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*APPLICATION NUMBER:*

**207999Orig1s000**

**OTHER REVIEW(S)**

## PMR Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA #	207999	
Product Name:	OCALIVA (obeticholic acid)	
PMR 3057-1 Description:	A randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady-state pharmacokinetics of OCALIVA (obeticholic acid) in patients with primary biliary cholangitis (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# 3057-3).	
PMR 3057-1 Schedule Milestones:	Final Protocol Submission:	12/01/2016
	Study/Trial Completion:	12/01/2022
	Final Report Submission:	04/01/2023
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

PBC is a rare, life-threatening disease with an unmet need. The clinical trials to establish safety and efficacy of OCALIVA under Subpart H were conducted predominantly in early stage PBC patients. While a few patients with Child-Pugh A cirrhosis were included in the clinical trials, we have inadequate information on the safety, efficacy and pharmacokinetics of obeticholic acid in patients with Child-Pugh Class B and C hepatic impairment.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

There were inadequate numbers of patients with Child-Pugh Classes B and C hepatic impairment to allow a determination of safety, tolerability, pharmacokinetics and effectiveness of obeticholic acid in this sub-population. There was a safety signal for liver-related adverse events in patients who received doses of OCALIVA higher than the approved dose. Furthermore, based on a dedicated hepatic impairment study and physiological pharmacokinetic modeling and simulation, patients with hepatic impairment are expected to experience higher exposures of obeticholic acid. While product labeling will not prohibit use of OCALIVA in this sub-population further information regarding the safety, tolerability, pharmacokinetics, and efficacy is needed to inform future labeling.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, placebo-controlled clinical trial to evaluate the safety, efficacy and steady state pharmacokinetics of OCALIVA (obeticholic acid) in patients with PBC with Child-Pugh Class B and C hepatic impairment.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/  
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LARA DIMICK-SANTOS  
05/16/2016

## PMR Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

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NDA # 207999  
Product Name: OCALIVA (obeticholic acid)

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PMR 3057-2 Description: A randomized, placebo-controlled trial to evaluate the safety and efficacy of OCALIVA (obeticholic acid) used as monotherapy in patients with primary biliary cholangitis (PBC) who are intolerant to 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 subset of patients in your confirmatory trial (PMR # 3057-3).

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PMR 3057-2 Schedule Milestones:	Final Protocol Submission:	12/01/2016
	Study/Trial Completion:	12/01/2022
	Final Report Submission:	04/01/2023
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The majority (greater than 95%) of patients with PBC tolerate UDCA; however, some patients are intolerant of UDCA, primarily due to gastrointestinal issues. Approximately 10% of PBC patients, especially younger patients, do not have a biochemical response to UDCA. In the phase 3 clinical trial, there were only 16 patients enrolled who were not receiving UDCA, and of these 11 were randomized to OCALIVA treatment and 5 to placebo. There were no concerning safety signals observed with OCALIVA monotherapy, and there appeared to be efficacy in the treated group relative to placebo; however, the long term data are not adequate to fully assess the safety and efficacy of OCALIVA in these patients.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The OCALIVA clinical trials enrolled an insufficient number of patients to allow a meaningful evaluation of OCALIVA as monotherapy. There were no concerning safety signals identified in this small group of patients, and a post-hoc analysis across phase 2 and 3 clinical trials suggests that OCALIVA may be efficacious. There are, however, insufficient data to assess the efficacy and safety of OCALIVA as monotherapy. It is anticipated that, upon approval, OCALIVA will be prescribed as monotherapy. Further information is needed to assess efficacy and safety in these patients.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, placebo-controlled trial to assess safety and efficacy of OCALIVA used as monotherapy in patients with PBC who are intolerant of or non-responsive to UDCA.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 

- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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LARA DIMICK-SANTOS  
05/16/2016

## PMR Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

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NDA # 207999  
Product Name: OCALIVA (obeticholic acid)

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PMR 3057-3 Description: A randomized, double-blind, placebo-controlled trial to verify and describe that OCALIVA (obeticholic acid)-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 (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.

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PMR 3057-3 Schedule Milestones:	Draft Amended Protocol Submission	09/01/2016
	Final Protocol Submission:	12/01/2016
	Study/Trial Completion:	12/01/2022
	Final Report Submission:	04/01/2023
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

This NDA is being approved under the accelerated approval pathway (Subpart H). The phase 3 clinical trial evaluated the efficacy of obeticholic acid (OCA) using reduction in alkaline phosphatase (ALP) levels as an unvalidated surrogate endpoint. In addition, the phase 3 trial evaluated primarily patients with early stage PBC, and data on moderately advanced and advanced stage PBC are insufficient or unavailable. This PMR is the trial necessary to verify and describe the clinical benefit anticipated on the basis of reduction in ALP. It is a randomized, double-blind, placebo-controlled trial that will evaluate the effects of OCA on clinical outcomes (survival, liver transplantation, etc) across a spectrum of PBC: early, moderately advanced and advanced stage PBC patients .

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

This trial is a confirmatory trial required under accelerated approval (Subpart H) and will describe and verify the clinical benefit in patients with PBC. .

3. If the study/clinical trial is a PMR, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)  
 Animal Efficacy Rule  
 Pediatric Research Equity Act  
 FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?  
 Assess signals of serious risk related to the use of the drug?  
 Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Randomized, double-blind, placebo-controlled clinical trial to verify and describe the clinical benefit of OCALIVA across the following stages of PBC (by the Rotterdam criteria): early, moderately advanced, and advanced.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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LARA DIMICK-SANTOS  
05/16/2016

## PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

---

NDA # 207999  
Product Name: OCALIVA (obeticholic acid)

PMC 3057-4  
Description: Develop a formulation that would allow once daily dosing of OCALIVA (obeticholic acid) for patients with hepatic impairment. Conduct a study in healthy subjects to characterize the bioavailability of the new formulation relative to an approved formulation. Submit your study protocol once you have a new formulation.

### PMC 3057-4 Schedule Milestones:

Final Protocol Submission:	<u>11/01/2017</u>
Study/Trial Completion:	<u>04/01/2019</u>
Final Report Submission:	<u>08/01/2019</u>
Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Good compliance may be difficult to achieve with only 5 mg and 10 mg tablets, given that patients with hepatic impairment need to be dosed at irregular intervals (i.e. two times weekly) after dose titration.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The proposed maintenance dose adjustment for patients with moderate and severe hepatic impairment is acceptable but not optimal. Developing a formulation that would allow once daily regimen will facilitate good patient compliance.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

*If not a PMR, skip to 4.*

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

*Do not select the above study/clinical trial type if:* such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

*Do not select the above study/clinical trial type if:* the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

*Do not select the above study type if:* a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

a) Conduct formulation development studies to develop (b) (4). Provide pertinent CMC information required for approval of (b) (4).

b) Conduct a PK study in healthy subjects to characterize bioavailability relative to (b) (4). Submit your pharmacokinetic study protocol once you have a new formulation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other  
Drug development/pharmacokinetic
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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ELIZABETH Y SHANG  
05/13/2016

SUE CHIH H LEE  
05/13/2016

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

Memorandum

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**\*\*PRE-DECISIONAL AGENCY MEMO\*\***

**Date:** April 29, 2016

**To:** Anissa Davis-Williams, RN, BSN, MPH, CPHM  
Senior Regulatory Project Manager  
Division of Gastroenterology and Inborn Errors Products

**From:** Meeta Patel, PharmD  
Regulatory Review Officer  
Office of Prescription Drug Promotion (OPDP)

**Subject:** NDA 207999  
OPDP Comments for draft OCALIVA (obeticholic acid) tablets, for oral use PI

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OPDP has reviewed the proposed draft PI for OCALIVA (obeticholic acid) tablets, for oral use, sent to us on April 22, 2016, and have the following comments.

Thank you for the opportunity to comment on the proposed PI.

If you have any questions or concerns, please contact Meeta Patel at 301-796-4284 or [meeta.patel@fda.hhs.gov](mailto:meeta.patel@fda.hhs.gov).

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

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/s/  
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MEETA N PATEL  
04/29/2016



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date completed:** November 20, 2015  
**Date consulted:** July 8, 2015  
**Requested completion date:** November 29, 2015

**From:** Christos Mastroyannis, M.D.  
Medical Officer, Maternal Health Team  
Division of Pediatric and Maternal Health

**Through:** Tamara Johnson, M.D., M.S.  
Team Leader, Maternal Health Team  
Division of Pediatric and Maternal Health

Lynne P. Yao, M.D., Division Director,  
Division of Pediatric and Maternal Health

**To:** The Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Drug:** Ocaliva [INT-747 (Obeticholic acid) (OCA)] tablets

**NDA:** 207999

**Subject:** Maternal Health Team Labeling Recommendations

**Applicant** Intercept Pharmaceuticals, Inc

**Materials Reviewed:**

- June 29, 2015, Original New Drug Application (NDA) rolling submission from Intercept
- June 29, 2015, Annotated Draft Labeling Text to comply with PLLR requirements by Intercept
- September 21, 2015, Applicant's comments to proposed label changes
- October 19, 2015, Pharmacology/Toxicology labeling comments

**Consult Question: The Division of Gastroenterology and Inborn Errors Products (DGIEP)**

requests assistance to apply the new Pregnancy and Lactation Labeling Rule requirements to the Ocaliva [obeticholic acid (OCA)] labeling. This NDA 207999 is Orphan Designated and being reviewed via “The Program” pathway as a NME. This new NDA is seeking approval 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 UCDA.

**INTRODUCTION**

On December 19, 2014, Intercept submitted NDA 207999 for Ocaliva [Obeticholic acid (OCA) (INT-747)], a rolling submission starting with the non-clinical section. On June 29, 2015, Intercept completed the rolling submission of the original NDA 207999 under 21CFR 314, Subpart H Accelerated Approval for the treatment of primary biliary cirrhosis (PBC), a rare, serious, life-threatening chronic liver disease. As per the applicant, OCA use is intended 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 adult patients unable to tolerate UDCA.

DGIEP consulted the Division of Pediatric and Maternal Health (DPMH) to review the Pregnancy, Lactation, and Females and Males of Reproductive Potential information in the Ocaliva labeling.

On December 4, 2014, the Food and Drug Administration (FDA) 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)<sup>1</sup>. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and a new subsection for information with regard to females and males of reproductive potential (if applicable). Specifically, the pregnancy categories (A, B, C, D and X) have been removed from all prescription drug and biological product labeling and a new format is required for all drug products that are subject to the 2006 Physician Labeling Rule (PLR)<sup>2</sup>, to include information about the risks and benefits of using these products during pregnancy and lactation. The PLLR took effect on June 30, 2015.

This review provides recommended revisions and structuring of information related to the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections in labeling in order to provide clinically relevant information for prescribing decisions and to comply with PLLR regulatory requirements.

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<sup>1</sup> Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

<sup>2</sup> Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, published in the Federal Register (71 FR 3922; January 24, 2006).

## **BACKGROUND**

### **Product Background**

Ocaliva is a modified bile acid and farnesoid X receptor (FXR) agonist. FXR is a regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.<sup>3,4</sup>

Ocaliva tablets are supplied in 5 mg and 10 mg strengths for oral administration. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating is Opadry II (Yellow) and contains polyvinyl alcohol-part hydrolyzed, titanium dioxide, Macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

### **REVIEW of Data**

#### **A. Ocaliva and Pregnancy**

##### **Animal Data**

From the Pharmacology-Toxicology review by Tracy Behrsing, PhD, when OCA was administered in mice and rats did not yield any neoplastic findings in doses that could have clinical significance. In different tests performed, no genotoxic findings were observed. Obeticholic acid administered to male and female rats did not alter male or female fertility or early embryonic development at any doses. Similarly, in an embryofetal development study, OCA did not demonstrate any maternal or developmental toxicity. In a pre- and postnatal development study, administration of obeticholic acid in rats during organogenesis through lactation did not produce effects on pregnancy, parturition or postnatal development at any doses.

