ‘non-responders’) and re-randomizes such patients may impact trial integrity.

- d. The proposed trial does not appear to be adequately powered.

Intercept Pharmaceutical comments dated March 21, 2016:

The determination of the sample size was based on a careful assessment of event rates in the Global PBC Study Group. However, in order to ensure adequate power, starting approximately 2 years after the first patient is randomized, the aggregate event rate and sample size based on recruitment and retention will be evaluated in a blinded manner quarterly. This evaluation will determine if any increases in number of patients are required in order to obtain a total of 121 adjudicated events for the final analysis in the combined groups in the projected timeframe of the trial. Specifically, the pooled number of events will be available during the trial in a blinded manner, without any knowledge of the comparative efficacy in the treatment groups. This method for evaluating the sample size does not inflate the type I error rate. Additional patients may be enrolled as appropriate.

Meeting Discussion:

FDA stated that Intercept should use the median survival time in addition to the hazard ratio from the PBC study group to determine the sample size needed in the phase 4 confirmatory trial. FDA encouraged Intercept to schedule a follow up discussion regarding this and other trial design/statistical issues.

- e. The follow-up of patients who discontinue from the trial may not be adequate.

Intercept Pharmaceutical comments dated March 21, 2016:

Patients enrolled in the Phase 4 trial are required to continue treatment with blinded study medication until trial completion. We acknowledge that some patients may choose to discontinue treatment over the course of such a long trial. As such, the protocol calls for several options to allow for long-term follow-up of patients who discontinue study medication while the trial is ongoing. Patients are strongly

encouraged to continue with scheduled study visits despite having discontinued therapy. In the case that a patient is not willing to continue her regularly scheduled clinic visits, the protocol allows for telephone contact by the study site every 6 months. If the patient refuses the telephone contact, study site personnel will attempt a review of the patient's medical records. For both the telephone contact and records review, the outcomes data to be discussed or collected include data related to adjudicated hepatic and cardiovascular event-related data.

Meeting Discussion:

Intercept indicated that the protocol for follow-up of discontinued patients in the phase 4 confirmatory trial had recently been expanded in a protocol amendment, which Intercept will be sharing with FDA.

f. Event adjudication for the main efficacy analyses requires further discussion.

Intercept Pharmaceutical comments dated March 21, 2016:

All potential endpoint events will be reviewed by an adjudication committee before inclusion in the primary endpoint analysis. The adjudication committee will function in accordance with a charter and the principles of the 2006 Guidance for Clinical Trial Sponsors - Establishment and Operation of Clinical Trial Data Monitoring Committees. We are currently in the process of drafting the adjudication committee charter. The purpose of this charter is to define the roles and responsibilities of the adjudication committee members, purpose and timing of meetings, and to provide the procedures for ensuring confidentiality and proper communication. This charter will describe and provide definitions to be applied in the evaluation of and adjudication of specific endpoints and events and will document the entire data flow and process.

Once completed, we will share the adjudication charter with the FDA to ensure acceptability of the process and definitions prior to implementation.

Meeting Discussion:

Intercept will submit the charter discussed above as soon as it is available for FDA to review.

7. Major Labeling Issues

- a. Labeling of dose adjustment for patients with moderate and severe hepatic impairment is still under review. The FDA reviewers propose the following dosing schema in patients with moderate and severe hepatic impairment: start treatment with 5 mg once weekly; if an adequate reduction in alkaline phosphatase has not been achieved after 3 months on 5 mg once weekly and the patient is tolerating the drug, increase the dose to 5 mg twice weekly and subsequently to 10 mg twice weekly depending on response and tolerability.

Intercept Pharmaceutical comments dated March 21, 2016:

We concur that a modified dosing scheme for patients with moderate and severe hepatic impairment is warranted. However, to improve compliance and optimal therapeutic response, we have proposed a slight modification based on modeling and simulation data. Instead of a 10 mg twice weekly dose we would propose modifying administration of the 5 mg dose further, as follows:

If an adequate reduction in alkaline phosphatase has not been achieved after 3 months on 5 mg once weekly, and the patient is tolerating the drug, increase the dose to 5 mg twice weekly and then subsequently to 5 mg every other day depending on response and tolerability. Patients should continue on 5 mg every other day and if tolerated, titrate to 5 mg every day to achieve maximum response.

Meeting Discussion:

Additional discussion did not take place during the meeting.

- b. An Accelerated Approval decision would be based solely on alkaline phosphatase reduction, because there was insufficient information on reduction in total bilirubin;

(b) (4)

Intercept Pharmaceutical comments dated March 21, 2016:

We agree that there are limited data from the Phase 3 trial (Study 747-301) regarding reduction of total bilirubin in patients with abnormally elevated total bilirubin at baseline (7 of 11 OCA treated patients normalized versus 1 of 7 placebo patients). However, unlike the requirement for alkaline phosphatase reduction as a basis for treatment response, the requirement for total bilirubin was to be within normal limits (i.e., therefore maintenance and prevention of progression for patients whose baseline total bilirubin levels were within normal limits). Given that total bilirubin elevation is a hallmark of more advanced disease, stabilization of total bilirubin within normal limits in the majority of patients who still have compensated liver disease was deemed a critical component of the primary endpoint based on expert feedback during the design of the trial.