##### **Human Data**

The applicant has conducted no studies with Ocaliva in pregnant women.

On July 29, 2015, an information request letter was sent to the applicant requesting:

- A review and summary of all available published literature regarding obeticholic acid
- A review and summary from the applicant's pharmacovigilance database.

On September 21, 2015, the applicant responded:

1. "There are no clinical studies with obeticholic acid in pregnant women that inform any drug associated risks. An extensive search of the published literature was conducted for obeticholic acid from January 2006 (when the IND went into effect) through July 2015. Based on this search, no literature was found describing any subject/patient data related to its use in pregnancy, lactation, or effects on fertility and/or reproduction".

<sup>3</sup> Modica S, Petruzzelli M, Bellafante E, et al. Selective activation of nuclear bile acid receptor FXR in the intestine protects mice against cholestasis. *Gastroenterology*. 2012 Feb;142(2):355-65 e1-4

<sup>4</sup> Lefebvre P, Cariou B, Lien F, et al. Role of bile acids and bile acid receptors in metabolic regulation. *Physiol Rev*. 2009 Jan;89(1):147-91

2. “A search of the pharmacovigilance database found one case of pregnancy reported from the obeticholic acid clinical development program in a female subject who was treated with obeticholic acid. Investigational drug was subsequently interrupted per protocol after learning of the pregnancy. The subject experienced a spontaneous abortion while waiting for a planned abortion. The investigator considered the spontaneous abortion as unlikely to be related to study medication because it occurred approximately 26 days after the investigational product was interrupted”.

**Reviewer’s comment:**

*A search of PubMed with pertinent terms did not produce any relevant publications. Therefore, this reviewer agrees with the applicant that no relevant literature exists in regards to obeticholic acid and pregnancy, lactation and female and male of reproductive potential. As per applicant, reportable  $t_{1/2}$  values for OCA were 1 to 2 hours, while  $t_{1/2}$  values for tauro-OCA were 6 to 10 hours on Day 0 and 12 to 23 hours on Day 13 after multiple dose administration (NDA submission, section 2.6.4, subsection 3.1, p:10). Therefore, in regards to the spontaneous abortion in the patient who stopped the drug 26 days before the spontaneous abortion occurred, this reviewer agrees with the investigator that the spontaneous abortion was not likely related to OCA because the abortion occurred at >26 half-lives of the drug.*

On October 30, 2015, the applicant provided the 120-day safety update stating that based on the information available at the time of the report, the overall safety evaluation of OCA remains unchanged.

**Reviewer comment:**

*The prevalence rates for PBC in Europe and North America, Asia, and Australia are reported ranging from 0.33 to 5.8 per 100,000 inhabitants and 1.91 to 40.2 per 100,000 inhabitants, respectively.<sup>5</sup> PBC disproportionately affects females versus males (approximately 10:1) and is typically diagnosed in patients with mean age 40 to 60 years.<sup>6</sup> This is suggestive that females of reproductive potential may be affected and as such may be exposed to Ocaliva during pregnancy. Even though the affected population may be small, DPMH recommends that more data should be collected in this group of female patients. This reviewer recommends a postmarketing pregnancy monitoring study or substudy within a patient registry to monitor the (b) (4) infants exposed to Ocaliva. This study should include both*

<sup>5</sup> Boonstra, K., Beuers, U., & Ponsioen, C. Y. Epidemiology of primary sclerosing cholangitis and primary biliary cirrhosis: a systematic review. *J Hepatol* 2012; 56(5): 1181-1188

<sup>6</sup> Carbone M, Mellis G, Pells G, et al. Sex and Age Are Determinants of the Clinical Phenotype of Primary Biliary Cirrhosis and Response to Ursodeoxycholic Acid. *Gastroenterology*. 2013 Mar;144(3):560-9

<sup>7</sup> United States National Library of Medicine. TOXNET Toxicology Data Network. *Drugs and Lactation Database (LactMed)*. <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>.

The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides any available information on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants, if known, as well as alternative drugs that can be considered. The database also includes the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding

*prospective and retrospective data collection, if possible, for better follow up of pregnancy and infant outcomes. See Appendix – Data Elements for Collecting Pregnancy Exposure Data.*

## **B. Ocaliva and Lactation**

There are no studies that have been conducted to determine whether obeticholic acid is present in human milk. Furthermore, no studies have been conducted in regards to the effects of obeticholic acid on the breast-fed infant or its effects on milk production. The Drugs and Lactation Database (LactMed)<sup>7</sup> was searched for available lactation data on with the use of obeticholic acid. No entries were found. There is no evidence if Ocaliva is present in human milk.

A low concentration of the tauro-obeticholic acid conjugate was detected in plasma of nursing rat pups on postnatal day 10. The tauro-obeticholic acid (an obeticholic acid's active metabolite conjugate) has a long half-life ( $t_{1/2}$  values for tauro-OCA were 6 to 10 hours on Day 0 and 12 to 23 hours on Day 13 after multiple dose administration). Existing data are not clear where the low concentration of tauro-obeticholic acid in the nursing rat pups is coming from, i.e. from in utero exposure or from the maternal rat milk; therefore, there is not definitive evidence if obeticholic acid is transferred through breastfeeding to the breastfed infant. No animal studies were conducted by the applicant to evaluate drug transfer to the infant via milk (see Pharmacology -Toxicology review by Tracy Behrsing, PhD for details).

### **Reviewer Comment:**

*It is not known whether Ocaliva is present in human milk. However, as a modified bile acid, Ocaliva's predominant distribution is in the enterohepatic circulation. Therefore, the maternal plasma concentration of Ocaliva is expected to be low and only a small amount of Ocaliva may transfer via breast milk to the breastfed infant. Serious adverse reactions observed in adults are not expected to affect the breastfeeding infants because these serious adverse reactions are dose depended (observed in higher doses)while the dose the breastfed infant is exposed to, is expected to be small if not at all. This reviewer recommends the following labeling language:*

*The developmental and health benefits of breastfeeding should be considered along with the mother's need for Ocaliva and any adverse effects on the breastfed infant from Ocaliva or from the underlying maternal condition.*

## **Females and Males of Reproductive Potential**

### **Infertility**

There are no human data available regarding the effects of Ocaliva on fertility. No fertility studies in humans were conducted. As stated earlier, effects of obeticholic acid on fertility and mating were assessed in rats. No effects on fertility endpoints were observed. There were no effects observed of OCA on mating, fertility, or male reproduction at exposure multiples up to 15 times the plasma exposures measured in humans.

### **Reviewer Comment:**

(b) (4)

## **CONCLUSION**

The Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling were structured to be consistent with the PLLR. Review of the literature revealed no information on risks with Ocaliva use in pregnant or lactating women. However, because a large proportion of patients using Ocaliva for the PBC indication will be females of reproductive potential, there is an opportunity to obtain additional safety data on the use of the drug during pregnancy to inform the labeling. Therefore, DPMH recommends a postmarketing pregnancy monitoring study (or substudy within a patient registry) to monitor the outcomes of pregnant women and infants exposed to Ocaliva.

## RECOMMENDATIONS

We have the following recommendations for Ocaliva labeling:

Full prescribing information:

### 8 Use in Specific Populations

#### 8.1 Pregnancy

##### Risk Summary

The limited available human data on the use of obeticholic acid during pregnancy <sup>(b)</sup><sub>(4)</sub> not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times, respectively, at the maximum recommended human dose (MRHD) of 10 mg [*see Data*].

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

##### Data

###### Animal Data

In an embryo-fetal development study in rats, obeticholic acid was administered orally during the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13 times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40 times the human exposure at the MRHD), decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight and food consumption as well as decreased body weight gain were observed at 75 mg/kg/. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic acid administered at doses up to 20 mg/kg/day (approximately 6 times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm.

In a pre- and postnatal development study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition or postnatal development at any dose (the 40 mg/kg/day dose is approximately 21 times the human exposure at the MRHD).

Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid's active metabolite conjugates (tauro-obeticholic acid and glyco-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg.

## **8.2 Lactation**

### Risk Summary

There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for [REDACTED]<sup>(b) (4)</sup> and any potential adverse effects on the breastfed infant from [REDACTED]<sup>(b) (4)</sup> or from the underlying maternal condition.

DPMH refers to the Approval Letter for final labeling.

## Appendix

### PMHS Recommended Data Elements for Collecting “Pregnancy Exposure Data”

#### A. General

- Patient identifier
- Name of reporter at initial contact
- Date of initial contact
- Dates of any follow-up contacts
- Telephone number of reporter
- Additional contact names and phone numbers (if reporter is the patient)

#### B. Maternal Information

- Source of information (e.g., obstetrician, pregnant woman, other)
- Birth date
- Race
- Occupation
- Maternal medical history (e.g., hypertension, diabetes, seizure disorder, thyroid disorder, allergic disorders, heart disease, connective disease, autoimmune disease, hepatitis, known risk factors for adverse pregnancy outcomes including environmental or occupational exposures, other)
- Obstetrical History:
  - Number of pregnancies and outcome of each (live birth, spontaneous abortion, elective termination, ectopic pregnancy, molar pregnancy)
  - Previous maternal pregnancy complications
  - Previous fetal/neonatal abnormalities and type
- Current Pregnancy:
  - Date of last menstrual period
  - Complications during pregnancy (including any adverse drug reactions) and dates
  - Number of fetuses
  - Labor/delivery complications
  - Disease course(s) during pregnancy and any complications
  - Medical product exposures (prescription drugs, OTC products & dietary supplements):
    - Name
    - Dosage & route
    - Date of first use & duration
    - Indication
  - Recreational drug use (e.g., tobacco, alcohol, illicit drugs) and amount

- Family History (specify type, maternal/paternal, etc.):
  - Spontaneous Abortions
  - Anomalies/Malformations
  - Multiple fetuses/births

### **C. Neonatal Information**

#### Initial:

- Source of information (e.g., obstetrician, pediatrician, mother)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome (live born, fetal death/stillborn, spontaneous abortion, elective termination)
- Sex
- Pregnancy weight gain of mother
- Obstetric complications ( e.g., pre-eclampsia, premature labor, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination including
- Anomalies diagnosed at birth or termination
- Anomalies diagnosed after birth
- Weight at birth indicating whether small, appropriate, or large for gestational age
- Length at birth
- Condition at birth (including when available Apgar scores at 1 and 5 minutes, umbilical cord vessels and gases, need for resuscitation, admission to intensive care nursery)
- Neonatal illnesses, hospitalizations, drug therapies

#### Follow-up:

- Source of information (e.g., pediatrician, mother)
- Date of receipt of information
- Anomalies diagnosed since initial report
- Developmental assessment
- Infant illnesses, hospitalizations, drug therapies

Note: Infants should be followed for 12 months with assessment times at birth, at 12 months, and some point in between.

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/s/  
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CHRISTOS MASTROYANNIS  
02/18/2016

TAMARA N JOHNSON  
02/18/2016

LYNNE P YAO  
02/23/2016

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### **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** February 22, 2016  
**Requesting Office or Division:** Division of Gastroenterology & Inborn Error Products (DGIEP)  
**Application Type and Number:** NDA 207999  
**Product Name and Strength:** Ocaliva (obeticholic acid) Oral Tablets 5 mg; 10 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Intercept Pharmaceuticals  
**Submission Date:** June 29, 2015 and October 19, 2015  
**OSE RCM #:** 2015-1477  
**DMEPA Primary Reviewer:** Matthew Barlow, RN, BSN  
**DMEPA Team Leader:** Mishale Mistry, PharmD, MPH

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## 1 REASON FOR REVIEW

This review is in response to DGIEP’s request for DMEPA to review the container labels and Prescribing Information for the application NDA 207999, submitted on June 29, 2015 and October 19, 2015. DMEPA was consulted to review the submitted labels and labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A-C
ISMP Newsletters	N/A-D
FDA Adverse Event Reporting System (FAERS)*	N/A-E
Other	N/A-F
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine post-market safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The applicant submitted the container labels and prescribing information on June 29, 2015, as a part of the product’s application review. Additionally, the applicant submitted revised/updated labels and labeling on October 19, 2015. We performed a risk assessment of the proposed labels and labeling to find any areas that may potentially lead to medication errors. We note that the proposed container labels can be improved to increase the readability and prominence of important information and provide adequate differentiation between the product’s strengths. Our recommendations can be found in Section 4.1.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to increase the readability and prominence of important information and promote the safe use of the product and mitigate any confusion.

#### 4.1 RECOMMENDATIONS FOR INTERCEPT PHARMACEUTICALS

We recommend the following be implemented prior to approval of this NDA:

##### A. 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.

**APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED**

**APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION**

Table 2 presents relevant product information for Ocaliva that Intercept Pharmaceuticals submitted on September 18, 2015.

<b>Table 2. Relevant Product Information for Ocaliva</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Obeticholic Acid
<b>Indication</b>	Indicated for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in (b) (4) with an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablets
<b>Strength</b>	5 mg; 10 mg
<b>Dose and Frequency</b>	The recommended starting dose is 5 mg once daily. Based on the assessment of efficacy and tolerability after 3 months, the dose may be increased to 10 mg once daily, to improve response.
<b>How Supplied</b>	<p><u>5 mg Tablets</u></p> <p>TRADENAME tablets are available as a yellow, round tablet debossed with INT on one side and 5 on the other side.</p> <ul style="list-style-type: none"> <li>• 30 tablets (NDC 69516-005-30)</li> </ul> <p><u>10 mg Tablets</u></p> <p>TRADENAME tablets are available as a yellow, triangular tablet debossed with INT on one side and 10 on the other side.</p> <ul style="list-style-type: none"> <li>• 30 tablets (NDC 69516-010-30)</li> </ul>
<b>Storage</b>	Store tablets (b) (4).
<b>Container Closure</b>	N/A

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On November 12, 2015, we searched the L:drive and AIMS using the terms, obeticholic acid, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified one previous review<sup>1</sup>. However, the review was a proprietary name review and is not relevant to this review.

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<sup>1</sup> Barlow, M. Proprietary Name Review for Ocaliva NDA 207999. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 Oct 26. RCM No.: 2015-1120652.

**APPENDIX C. HUMAN FACTORS STUDY – N/A**

**APPENDIX D. ISMP NEWSLETTERS – N/A**

**APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A**

**APPENDIX F. OTHER – N/A**

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>2</sup> along with post-market medication error data, we reviewed the following Ocaliva labels and labeling submitted by Intercept Pharmaceuticals on October 19, 2015.

- Container label
- Prescribing Information Labeling

### **G.2 Label and Labeling Images**

Container labels:



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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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MATTHEW J BARLOW  
02/22/2016

MISHALE P MISTRY  
02/22/2016

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY-UPDATE**

DATE: February 11, 2016

TO: Anissa Davis, Regulatory Project Manager  
Ruby Mehta, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207999

APPLICANT: Intercept Pharmaceuticals, Inc.

DRUG: Obeticholic Acid

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

CONSULTATION REQUEST DATE: July 30, 2015

INSPECTION SUMMARY GOAL DATE: February 20, 2016

DIVISION ACTION GOAL DATE: May 29, 2016

PDUFA DATE: May 29, 2016

## I. BACKGROUND:

Intercept Pharmaceuticals, Inc. submitted NDA 207999 for obeticholic acid (OCA) for the indication 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 UDCA.

The review division requested inspection of the clinical trials below that were submitted in support of the indication:

1. Protocol 747-301 entitled “A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis”
2. Protocol 747-201 entitled “A Study of INT-747 (6-ECDCA) Monotherapy in Patients with Primary Biliary Cirrhosis”
3. Protocol 747-201 entitled “A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid (URSO, UDCA) in Patients with Primary Biliary Cirrhosis

The foreign sites were chosen because they are the highest enrollers in the Phase 3 study Protocol 747-301. Domestic sites were chosen to obtain coverage for all the clinical studies, specifically the Phase 3 study and both of the Phase 2 studies. Domestic sites were either high enrollers in the Phase 3 study or participated in all three studies and were high enrollers in at least one of the Phase 2 studies.

On November 17, 2016, when the preliminary Clinical Inspection Summary (CIS) was entered into DARRTS, a major amendment had not yet been submitted and the sponsor inspection had not begun. This updated CIS includes the final classifications of clinical investigator inspections discussed below and the preliminary results of the routine sponsor inspection. The final classifications for the clinical investigator (CI) inspections are not changed from the preliminary classifications. The sponsor classification is preliminary VAI.

## II. RESULTS (by Site):

Type of Inspected Entity, Name, and Address	Protocol #/ Site #/ # of Subjects	Inspection Date	Classification*
CI: Velimir Luketic, M.D. McGuire VAMC, 1201 Broad Rock Blvd. Richmond, VA 23249	747-201/10/5  747-202/4/14  747-301/104/5	September 14 and 15, 2015	NAI
CI: Mitchell Shiffman, M.D. Liver Institute of Virginia, 12720 McManus Blvd Suite 313 Newport News, VA 23602	747-301/145/5	September 8 to 15, 2015	VAI
CI: Krishnamurthy Kowdley, M.D. Virginia Mason Medical Center 1100 Ninth Avenue Seattle, WA 98101	747-201/18/10  747-202/18/9  747-301/118/4	September 14 to 29, 2015	VAI
CI: Paul Pockros, M.D. Scripps Clinic, 10666 N. Torrey Pines Road La Jolla, CA 92037	747-301/139/6	October 26 to 28, 2015	NAI
CI: Frederik Nevens, M.D. UZ Leuven, Campus Gasthuisberg, Herestraat 49 Leuven, Belgium	747-301/142/16	October 5 to 9, 2015	NAI
CI: Giuseppe Mazzella, M.D. Azienda Ospedaliero Universitaria S.Orsola Malpighi, Gastroenterologia, Dipartimento di Medicina Clinica, Via Massarenti, 9 Bologna, Italy	747-301/183/10	October 19 to 23, 2015	NAI
Sponsor: Intercept Pharmaceuticals, Inc. 4760 Eastgate Mall San Diego, CA 92121	Protocols 201, 202, 301	January 19 to February 1, 2016	Pending VAI

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. Velimir Luketic, M.D.****McGuire VAMC, 1201 Broad Rock Blvd., Richmond, VA 23249**

- a. **What was inspected:** At this site for Protocol 201, five subjects were screened and enrolled into the study. The records for all five enrolled subjects were reviewed. The records were compared with data listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. For Protocol 202, a total of 16 subjects were screened, and 14 subjects were randomized into the study. The records for all 14 enrolled subjects were reviewed and were compared with line listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points. For Protocol 301, five subjects were screened and five subjects enrolled into the study. The records for all five enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Mitchell Shiffman, M.D.****Liver Institute of Virginia, 12720 McManus Blvd, Newport News, VA 23602**

- a. **What was inspected:** For Protocol 301, eight subjects were screened and five subjects were enrolled into the study. The records for all five enrolled subjects were reviewed and compared to line listings from the NDA provided for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents. A one item Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, Subject 002 should have been excluded because of cardiac arrhythmias, and Subject 001 did not have genetic testing done per protocol.
- c. **Assessment of data integrity:** The violations above appear isolated and do not impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective

indication.

**3. Krishnamurthy Kowdley, M.D.**  
**Virginia Mason Medical Center, Seattle, WA 98101**

- a. **What was inspected:** At this site for Protocol 201, a total of 11 subjects were screened, and 10 subjects were enrolled into the study. The records for all ten enrolled subjects were reviewed. The records were compared with data listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. For Protocol 202, a total of 14 subjects were screened, and 9 subjects were randomized into the study. The records for all 9 enrolled subjects were reviewed and were compared with line listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points. For Protocol 301, nine subjects were initially screened and six subjects were initially screen failures. Two screen failed subjects (118001, 118002) were re-screened. Subject 118002 was rescreened as Subject 118008 and was enrolled in the study. The records for all four enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued because incorrect dosing instructions were given to certain subjects. Specifically, concerning Study 202, for medication dispensed on Day 29 for four subjects, the subjects were instructed to take one capsule three hours after the last meal whereas the protocol instructions were to take one capsule 30 minutes before breakfast. These incorrect instructions were also provided to one subject on Days 0 and 57 and to another subject on Day 57 only.
- c. **Assessment of data integrity:** The violations above appear isolated and do not impact data integrity. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

**4. Paul Pockros, M.D.**  
**Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA 92037**

- a. **What was inspected:** For Protocol 301, six subjects were screened and enrolled in the study. The records for all six enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the

assignment.

- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. During the inspection, it was noted that there had been an issue in programming the IVRS test article dispensing system. For Subject 139001 visit on 09/24/2012, the site requested one bottle of the investigational product (IP), but the system dispensed two. The study coordinator marked the extra dispensed bottle as an extra and told the subject only to use if all tablets from the other dispensed bottles were used. Subjects were typically dispensed three bottles at a time. The sponsor questioned the site as to why they dispensed an extra bottle. The study coordinator told the sponsor that she only requested one from the system. The sponsor then told the study coordinator that they found out that there was a programming issue that was being corrected. The sponsor requested that the study coordinator retrieve the extra bottle from the subject as it was the wrong dose for the patient. The bottle was returned to the site unused and the bottle was marked as unusable in the IVRS system. This was the only event of its type that occurred at the site.
- c. **Assessment of data integrity:** At this site, the IVRS dosing error was isolated to a single subject. The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

**5. Frederik Nevens, M.D.**

**UZ Leuven, Campus Gasthuisberg, Herestraat 49 Leuven, Belgium**

- a. **What was inspected:** At this site, for Protocol 301, a total of 22 subjects were screened and 16 subjects were enrolled and received study medication. Fifteen subjects completed the study. All 16 enrolled subjects' records were reviewed.
- b. **General observations/commentary:** There was no evidence of underreporting of AEs. The primary efficacy endpoint data were able to be verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication

**6. Giuseppe Mazzella, M.D.**

**Dipartimento di Medicina Clinica, Bologna, Italy**

- a. **What was inspected:** At this site, for Protocol 301, a total of 11 subjects were screened, and 10 subjects were enrolled and received study medication. All 11

enrolled subjects' records were reviewed.

- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. Data listings could be verified for the existing source records for all of the subjects. There was a discussion with the CI concerning the wrong IP dispensing for Subjects 183002 and 183003 because they received 10 mg bottles instead of 5 mg bottled at the Day 1 for the Long Term Safety Evaluation (LTSE) Study. This was due to human error and was discovered by the medical monitor and corrected. The subjects had no reported safety issued due to the short term increase in dose.
- c. **Assessment of data integrity:** Two subjects encountered dosing errors in the LTSE due to human error. These were detected by the sponsor monitor and were corrected. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

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

**Note:** Observations below for this sponsor inspection are based on review of the Form FDA 483 and communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report.

- a. **What was inspected:** This inspection evaluated compliance with sponsor responsibilities for Protocols 747-201, 747-202, and 747-301 including selection and oversight of contract research organizations, monitoring, financial disclosure, FDA Form 1572s, quality assurance (QA), and handling of data. The inspection included review of general correspondence and study master files, site monitoring, and handling of adverse events and other sponsor/monitor related activities.
- b. **General observations/commentary:** Review of the sponsor documents did not note any significant deficiencies. Monitoring practices of five sites were reviewed in detail. Results of the inspection indicated that, in general, monitoring of investigators was adequate and the sponsor maintained adequate oversight of the trials. There was no noncompliance site recorded for the Study Protocol 747-301. However, during the Phase 2 clinical trials for Protocols 201 and 202, there was one clinical site in the United Kingdom (UK) (Site 125) that was out of compliance. The site lost two subjects' records during the office move. A plan was initiated to determine the root cause and put in place corrective actions (CAPA # 2013-0005) and a third party audit was performed to determine whether the corrections had been implemented. A Form FDA 483 was issued for the following three observations:

1. Failure to ensure proper monitoring of the study. Specifically, numerous monitoring reports were approved after 40 days to 595 days by the Clinical Trial Manager (CTM) and some monitoring reports have not been reviewed and approved by the CTM.
2. Records and reports were not retained for two years after marketing application approval and discontinuance of the investigation and notification of FDA. Specifically, most of the regulatory binder documents that were sent to (b) (4) for scanning into (b) (4) System before 12/30/2013 were maintained by (b) (4) after scanning and they were not destroyed. After 12/30/2013, the documents related to the regulatory binder that were collected by the monitors were scanned into (b) (4) by Intercept or monitors and the hard copies were destroyed after scanning. Examples of the types of documents destroyed are monitoring reports with original wet signature pages, original wet signature pages of project plan, original wet signature pages of personnel training forms, original wet signature pages of the protocol and protocol amendments, and original wet signature pages of investigator's meeting training forms/attendance records. The original Forms FDA-1572 and the IRB approval letters are still maintained by the sites.

*Reviewer note: This is considered a violation because the scans were not certified as copies before being destroyed. Although this is a violation, it appears that significant documents such as Forms FDA-1572 and the IRB approval letters are still maintained by the sites. No significant violations at clinical sites for which monitoring reports were critical were encountered. As evidenced by the above observation, sites were adequately monitored and brought into compliance when appropriate.*

3. Transfer of obligations to a contract research organization was not described in writing. Specifically, there was a failure to have a master laboratory service agreement transferring the responsibility for testing of enhanced liver fibrosis (ELF) to (b) (4).
- c. **Assessment of data integrity:** The above violations are considered not to have a significant impact on data integrity and reliability. The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites and the sponsor were inspected for this application. The classification for the routine sponsor inspection for this new molecular entity is pending. Four of the inspections have a final classification of NAI. The isolated instances of dosing error are not considered systemic or systematic. The violations cited for the VAI classifications at the sponsor and at the clinical sites of Drs. Schiffman and Kowdley sites are considered minor.

The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Medical Reviewer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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Kassa Ayalew, M.D., M.P.H  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Enforcement  
Office of Scientific Investigations

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/s/  
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SUSAN LEIBENHAUT  
02/11/2016

SUSAN D THOMPSON  
02/11/2016

KASSA AYALEW  
02/12/2016

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

DATE: November 16, 2015

TO: Anissa Davis, Regulatory Project Manager  
Ruby Mehta, M.D., Medical Officer  
Division of Gastroenterology and Inborn Errors Products

FROM: Susan Leibenhaut, M.D.  
Medical Officer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 207999

APPLICANT: Intercept Pharmaceuticals, Inc.

DRUG: Obeticholic Acid

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA

CONSULTATION REQUEST DATE: July 30, 2015

INSPECTION SUMMARY GOAL DATE: November 20, 2015\*

DIVISION ACTION GOAL DATE: February 29, 2016

PDUFA DATE: February 29, 2016

\*At the time of this review, a major amendment is anticipated that will revise the clock three

months into the future. An updated CIS will be submitted by February 20, 2016. The updated CIS will include the available final classifications of clinical investigator inspections discussed below and the preliminary results of the routine sponsor inspection.

## **I. BACKGROUND:**

Intercept Pharmaceuticals, Inc. submitted NDA 207999 for obeticholic acid (OCA) for the indication 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 UDCA.

The review division requested inspection of the clinical trials below that were submitted in support of the indication:

1. Protocol 747-301 entitled “A Phase 3, Double Blind, Placebo Controlled Trial and Long Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis”
2. Protocol 747-201 entitled “A Study of INT-747 (6-ECDCA) Monotherapy in Patients with Primary Biliary Cirrhosis”
3. Protocol 747-201 entitled “A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid (URSO, UDCA) in Patients with Primary Biliary Cirrhosis

The foreign sites were chosen because they are the highest enrollers in the Phase 3 study Protocol 747-301. For domestic sites, sites conducting the single Phase 3 protocol were selected on the basis of high enrollment at domestic sites. Other domestic sites were selected because they participated in all three studies.

## II. RESULTS (by Site):

Type of Inspected Entity, Name, and Address	Protocol #/ Site #/ # of Subjects	Inspection Date	Classification*
CI: Velimir Luketic, M.D. McGuire VAMC, 1201 Broad Rock Blvd. Richmond, VA 23249	747-201/10/5 747-202/4/14 747-301/104/5	September 14 and 15, 2015	NAI
CI: Mitchell Shiffman, M.D. Liver Institute of Virginia, 12720 McManus Blvd Suite 313 Newport News, VA 23602	747-301/145/5	September 8 to 15, 2015	Pending VAI
CI: Krishnamurthy Kowdley, M.D. Virginia Mason Medical Center 1100 Ninth Avenue Seattle, WA 98101	747-201/18/10 747-202/18/9 747-301/118/4	September 14 to 29, 2015	Pending VAI
CI: Paul Pockros, M.D. Scripps Clinic, 10666 N. Torrey Pines Road La Jolla, CA 92037	747-301/139/6	October 26 to 28, 2015	Pending NAI
CI: Frederik Nevens, M.D. UZ Leuven, Campus Gasthuisberg, Herestraat 49 Leuven, Belgium	747-301/142/16	October 5 to 9, 2015	Pending NAI
CI: Giuseppe Mazzella, M.D. Azienda Ospedaliero Universitaria S.Orsola Malpighi, Gastroenterologia, Dipartimento di Medicina Clinica, Via Massarenti, 9 Bologna, Italy	747-301/183/10	October 19 to 23, 2015	Pending NAI
Sponsor: Intercept Pharmaceuticals, Inc. 4760 Eastgate Mall San Diego, CA 92121	Protocols 201, 202, 301	Pending	Pending

### Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. Velimir Luketic, M.D.****McGuire VAMC, 1201 Broad Rock Blvd., Richmond, VA 23249**

- a. **What was inspected:** At this site for Protocol 201, five subjects were screened and enrolled into the study. The records for all five enrolled subjects were reviewed. The records were compared with data listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. For Protocol 202, a total of 16 subjects were screened, and 14 subjects were randomized into the study. The records for all 14 enrolled subjects were reviewed and were compared with line listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points. For Protocol 301, five subjects were screened and five subjects enrolled into the study. The records for all five enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**2. Mitchell Shiffman, M.D.****Liver Institute of Virginia, 12720 McManus Blvd, Newport News, VA 23602**

**Note:** Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol 301, eight subjects were screened and five subjects were enrolled into the study. The records for all five enrolled subjects were reviewed and compared to line listings from the NDA provided for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. There were no discrepancies between the data in the line listings and the source documents. A one item Form FDA 483 was issued because the investigation was not conducted in accordance with the investigational plan. Specifically, Subject 002 should have been excluded because of cardiac arrhythmias, and Subject 001 did not have genetic testing done per protocol.

- c. **Assessment of data integrity:** The violations above appear isolated and do not impact data integrity. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

**3. Krishnamurthy Kowdley, M.D.  
Virginia Mason Medical Center, Seattle, WA 98101**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** At this site for Protocol 201, a total of 11 subjects were screened, and 10 subjects were enrolled into the study. The records for all ten enrolled subjects were reviewed. The records were compared with data listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment. For Protocol 202, a total of 14 subjects were screened, and 9 subjects were randomized into the study. The records for all 9 enrolled subjects were reviewed and were compared with line listings for primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points. For Protocol 301, nine subjects were initially screened and six subjects were initially screen failures. Two screen failed subjects (118001, 118002) were re-screened. Subject 118002 was rescreened as Subject 118008 and was enrolled in the study. The records for all four enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events. A Form FDA 483 was issued because incorrect dosing instructions were given to certain subjects. Specifically, concerning Study 202, for medication dispensed on Day 29 for four subjects, the subjects were instructed to take one capsule three hours after the last meal whereas the protocol instructions were to take one capsule 30 minutes before breakfast. These incorrect instructions were also provided to one subject on Days 0 and 57 and to another subject on Day 57 only.
- c. **Assessment of data integrity:** The studies appear to have been conducted adequately, and the data generated by these studies appear acceptable in support of the respective indications.

**4. Paul Pockros, M.D.****Scripps Clinic, 10666 N. Torrey Pines Road, La Jolla, CA 92037**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** For Protocol 301, six subjects were screened and enrolled in the study. The records for all six enrolled subjects were reviewed and compared to primary and secondary endpoints, adverse events, eligibility criteria, and other selected data points against the line listings provided with the assignment.
- b. **General Observations/Commentary:** The primary efficacy data were able to be verified. There was no evidence of under-reporting of adverse events.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this study appear acceptable in support of the respective indications.

**5. Frederik Nevens, M.D.****UZ Leuven, Campus Gasthuisberg, Herestraat 49 Leuven, Belgium**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the EIR.

- a. **What was inspected:** At this site, for Protocol 301, a total of 22 subjects were screened and 16 subjects were enrolled and received study medication. Fifteen subjects completed the study. All 16 enrolled subjects' records were reviewed.
- b. **General observations/commentary:** There was no evidence of underreporting of AEs. The primary efficacy endpoint data were able to be verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication

**6. Giuseppe Mazzella, M.D.****Dipartimento di Medicina Clinica, Bologna, Italy**

**Note:** Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final EIR.

- a. **What was inspected:** At this site, for Protocol 301, a total of 11 subjects were screened and 10 subjects were enrolled and received study medication. All 11 enrolled subjects' records were reviewed.
- b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. Data listings could be verified for the existing source records for the 27 subjects. The source documentation that was available was well organized and in good condition. Swiss law requires that records be maintained for 15 years after the completion of the study and this had passed in 2013, so an FDA 483 was not issued for missing records.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Six clinical investigator sites were inspected for this application. The routine sponsor inspection for this new molecular entity is pending. All reviews except Dr. Luketic are preliminary and based on e-mail communications. Four of the inspections have a final or preliminary classification of NAI. The violations noted at Dr. Schiffman and Kowdley sites are considered minor.

The studies appear to have been conducted adequately, and the data generated by the studies appear acceptable in support of the respective indication.