The clinical importance of monitoring patients for stable total bilirubin over time is highlighted by the fact that the placebo group experienced an increase in total bilirubin over the course of the Phase 3 trial. Importantly, analysis of data from the Global PBC Study Group and the UK-PBC Consortium show that total bilirubin levels within the normal range differentiate risk of outcomes (ie, a patient at the midpoint of the range is at lower risk than a patient towards the upper limit of normal). The increase in total bilirubin in the placebo group signals potential disease progression in these patients, whereas total bilirubin levels were slightly reduced below baseline in both OCA groups. Therefore, we believe that labeling should reflect the important contribution of OCA treatment with respect to the maintenance of total bilirubin within the normal range.

Meeting Discussion:

FDA will further consider Intercept's comments above.

- c. Labeling (Section 14) will reflect the population that was studied in the clinical trials, i.e., patients with early stage disease.

Intercept Pharmaceutical comments dated March 21, 2016:
Please see response to Questions 2a above.

Meeting Discussion:

Additional discussion did not take place during the meeting.

- d. Labeling of hepatic-related adverse events is still under review.

Intercept Pharmaceutical comments dated March 21, 2016:
Please see response to Questions 2a above.

Meeting Discussion:

Additional discussion did not take place during the meeting.

- e. FDA considers the tumor findings observed in rodents to be significant, and they will be conveyed in labeling.

Intercept Pharmaceutical comments dated March 21, 2016:
The tumor findings were only seen in the rat; they were considered by the study pathologists (primary + peer review) to be benign, unrelated to treatment with obeticholic acid and within the normal expected incidence based on historic control datasets. (b) (4)

Meeting Discussion:

Additional discussion did not take place during the meeting.

8. Review Plans

The Division is planning to continue labeling negotiations after the AC meeting.
PDUFA date: May 29, 2016

Meeting Discussion:

9. 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.

* 3681/4635 patients were included for this analysis
** 2109/3161 patients were included for this analysis
Lammers WJ, et al. *Gastroenterology*. 2014 Dec;147(6):1338-1349.

P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as covariate and fixed effects for treatment, double-blind baseline UDCA usage (yes/no) and double-blind baseline total bilirubin (\leq ULN/ $>$ ULN).

P-value for comparing active treatments to placebo is obtained using an ANCOVA model with baseline value as covariate and fixed effects for treatment, double-blind baseline UDCA usage (yes/no) and double-blind baseline total bilirubin (\leq ULN/ $>$ ULN).

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/s/

LARA DIMICK-SANTOS
03/25/2016



NDA 207999

**LATE CYCLE MEETING
BACKGROUND PACKAGE**

Intercept Pharmaceuticals, Inc.
Attention: Linda Robertson, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance
4760 Eastgate Mall
San Diego, CA 92122

Dear Dr. Robertson:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for OCALIVA (obeticholic acid) tablets, 5 mg and 10 mg.

We also refer to the Late-Cycle Meeting (LCM) scheduled for March 22, 2016. Attached is our background package, including our agenda for this meeting.

If you have any questions, call CDR Anissa Davis-Williams, Senior Regulatory Project Manager, at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Dragos Roman, M.D.
Associate Director
Division of Gastroenterology and Inborn Errors
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: March 22, 2016; 11:00 AM – 12:30 PM
Meeting Location: FDA White Oak Bldg. 22/Room 1421
Application Number: NDA 207999
Product Name: OCALIVA (obeticholic acid)
Indication: Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA
Sponsor/Applicant Name: Intercept Pharmaceuticals, 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, 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. If you submit any new information in response to the issues identified in this background package prior to this LCM or the AC meeting, 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 (AC) MEETING

Date of AC meeting: April 7, 2016

An AC briefing package was sent under separate cover by the Division of Advisory Committee and Consultant Management: March 18, 2016

The following are the preliminary questions for the AC Committee members; they are reproduced from FDA's Briefing Document:

- a. Discuss whether you think the evidence from the Global PBC Study Group data presented today on the reduction in alkaline phosphatase (ALP) supports the use of alkaline phosphatase as a surrogate endpoint reasonably likely to predict clinical benefit in the treatment of early stage Primary Biliary Cirrhosis. Comment on the strength of evidence that supports the stratified responder criteria that were developed by the FDA statistical team's review of Global PBC Study Group data.
- b. Discuss the appropriateness of the Applicant's proposed dosage schema, i.e., a starting dose of 5 mg of obeticholic acid with up titration to 10 mg after 3 months. Include in your discussion and dosing recommendation the safety and tolerability of obeticholic acid in addition to the biochemical response (alkaline phosphatase reduction).
- c. Discuss the adequacy of the data to support the use of OCA as monotherapy for patients intolerant to ursodeoxycholic acid (UDCA). Include in your discussion whether the applicant should be required to further study the use of OCA as monotherapy.
- d. Discuss the adequacy of the data to support the use of OCA in moderately advanced and advanced stages of PBC. Include in your discussion whether the applicant should be required to further study the use of OCA in moderately advanced and advanced stages of PBC.
- e. Discuss whether you think the available evidence (i.e., PK modeling, dose response) supports the FDA's proposed dosage of obeticholic acid in PBC patients with moderately advanced (Child-Pugh B) and advanced (Child-Pugh C) cirrhosis.
- f. Discuss the pros and cons of continuing obeticholic acid treatment in patients who do not demonstrate reduction in alkaline phosphatase after 6 months of treatment on a maximally tolerated dose. Take into consideration the risk of alterations in lipid profile vs. the potential for benefit.
- g. Taking into account the risks and benefit of OCA in the population studied, do you think there is the necessary substantial evidence to support accelerated approval of OCA for the treatment of PBC, based on its effect on alkaline phosphatase?
YES or NO
- h. Discuss what if any changes in the enrollment criteria or design of the postmarketing confirmatory trial would be necessary to obtain any missing information that you think is necessary for full/regular approval of OCA for the treatment of PBC. Alternatively,

discuss what additional post-marketing studies you think would be necessary to obtain any missing data or information that has not been provided.

We look forward to discussing your 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 – 3 minutes (RPM/CDTL)

Welcome, Introductions, Ground rules, Objectives of the meeting

2. Discussion of Minor Review Issues – 35 minutes

- a. Your Phase 3 trial enrolled primarily patients with early stage disease, and provided limited data on patients with moderately severe or severe stages of PBC (Rotterdam criteria).
- b. There are limited data in the NDA submission on the use of obeticholic acid as monotherapy.
- c. Clarify what outcome analysis you plan to conduct in patients with an inadequate response in alkaline phosphatase, in particular what will be the comparator for this analysis and justify the choice of such a comparator.
- d.  (b) (4)
- e. For your phase 3 trial data, you applied correction factors to harmonize the values of ALP, total and direct bilirubin. In the original NDA submission, there was no information on the harmonization methodology and validation. During the review cycle, some of your responses to Agency's information requests related to this analytical harmonization issue were incomplete or erroneous necessitating extra review time and efforts. We would like to discuss how this could be avoided in future submissions.

3. Additional Applicant Data to Discuss– 5 minutes (Applicant)

4. Information Requests (IR)– 2 minutes

Clinical

Information Request dated March 17, 2016 is outstanding. Response is due by March 20, 2016.

5. Discussion of Upcoming Advisory Committee Meeting – 5 minutes

Intercept will be providing an outside speaker to present in an unbiased fashion the natural history, diagnosis, and current treatment of primary biliary cirrhosis. We have allotted 20-30 minutes for this presentation. Intercept should submit the slides for this presentation to the FDA at soon as possible.

6. Postmarketing Requirements – 20 minutes

Clinical - Post Marketing Requirements (PMR)

We have identified several issues with your proposed protocol for the confirmatory phase 4 clinical trial intended to verify and describe the anticipated clinical benefit of obeticholic acid treatment. These issues are as follows:

- a. The population proposed for enrollment may not provide adequate information on the safety and efficacy (clinical benefit) across the entire spectrum of the disease, i.e., patients with early, moderately advanced and advanced stage disease.
- b. It is possible that, as designed, the confirmatory trial may not enroll a sufficient number of patients on obeticholic acid monotherapy. This issue could be addressed by specifying a sufficient number of patients on OCALIVA monotherapy in the confirmatory trial, or evaluating monotherapy treated patients in a separate trial.
- c. The trial will not address the issue of whether there is a clinical benefit of continuing obeticholic acid treatment in patients with an inadequate response in alkaline phosphatase relative to thresholds used to define clinical response, as at this time you are continuing all patients on drug, irrespective of their response.
- d. The proposed trial does not appear to be adequately powered.
- e. The follow-up of patients who discontinue from the trial may not be adequate.
- f. Event adjudication for the main efficacy analyses requires further discussion.

7. Major labeling issues – 10 minutes

- a. Labeling of dose adjustment for patients with moderate and severe hepatic impairment is still under review. The FDA reviewers propose the following dosing schema in patients with moderate and severe hepatic impairment: start treatment with 5 mg once weekly; if an adequate reduction in alkaline phosphatase has not been achieved after 3 months on 5 mg once weekly and the patient is tolerating the drug, increase the dose to 5 mg twice weekly and subsequently to 10 mg twice weekly depending on response and tolerability.
- b. An Accelerated Approval decision would be based solely on alkaline phosphatase reduction, because there was insufficient information on reduction in total bilirubin; (b) (4).
- c. Labeling (Section 14) will reflect the population that was studied in the clinical trials, i.e., patients with early stage disease.
- d. Labeling of hepatic-related adverse events is still under review.

- e. FDA considers the tumor findings observed in rodents to be significant, and they will be conveyed in labeling.

8. Review Plans – 5 minutes

The Division is planning to continue labeling negotiations after the AC meeting.

PDUFA date: May 29, 2016

9. Wrap-up and Action Items – 5 minutes

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/s/

ANISSA A DAVIS
03/18/2016