A final clinical inspection summary will be entered into DARRTS after the results of the sponsor inspection are received.

*{See appended electronic signature page}*

Susan Leibenhaut, M.D.  
Medical Reviewer  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

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/s/  
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SUSAN LEIBENHAUT  
11/16/2015

SUSAN D THOMPSON  
11/17/2015

**MEMORANDUM**

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

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DATE: November 12, 2015

TO: Donna Griebel, M.D.  
Director  
Division of Gastroenterology and Inborn Errors Products  
(DGIEP)  
Office of Drug Evaluation III  
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.  
Staff Fellow  
Division of Generic Drug Bioequivalence Evaluation (DGDBE)  
Office of Study Integrity and Surveillance (OSIS)

Yiyue Zhang, Ph.D.  
Visiting Associate  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

Arindam Dasgupta, Ph.D.  
Lead Pharmacologist  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Charles Bonapace, Pharm.D.  
Director  
Division of New Drug Bioequivalence Evaluation (DNDBE)  
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of EIR covering **NDA 207999**, Obeticholic Acid  
Tablets, 10 mg, sponsored by Intercept Pharmaceuticals,  
Inc., San Diego, CA

**Summary:**

At the request of the Division of Gastroenterology and Inborn Errors Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of the analytical portion and arranged an inspection of the clinical portion of the following pharmacokinetic study:

**Study Number:** 747-115

**Study Title:** "An Open-Label, Two-Way Crossover Trial to Assess the Biocomparability of Two Tablet Formulations of Obeticholic Acid After a Single Dose in Healthy Adult Subjects"

**Analytical Site**

The inspection of the analytical portion of this study was conducted by Arindam Dasgupta, Ph.D. (Lead Pharmacologist, DNDBE/OSIS), Yiyue Zhang, Ph.D. (Visiting Associate, DNDBE/OSIS), and (b) (4)

(b) (4) from (b) (4). The audit covered the bioanalytical method validation and sample analysis of OCA, Glyco-OCA, and Tauro-OCA as well as the ELISA analysis of FGF-19. The audit also included a thorough examination of facilities and equipment, review of study (b) (4) ce, and interviews and discussions with (b) (4) management and staff. As a global assessment of the firm's bioanalytical operations, several key study components were selected for audit to represent the firm's bioanalytical operations since the previous inspection.

Form FDA 483, Inspectional Observations (b) (4) e close-out of the inspection (**Attachment 1**). (b) (4) responded to Form FDA 483 on November 2, 2015 (**Attachment 2**). The Form FDA 483 observations, (b) (4) response, and our evaluation of the observations follow.

**Observation 1:**

**Not all runs were included in the global assessment of the accuracy and precision during method validation.**

**Specifically, QCs for OCA, G-OCA, and T-OCA in runs 1 (QCL) and 4 (QCL) failed to meet the acceptance criteria and were excluded from the determination of assay accuracy and precision.**

During the inspection of (b) (4) we noted that (b) (4)'s method validation SOP ((b) (4)) for accuracy and precision allowed exclusion of data from the global assessment of precision and accuracy when individual batches failed to meet 15% acceptance criteria at any QC level (20% at LLOQ) for unknown reasons. In the event that individual batches were rejected, additional precision and accuracy batches were performed and included in the assessment of global precision and accuracy. The failing data were not reported to the Agency.

On the basis of their SOP, (b) (4) rejected and repeated Runs 1 and 4. For Run 1, only 1 of the 6 replicates of OCA (6-ECDCA) and G-OCA (6-EGCDCA) failed to meet acceptance criteria at the Low QC (QCL) (**Attachment 3**). For Run 4, 3 of the 6 replicates for all the three analytes (OCA, G-OCA, and T-OCA) failed to meet acceptance criteria at QCL and LLOQ (**Attachment 4**).

**Firm's response:** In their written response (**Attachment 2**), (b) (4) acknowledged the observation. As a corrective action, (b) (4) updated their method validation SOP (b) (4) effective November 3, 2015) to require inclusion of all data in the global assessment of precision and accuracy (**Attachment 5**). In the amended report (b) (4) study #12057 in support of (b) (4) study # 14059) submitted to the sponsor, (b) (4) included all QC data that were excluded in the original method validation report. Precision and accuracy results were presented after including data from Run 1. Run 4 data were not included in the global assessment of precision and accuracy due to suspected sample preparation error. A copy of the revised report is attached (**Attachment 6**). The precision and accuracy results excluding Runs 1 and 4 were presented in the original method validation report (Report #RPT02968) Tables 8-19. (b) (4) also committed to include all QC data (except those failing due to assignable cause) for global assessment of precision and accuracy for all active studies.

**OSIS Evaluation:**

The measured concentrations of the QC samples that failed acceptance criteria in Runs 1 and 4 appeared to be extreme outliers. When data from Runs 1 and 4 were included, the global precision and accuracy at the LLOQ and QCL failed to meet the acceptance criteria (<15% accuracy and precision) for all three analytes.

The results support the conclusion that the QC values were outliers and their abnormal concentrations are likely due to a sample processing error or other cause and not representative of the overall precision and accuracy of the analytical method. The method's precision and accuracy was further confirmed during analysis of study samples. Thus, the exclusion of Runs 1 and 4 from the global assessment of precision and accuracy is not likely to impact the integrity of the study data.

### **Clinical Site**

The inspection of the clinical portion of study #747-115 was conducted by ORA Investigator Douglas Fiorentino (FLA-DO) at Orlando Clinical Research Center, Orlando, FL from September 30-October 7, 2015. The audit included a review of subject case histories, including source documentation, informed consent forms, case report forms, and other documentation, protocol adherence, adverse events, institutional review board (IRB) approvals, site reporting, sponsor correspondence, monitoring, and investigational product accountability.

Following the inspection of Orlando Clinical Research Center, no significant issues were observed and no Form FDA 483 was issued. However, the following two items were discussed at the close-out meeting.

**Discussion item 1:** There was no nomenclature or clear statement included in the SOPs evaluated which indicated that if the site receives multiple shipments of pharmaceutical product for the same study, retention samples will be held from each shipment.

Mr. Christopher Ferone, the Quality Assurance Manager, agreed that a clear statement is not included in any SOP, but it is a common practice to hold retention samples from each shipment.

**Discussion item 2:** The date on the monitoring log for the closeout visit for this study was originally listed as 01/23/2014, but the visit actually occurred on 01/23/2015.

The monitoring log was amended and the new date was added to the log. Mr. Ferone presented a new log with the date corrected from the sponsor representative.

The above discussion items are not likely to impact the integrity of the study data.

### **Conclusion:**

Following the evaluation of the inspectional findings and EIR, the analytical and clinical data from the audited study were found to be reliable. Therefore, we recommend that the analytical and clinical data for study #747-115 be accepted for further Agency review.

Melkamu Getie-Kehtie, Ph.D., R.Ph.  
Staff Fellow  
DGDBE, OSIS

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**VAI -** [REDACTED] (b) (4)

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OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho/Zhang/Raha  
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11/13/2015

CHARLES R BONAPACE  
11/13/2015

**Interdisciplinary Review Team for QT Studies Consultation:  
Thorough QT Study Review**

<b>NDA</b>	NDA 207999
<b>Generic Name</b>	Obeticholic acid
<b>Sponsor</b>	Intercept Pharmaceuticals, Inc.
<b>Indication</b>	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.
<b>Dosage Form</b>	Tablet
<b>Drug Class</b>	Agonist for FXR, a nuclear receptor expressed at high levels in the liver and intestine
<b>Therapeutic Dosing Regimen</b>	The recommended starting dose is 5 mg once daily. Based on the assessment of efficacy and tolerability after 3 months, the dose may be increased to 10 mg once daily to improve response.
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	100 mg QD (2 weeks), 500 mg single dose.
<b>Submission Number and Date</b>	SDN 002; 29 Jul 2015
<b>Review Division</b>	DGIEP

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## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of obeticholic acid (OCA 100 mg) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between obeticholic acid (OCA 100 mg) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 2, indicating that assay sensitivity was established.

In this randomized, blinded, parallel study, 191 healthy subjects received OCA 100 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Obeticholic Acid (OCA 100 mg/Day) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment	Day	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
OCA 100 mg	1	11	2.5	(0.7, 4.4)
OCA 100 mg	3	0	2.3	(0.2, 4.5)
OCA 100 mg	5	3	3.2	(0.4, 5.9)
Moxifloxacin 400 mg*	5	3	9.3	(5.5, 13.0)

\* Multiple endpoint adjustment of 4 time points was applied.

The selected suprathreshold dose, 100 mg once-daily for 5 days, is reasonable. OCA 100 mg for 5 days is considered the maximum tolerated dose. On Day 5, the predicted  $C_{\text{max}}$  ratios of total OCA, OCA, glyco-OCA and tauro-OCA relative to the steady-state exposure after a 10-mg dose are approximately 3.9, 7.2, 5.0 and 2.8. There are no indication of a relationship between QT interval and OCA concentrations.

## 2 PROPOSED LABEL

*The sponsor did not propose any QT-related labeling language. Our proposed language is a recommendation only. We defer final labeling language to the Division.*

### 12.2. Pharmacodynamics

#### Cardiac Electrophysiology

The effect of TRADENAME on the QTc interval was evaluated in a Phase 1 randomized placebo and positive controlled double-blind, parallel thorough QTc study in 191 healthy subjects. At the dose 10-fold the therapeutic dose for 5 days, TRADENAME did not prolong QTc to any clinically relevant extent.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Obeticholic acid (OCA) is a modified bile acid and farnesoid X receptor (FXR) agonist that is derived from the primary human bile acid chenodeoxycholic acid (CDCA). It is developed for the treatment of primary biliary cirrhosis.

### 3.2 MARKET APPROVAL STATUS

Obeticholic acid is not approved for marketing in any country.

### 3.3 PRECLINICAL INFORMATION

See Appendix 6.1.

#### In vitro

OCA at concentrations  $\leq 82.8 \mu\text{M}$  had no clear effect on cloned hERG channel currents in HEK293 cells.

#### In vivo

The potential of OCA to affect the cardiovascular system was assessed in telemeterized beagle dogs with no effects on the cardiovascular system at the highest dose tested (20 mg/kg).

### **3.4 PREVIOUS CLINICAL EXPERIENCE**

See Appendix 6.1.

### **3.5 CLINICAL PHARMACOLOGY**

Appendix 6.1 summarizes the key features of Obeticholic acid's clinical pharmacology.

## **4 SPONSOR'S SUBMISSION**

### **4.1 OVERVIEW**

The QT-IRT reviewed the protocol prior to conducting this study under IND 63307. The sponsor submitted the study report 747-108 for obeticholic acid, including electronic datasets and waveforms to the ECG warehouse.

### **4.2 TQT STUDY**

#### **4.2.1 Title**

A randomized, double-blind, double-dummy, placebo- and positive-controlled, parallel-group trial to assess the electrophysiological effects of obeticholic acid at therapeutic and suprathreshold concentrations on the 12-Lead electrocardiogram QT interval in healthy subjects

#### **4.2.2 Protocol Number**

747-108

#### **4.2.3 Study Dates**

03 Jun 2014 -- 17 Jul 2014

#### **4.2.4 Objectives**

The primary objective of the study was to:

- determine, in healthy subjects, that OCA and its conjugates (glyco-OCA and tauro-OCA) at therapeutic and suprathreshold concentrations do not differ from placebo in the largest time-matched mean change from baseline in 12-lead ECG corrected QT interval

The secondary objectives of the study were to:

- establish the ability of the study to detect if OCA and its conjugates (glyco-OCA and tauro-OCA) have an effect on QT intervals by demonstrating that

- moxifloxacin QT intervals differ from placebo in the largest time-matched mean change from baseline in 12-lead ECG corrected QT interval
- evaluate the effect of OCA and its conjugates (glyco-OCA and tauro-OCA) on other cardiac electrophysiological parameters at therapeutic and supratherapeutic concentrations including wave morphology changes
  - evaluate the relationship between the concentration of plasma OCA and its conjugates (glyco-OCA and tauro-OCA) and QT intervals at therapeutic and supratherapeutic concentrations
  - evaluate the pharmacokinetics (PK) of OCA and its conjugates (glyco-OCA and tauro-OCA) at therapeutic and supratherapeutic concentrations
  - evaluate the pharmacodynamics (PD) of the physiological covariates of serum glucose, insulin, potassium, and magnesium on the corrected QTc interval
  - evaluate the safety and tolerability of OCA and its conjugates (glyco-OCA and tauro-OCA) at therapeutic and supratherapeutic concentrations

## 4.2.5 Study Description

### 4.2.5.1 Design

This is a randomized, double-blind, double-dummy, 3-arm, parallel study.

### 4.2.5.2 Controls

The sponsor used both placebo and positive (moxifloxacin) controls.

### 4.2.5.3 Blinding

The study was double-blinded. OCA tablets and the OCA-matched placebo were visually identical; moxifloxacin tablets and moxifloxacin-matched placebo were overencapsulated.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

There were 3 arms:

**OCA:** OCA 100 mg/day and moxifloxacin-matched placebo on Day 1 to Day 5

**Placebo:** OCA-matched placebo and moxifloxacin-matched placebo on Day 1 to Day 5

**Moxifloxacin:** OCA-matched placebo on Day 1 to Day 5, moxifloxacin-matched placebo on Day 1 to Day 4, and active moxifloxacin 400 mg on Day 5.

### 4.2.6.2 Sponsor's Justification for Doses

The dosing regimen for the thorough QT study was based on two phase 1 OCA PK studies (Studies 747-105 and 747-107), which carefully evaluated the PK of OCA and its conjugates in healthy subjects after once-daily dosing of OCA 5 mg, 10 mg, and 25 mg (Study 747-105) and OCA 100 mg (Study 747-107). The mean predicted maximum concentration ratio of total OCA on Days 1 and 5 with the 100 mg dose relative to that achieved at steady state following once-daily dosing of 10 mg OCA is approximately 2 (therapeutic) and 5 (supratherapeutic), respectively.

The majority of the exposure of total OCA is primarily from the exposure of the glycine and taurine conjugates. The mean predicted maximum concentration ratio of glyco-OCA and tauro-OCA on Day 1 (therapeutic) with the 100 mg dose relative to that achieved at steady state following once-daily dosing of 10 mg OCA is approximately 2 and 1, respectively. The predicted C<sub>max</sub> ratios of glyco-OCA and tauro-OCA after a 100-mg dose on Day 5 (supratherapeutic) relative to the steady-state exposure after a 10-mg dose are approximately 6 and 3, respectively..

Repeat dosing of OCA at doses higher than 100 mg have been associated with clinically significant elevations in aminotransferases in healthy subjects, hence repeat dosing of OCA 100 mg for 5 days is considered the maximum tolerated dose appropriate for this study.

*Reviewer’s comment: The selected supratherapeutic dose, 100 mg once-daily for 5 days, is reasonable. OCA 100 mg for 5 days is considered the maximum tolerated dose. On Day 5, the predicted C<sub>max</sub> ratios of total OCA, OCA, glyco-OCA and tauro-OCA relative to the steady-state exposure after a 10-mg dose are approximately 3.9, 7.2, 5.0 and 2.8.*

#### 4.2.6.3 Instructions with Regard to Meals

All subjects were to have fasted for at least 10 hours prior to OCA administration

*Reviewer’s comment: There is no substantial effect of food on OCA exposure. Applicant’s instructions are acceptable.*

#### 4.2.6.4 ECG and PK Assessments

**PK blood samples were collected on the following days and times:**

Trial Day	Target Nominal Post Dose Time (Hour)
1	– Predose (0.0 hour) (within 30 minutes before OCA administration) – Postdose samples: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, and 12 hours
2	– Predose (0.0 hour) (within 30 minutes before OCA administration)
3	– Predose (0.0 hour) (within 30 minutes before OCA administration) – Postdose samples: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, and 12 hours
4	– Predose (0.0 hour) (within 30 minutes before OCA administration)
5	– Predose (0.0 hour) (within 30 minutes before OCA administration) – Postdose samples: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 11, and 12 hours

On Day 0, subjects will begin approximately 132 hours (Day 0 starting at 08:00 through 20:00 on Day 5) of continuous ECG monitoring for baseline and on-treatment assessments. Three replicate 12-lead ECG measurements will be extracted at 1-hour intervals for 12 hours beginning at t = -24 hour (Day 0), coincident with blood sample collection for PD assessments, as the Baseline ECG assessment period. On Days 1, 3, and 5: three replicate 12-lead ECG measurements will be extracted at 1-hour intervals for 12

hours after OCA, placebo, or moxifloxacin administration, coincident with blood sample collection for PK and PD assessments..

*Reviewer's Comment: Acceptable. The ECG/PK assessments are able to capture the T<sub>max</sub> of OCA and its conjugates.*

#### **4.2.6.5 Baseline**

The time-matched average values of QT/QTc on Day -1 were used as baselines.

#### **4.2.7 ECG Collection**

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Standard 12-Lead ECGs were obtained while subjects were recumbent.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

A total of 192 healthy subjects were randomized to the study; 64 subjects were each randomized to placebo, moxifloxacin, or OCA treatment groups. One hundred ninety-one (191) subjects in the safety and ITT Populations received at least 1 dose of investigational product. One hundred eighty-eight (188) subjects completed the study.

For the overall population, the mean age was 34.7 years and ranged from 18 years to 54 years. The majority of subjects were male (97%) and white (61%) or African American (38%). The majority of subjects (91%) were non-Hispanic or Latino.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

For the primary endpoint analysis comparison between OCA 100 mg and placebo at Day 5 of the corresponding treatment period, the largest difference in  $\Delta\Delta\text{QTcF}$  was 3.2 msec (adjusted upper 95% confidence limit [CL] of 6.5 msec) which was lower than the 10 msec threshold. As this upper limit of the 95% CI was <10 msec, it was therefore below the threshold of regulatory concern defined in the ICH E14 Guidance, indicating no effect of OCA on QTcF at therapeutic or suprathreshold levels. Additionally, the LS mean estimate and upper CL for  $\Delta\Delta\text{QTcF}$  were lower than 10 msec at all 12 prespecified timepoints.

There was no difference in the results of the analyses between the QT Evaluable Population and the ITT Population.

The sponsor's results for primary analysis are displayed in the following

.

**Table 2:  $\Delta\Delta$ QTcF on Day 5 Following Treatment with OCA 100 mg/Day  
(Sponsor’s Results Based on QT Evaluable Population)**

Timepoint (hours)	LS Mean (SE) Change in QTcF from Baseline in ( $\Delta$ QTcF) (msec)		Difference in LS Mean (SE) ( $\Delta\Delta$ QTcF)	Adjusted Upper 95% CL <sup>a</sup>
	Placebo (N = 63)	OCA (100 mg) (N = 62)		
0	-0.9 (1.04)	1.3 (1.05)	2.2 (1.48)	5.1
1	-1.9 (1.09)	-1.7 (1.10)	0.3 (1.55)	3.3
2	-1.8 (1.12)	0.0 (1.13)	1.8 (1.59)	4.9
3	<b>-2.6 (1.17)</b>	<b>0.6 (1.18)</b>	<b>3.2<sup>b</sup>(1.66)</b>	<b>6.5</b>
4	-1.2 (0.92)	0.8 (0.93)	2.1 (1.30)	4.6
5	-2.2 (1.16)	0.4 (1.17)	2.6 (1.64)	5.9
6	-0.6 (1.00)	1.3 (1.00)	2.0 (1.42)	4.8
7	0.5 (1.02)	3.3 (1.03)	2.8 (1.45)	5.7
8	1.2 (1.03)	2.0 (1.04)	0.8 (1.47)	3.7
9	0.2 (1.12)	2.6 (1.13)	2.4 (1.60)	5.5
10	-0.9 (0.98)	0.2 (0.99)	1.1 (1.39)	3.8
11	0.0 (0.95)	3.0 (0.96)	3.0 (1.36)	5.7
12	0.0 (0.97)	-0.2 (0.98)	-0.3 (1.38)	2.5

CL = confidence limit; LS = least squares; OCA = obeticholic acid; QTcF = QT interval corrected by Fridericia’s formula; SE = standard error

<sup>a</sup> Adjusted confidence limits are adjusted using the Hochberg procedure. 97.5% upper confidence limit is presented for Day 1 and Day 5.

<sup>b</sup>  $\Delta$ QTcF at 3.0 hours was the primary endpoint. If the upper confidence limit within the OCA treatment group was less than 10 msec then the primary endpoint was met.

Source: clinical study report 747-108, Table 17, page 62

Reviewer’s Comments: please see the reviewer’s analysis in section 5.2.

#### 4.2.8.2.2 Assay Sensitivity

The sensitivity of the study was to be considered validated if the lower bound of the 95% 1-sided CI, adjusted for multiplicity using the Hochberg procedure, for  $\Delta\Delta$ QTc (moxifloxacin - placebo) was greater than 5 msec for the mean time-matched difference for at least 1 of the postdose timepoints (1, 2, 3, or 4 hours postdose). Assay sensitivity was validated at 2 timepoints postdose (3 hours and 4 hours postdose).

The sponsor’s results for assay sensitivity analysis are displayed in the following Table 3.

**Table 3: Mean Time-Matched  $\Delta\Delta$ QTcF Following Treatment with Moxifloxacin 400 mg on Day 5 (Sponsor’s Results Based on QT Evaluable Population)**

Timepoint (hours)	LS Mean (SE) Change in QTcF from Baseline in ( $\Delta$ QTcF) (msec)		Difference in LS Mean (SE) ( $\Delta\Delta$ QTcF)	Adjusted CL <sup>a</sup>
	Placebo (N = 63)	Moxifloxacin (400 mg) (N = 63)		
0	-0.9 (1.04)	-0.7 (1.04)	NA	NA
1	-1.9 (1.09)	6.3 (1.09)	8.3 (1.54)	4.8
2	-1.8 (1.12)	6.5 (1.12)	8.3 (1.59)	4.8
3	-2.6 (1.17) <sup>b</sup>	6.7 (1.17) <sup>b</sup>	9.3 (1.66) <sup>b</sup>	5.5 <sup>a</sup>
4	-1.2 (0.92) <sup>b</sup>	6.8 (0.92) <sup>b</sup>	8.0 (1.30) <sup>b</sup>	5.1 <sup>a</sup>

CL = confidence limit; LS = least squares; NA = not applicable; QTcF = QT interval corrected by Fridericia’s formula; SE = standard error

<sup>a</sup> Adjusted confidence limits are adjusted using the Hochberg procedure. A 98.75% lower confidence limit was presented. If the lower confidence limit was greater than 5 msec at any of 1, 2, 3, or 4 hour timepoints then assay sensitivity was validated

<sup>b</sup> Based on ANCOVA model with time-matched difference as the dependent variable and a fixed effect for treatment group and baseline as a covariate

Source: clinical study report 747-108, Table 18, page 64

Reviewer’s Comments: please see the reviewer’s analysis in section 5.2.

#### 4.2.8.2.3 Categorical Analysis

Overall, for QTcF, no subjects in the placebo and OCA treatment groups had an interval increase greater than 480 msec or an interval change from time-matched baseline greater than 60 msec at any time during the study. One subject in each of the placebo and OCA treatment groups had a QTcF interval greater than 450 msec or an interval change from time-matched baseline greater than 30 msec.

#### 4.2.8.3 Safety Analysis

There were no deaths or SAEs reported in the study. One subject in the placebo group was discontinued due to a TEAE.

#### 4.2.8.4 Clinical Pharmacology

##### 4.2.8.4.1 Pharmacokinetic Analysis

The mean C<sub>max</sub> (1120 ng/mL) of total OCA following administration of 100 mg OCA on Day 5 in the thorough QT study were 3.9-fold the steady state C<sub>max</sub> (285 ng/mL from Study 747-105) with 10 mg OCA, the maximal intended clinical dose (Table 4).

On Day 5, the mean C<sub>max</sub> of OCA, glyco-OCA and tauro-OCA following administration of 100 mg OCA in the thorough QT study were 7.2-, 5.0- and 2.8-fold the steady state

$C_{max}$  of OCA, glyco-OCA and tauro-OCA, respectively (38, 779 and 511 ng/mL from Study 747-105) with 10 mg OCA (Table 5).

**Table 4. Pharmacokinetic Parameters for Total OCA- QT: Evaluable Population (N = 62)**

PK Parameters	Total OCA 100 mg/d <sup>a</sup>		
	Day 1	Day 3	Day 5
<b><math>C_{max}</math> (ng/mL)</b>			
n	62	62	62
Mean (SD)	400 (173)	769 (335)	1120 (422)
Median	369	699	1050
Min, Max	170, 882	347, 1918	489, 2550

OCA = obeticholic acid; SD = standard deviation

<sup>a</sup> Total OCA calculated as sum of OCA, glyco-OCA, and tauro-OCA concentrations at each timepoint expressed as mass equivalents of OCA.

Source: 747-108 CSR; Section 14, [Table 14.2.7](#).

**Table 5. Pharmacokinetic Parameters for OCA on Day 5: Evaluable Population (N = 62)**

Visit	Parameter	OCA Treatment Group (N=62)		
		OCA	Glyco-OCA	Tauro-OCA
Day 5	$C_{max}$ (ng/mL)			
	Mean (SEM)	272.27 (12.830)	779.47 (41.756)	510.82 (31.635)
	Geometric Mean	254.13	720.12	458.05
	$T_{max}$ (hr)			
	Median	1.5	10.08	10.08
	AUC <sub>0-t</sub> (h*ng/mL)			
	Mean (SEM)	640.386 (17.7797)	4953.541 (310.7054)	2958.969 (201.4615)
	Geometric Mean	20.8757	42.4235	51.943

#### 4.2.8.4.2 Exposure-Response Analysis

After correcting for the observed effect of day and the circadian rhythm on  $\Delta QTc$  in the mixed-effect analysis (placebo and OCA treated subjects), no relationship between total OCA exposure and  $\Delta QTcF$  was observed as indicated by a slope (total OCA estimate = 0.00011,  $p = 0.9020$ ) that was not statistically different from zero.

*Reviewer's Analysis:* A plot of  $\Delta QTc$  vs. drug concentrations is presented in Figure 4.

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcB, QTcF and QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

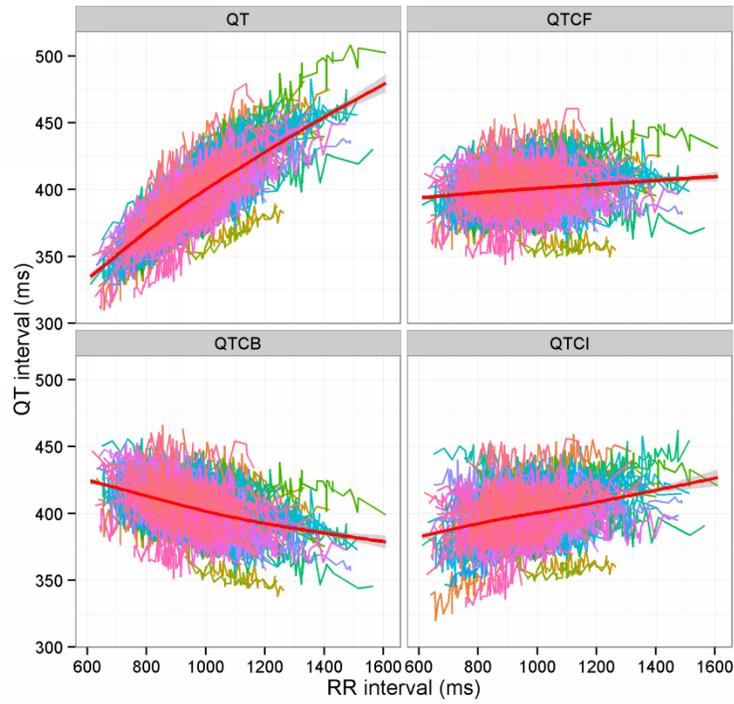
We used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 6, it appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis.

**Table 6: Average of Sum of Squared Slopes for Different QT-RR Correction Methods**

Treatment Group	QTcB		QTcF		QTcI	
	N	MSSS	N	MSSS	N	MSSS
Placebo	64	0.00448	64	0.00068	64	0.00227
Moxifloxacin 400 mg	64	0.00596	64	0.00085	64	0.00145
OCA 100 mg	63	0.00433	63	0.00087	63	0.00275
All	191	0.00493	191	0.00080	191	0.00215

The relationship between different correction methods and RR is presented in Figure 1.

**Figure 1: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for Obeticholic Acid

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect at each time point. The model includes treatment as fixed effect; baseline values are also included in the model as a covariate. The analysis results are listed in the following tables (results for day 3 were not posted).

**Table 7: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Obeticholic Acid (OCA 100 mg/Day) on Day 1**

Time (hour)	$\Delta$ QTcF (ms) OCA 100 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) OCA 100 mg	
	LSmean	LSmean	LSmean	90% CI
1	-3.1	-1.4	-1.2	(-3.6, 1.2)
2	-3.0	-3.6	0.8	(-1.4, 2.9)
3	-3.3	-2.3	-0.8	(-2.9, 1.2)
4	-1.5	-2.3	1.1	(-1.1, 3.3)
5	-3.0	-2.3	-0.6	(-2.6, 1.5)
6	-2.3	-2.7	0.7	(-1.3, 2.7)
7	-1.2	-2.4	1.4	(-0.8, 3.6)
8	-1.0	-1.4	0.8	(-1.3, 2.8)
9	0.5	-0.7	1.7	(-0.5, 3.8)
10	-1.9	-2.2	0.7	(-1.4, 2.7)
11	-0.2	-2.4	2.5	(0.7, 4.4)
12	-2.1	0.0	-1.8	(-3.7, 0.2)

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Treatment Group = Obeticholic Acid (OCA 100 mg/Day) on Day 5**

Time (hour)	$\Delta$ QTcF (ms) OCA 100 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) OCA 100 mg	
	LSmean	LSmean	LSmean	90% CI
0	1.1	-0.8	2.2	(-0.2, 4.6)
1	-1.9	-1.7	0.3	(-2.3, 2.8)
2	-0.2	-1.6	1.8	(-0.8, 4.4)
3	0.5	-2.4	3.2	(0.4, 5.9)
4	0.7	-1.1	2.1	(-0.1, 4.2)
5	0.2	-2.1	2.6	(-0.1, 5.3)
6	1.2	-0.5	2.0	(-0.4, 4.3)
7	3.2	0.6	2.8	(0.4, 5.2)
8	1.7	1.4	0.8	(-1.7, 3.2)

	$\Delta$ QTcF (ms) OCA 100 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) OCA 100 mg	
Time (hour)	LSmean	LSmean	LSmean	90% CI
9	2.5	0.4	2.4	(-0.3, 5.0)
10	-0.1	-0.6	1.1	(-1.2, 3.4)
11	2.8	0.2	3.0	(0.8, 5.3)
12	-0.5	0.2	-0.3	(-2.5, 2.0)

The largest upper bounds of the 2-sided 90% CI for the mean differences between OCA 100 mg and placebo on day 1 and day 5 were 4.4 ms and 5.9 ms, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 9. The largest unadjusted 90% lower confidence interval was 6.5 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval was 5.5 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 9: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin**

	$\Delta$ QTcF (ms) Moxifloxacin 400 mg	$\Delta$ QTcF (ms) Placebo	$\Delta\Delta$ QTcF (ms) Moxifloxacin 400 mg		
Time (hour)	LSmean	LSmean	LSmean	90% CI	Adjust 90% CI*
1	6.4	-1.7	8.3	(5.7, 10.8)	(4.8, 11.8)
2	6.5	-1.6	8.3	(5.7, 11.0)	(4.8, 11.9)
3	6.6	-2.4	9.3	(6.5, 12.0)	(5.5, 13.0)
4	6.8	-1.1	8.0	(5.9, 10.2)	(5.1, 11.0)
5	5.5	-2.1	7.7	(5.0, 10.4)	(4.0, 11.4)
6	6.1	-0.5	6.8	(4.4, 9.1)	(3.6, 10.0)
7	7.7	0.6	7.2	(4.8, 9.5)	(3.9, 10.4)
8	8.4	1.4	7.1	(4.7, 9.5)	(3.8, 10.4)
9	6.4	0.4	6.2	(3.6, 8.8)	(2.6, 9.8)
10	4.2	-0.6	5.1	(2.9, 7.4)	(2.0, 8.3)
11	5.5	0.2	5.5	(3.3, 7.7)	(2.4, 8.5)
12	5.5	0.2	5.5	(3.2, 7.8)	(2.4, 8.6)

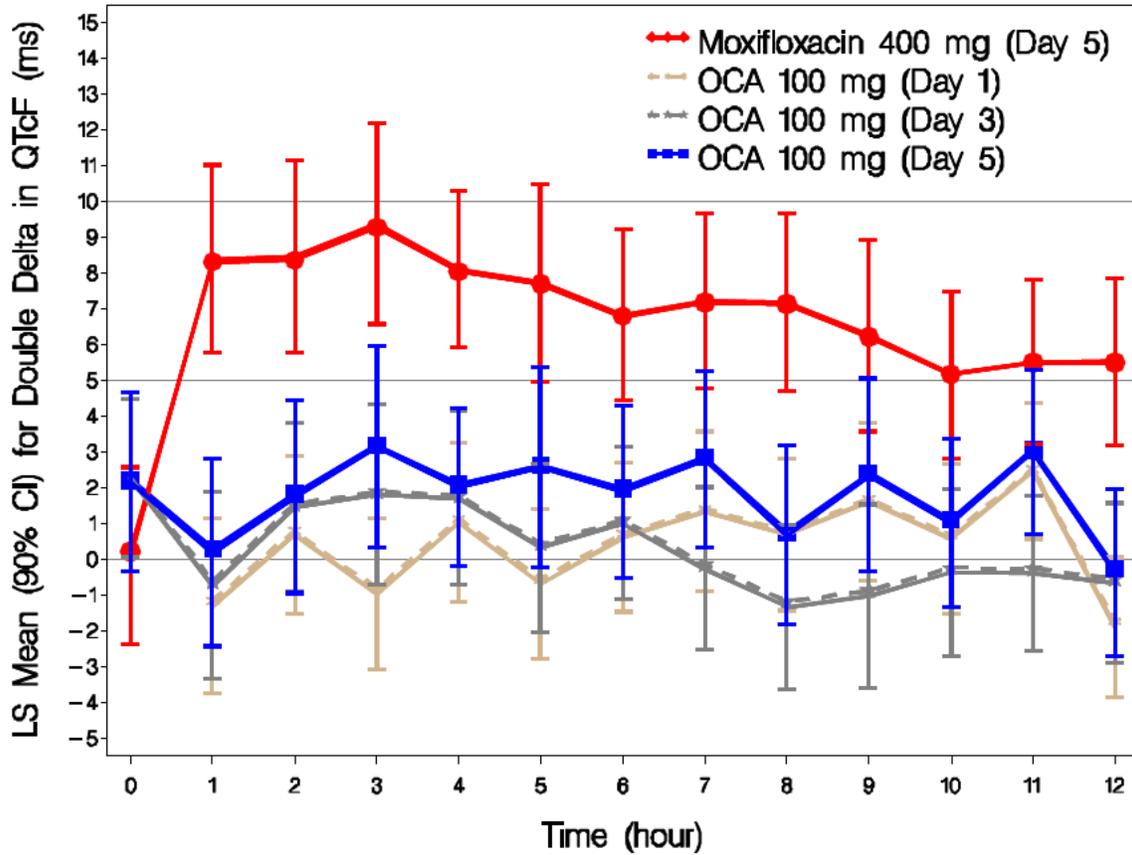
\* Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for OCA 100 mg and moxifloxacin 400 mg.

(Note: CIs are all unadjusted including moxifloxacin)

**Figure 2: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse**



### 5.2.1.4 Categorical Analysis

Table 10 lists the number of subjects as well as the number of observations whose QTcF values were  $\leq 450$  ms and between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 10: Categorical Analysis for QTcF**

Treatment Group	Total N		QTcF $\leq 450$ ms		450 < QTcF $\leq 480$ ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline & Predose	188	2632	186 (98.9%)	2627 (99.8%)	2 (1.1%)	5 (0.2%)

Treatment Group	Total N		QTcF ≤ 450 ms		450 < QTcF ≤ 480 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	63	2394	62 (98.4%)	2393 (100%)	1 (1.6%)	1 (0.0%)
Moxifloxacin Arm Pre-Dose Admin.	63	1638	63 (100%)	1638 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	63	756	62 (98.4%)	755 (99.9%)	1 (1.6%)	1 (0.1%)
OCA 100 mg	62	2356	61 (98.4%)	2352 (99.8%)	1 (1.6%)	4 (0.2%)

Table 11 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline in QTcF was above 60 ms.

**Table 11: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		$\Delta$ QTcF ≤ 30 ms		30 < $\Delta$ QTcF ≤ 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Placebo	63	2394	62 (98.4%)	2393 (100%)	1 (1.6%)	1 (0.0%)
Moxifloxacin Arm Pre-Dose Admin.	63	1638	63 (100%)	1638 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	63	756	60 (95.2%)	751 (99.3%)	3 (4.8%)	5 (0.7%)
OCA 100 mg	62	2356	61 (98.4%)	2351 (99.8%)	1 (1.6%)	5 (0.2%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the HR mean differences between OCA 100 mg and placebo on day 1 and day 5 were 3.0 bpm and 2.5 bpm, respectively.

The outlier analysis results for HR are presented in Table 13.

**Table 12: Analysis Results of  $\Delta$ HR and  $\Delta\Delta$ HR for Treatment Group = Obeticholic Acid (OCA 100 mg/Day)**

Time (hour)	Day 1			Day 5		
	ΔHR (bpm)		ΔΔHR (bpm)	ΔHR (bpm)		ΔΔHR (bpm)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0	2.3	2.0	0.7 (-1.2, 2.5)	2.8	3.3	-0.1 (-2.0, 1.7)
1	0.7	0.5	0.8 (-1.0, 2.5)	1.1	2.4	-0.9 (-2.6, 0.8)
2	-1.2	-1.2	0.5 (-1.0, 2.1)	0.9	1.2	0.6 (-1.3, 2.5)
3	0.2	1.0	-0.6 (-2.1, 0.8)	2.3	3.5	-0.7 (-2.9, 1.4)
4	0.4	-0.8	1.5 (-0.0, 3.0)	1.4	1.5	0.3 (-1.4, 2.0)
5	0.7	0.5	0.4 (-1.3, 2.0)	4.8	4.5	0.5 (-1.6, 2.5)
6	0.9	0.9	0.2 (-1.5, 1.9)	3.9	3.8	0.5 (-1.6, 2.5)
7	1.2	2.1	-0.3 (-2.1, 1.4)	3.9	4.3	0.2 (-1.7, 2.1)
8	1.2	1.7	-0.0 (-1.6, 1.6)	3.5	4.4	-0.5 (-2.3, 1.3)
9	2.1	1.4	0.9 (-0.6, 2.5)	3.8	4.0	0.1 (-1.7, 2.0)
10	1.9	1.9	0.2 (-1.3, 1.7)	4.6	5.4	-0.5 (-2.4, 1.3)
11	2.4	2.5	0.2 (-1.4, 1.7)	5.7	6.5	-0.4 (-2.2, 1.5)
12	1.7	2.9	-1.0 (-2.4, 0.4)	6.4	7.8	-0.9 (-2.9, 1.1)

**Table 13: Categorical Analysis for HR**

	Total N	HR≤100 bpm	HR>100 bpm	HR>45 bpm	HR≤45 bpm
Treatment Group	Subj. #	Subj. #	Subj. #	Subj. #	Subj. #
Baseline & Predose	188	188 (100%)	0 (0.0%)	172 (91.5%)	16 (8.5%)
Placebo	63	63 (100%)	0 (0.0%)	55 (87.3%)	8 (12.7%)
Moxifloxacin Arm Pre-Dose Admin.	63	63 (100%)	0 (0.0%)	59 (93.7%)	4 (6.3%)
Moxifloxacin 400 mg	63	63 (100%)	0 (0.0%)	61 (96.8%)	2 (3.2%)
OCA 100 mg	62	62 (100%)	0 (0.0%)	57 (91.9%)	5 (8.1%)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 14. The largest upper limits of 90% CI for the PR mean differences between OCA 100 mg and placebo on day 1 and day 5 were 3.2 ms and 2.2 ms, respectively.

The outlier analysis results for PR are presented in Table 15.

**Table 14: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Group = Obeticholic Acid (OCA 100 mg/Day)**

Time (hour)	Day 1			Day 5		
	$\Delta$ PR (ms)		$\Delta\Delta$ PR (ms)	$\Delta$ PR (ms)		$\Delta\Delta$ PR (ms)
	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0	-2.2	-0.5	-1.9 (-3.9, 0.1)	1.3	3.9	-2.7 (-5.0, -0.3)
1	-3.0	-1.8	-1.4 (-3.5, 0.6)	-0.1	3.8	-4.1 (-6.7, -1.6)
2	-1.6	-1.1	-0.8 (-2.6, 1.1)	1.6	3.9	-2.5 (-5.1, 0.1)
3	-0.9	-0.3	-0.8 (-2.6, 1.1)	0.4	3.6	-3.4 (-5.7, -1.0)
4	-0.9	-0.6	-0.6 (-2.4, 1.3)	1.4	2.5	-1.3 (-3.6, 1.0)
5	-0.9	-1.3	0.1 (-1.7, 1.8)	1.5	2.4	-1.1 (-3.4, 1.2)
6	-1.2	-1.1	-0.3 (-2.0, 1.4)	1.5	3.3	-1.9 (-4.0, 0.2)
7	-2.1	0.3	-2.4 (-4.3, -0.5)	-0.4	2.6	-3.1 (-5.4, -0.7)
8	0.6	-1.0	1.4 (-0.4, 3.2)	0.9	1.3	-0.7 (-3.0, 1.6)
9	0.2	0.0	0.1 (-1.7, 1.9)	1.6	1.5	-0.1 (-2.3, 2.2)
10	-0.7	-0.2	-0.6 (-2.3, 1.1)	-0.2	1.4	-1.8 (-4.0, 0.3)
11	-0.9	0.9	-1.9 (-3.9, 0.0)	-0.2	1.7	-2.0 (-4.3, 0.3)
12	-0.4	1.0	-1.4 (-3.2, 0.3)	-1.3	1.6	-3.0 (-5.3, -0.7)

**Table 15: Categorical Analysis for PR**

Treatment Group	Total N		PR≤200 ms		PR>200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline & Predose	188	2632	168 (89.4%)	2512 (95.4%)	20 (10.6%)	120 (4.6%)
Placebo	63	2394	52 (82.5%)	2242 (93.7%)	11 (17.5%)	152 (6.3%)
Moxifloxacin Arm Pre-Dose Admin.	63	1638	55 (87.3%)	1544 (94.3%)	8 (12.7%)	94 (5.7%)
Moxifloxacin 400 mg	63	756	58 (92.1%)	719 (95.1%)	5 (7.9%)	37 (4.9%)
OCA 100 mg	62	2356	56 (90.3%)	2296 (97.5%)	6 (9.7%)	60 (2.5%)

**5.2.4 QRS Analysis**

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 16. The largest upper limits of 90% CI for the QRS mean differences between OCA 100 mg and placebo on day 1 and day 5 were 1.0 ms and 1.8 ms, respectively.

The outlier analysis results for QRS are presented in Table 17.

**Table 16: Analysis Results of  $\Delta$ QRS and  $\Delta\Delta$ QRS for Treatment Group = Obeticholic Acid (OCA 100 mg/Day)**

	Day 1			Day 5		
	$\Delta$ QRS (ms)		$\Delta\Delta$ QRS (ms)	$\Delta$ QRS (ms)		$\Delta\Delta$ QRS (ms)
Time (hour)	LSmean	LSmean Placebo	LSmean (90% CI)	LSmean	LSmean Placebo	LSmean (90% CI)
0	-0.5	-0.7	0.2 (-0.7, 1.0)	1.1	0.8	0.3 (-0.6, 1.3)
1	-0.6	-0.1	-0.5 (-1.5, 0.4)	1.2	0.9	0.4 (-0.6, 1.4)
2	-0.4	-0.0	-0.3 (-1.3, 0.6)	0.6	1.5	-0.9 (-1.9, 0.1)
3	-1.0	-0.3	-0.6 (-1.8, 0.5)	0.4	0.4	0.1 (-1.0, 1.3)
4	-1.1	-0.4	-0.7 (-1.8, 0.3)	0.9	0.6	0.2 (-0.8, 1.3)
5	-1.0	-0.2	-0.8 (-1.8, 0.2)	1.2	1.0	0.3 (-0.7, 1.3)
6	-0.9	-0.3	-0.6 (-1.5, 0.3)	1.0	0.7	0.3 (-0.7, 1.3)
7	-0.4	-0.4	0.1 (-0.9, 1.0)	1.5	0.9	0.6 (-0.4, 1.7)
8	-0.4	-0.1	-0.3 (-1.2, 0.6)	0.8	1.1	-0.2 (-1.2, 0.8)
9	-1.0	-0.2	-0.7 (-1.7, 0.3)	0.7	0.1	0.7 (-0.5, 1.8)
10	-1.0	-1.0	0.0 (-0.9, 1.0)	1.2	0.6	0.6 (-0.5, 1.7)
11	-1.2	-1.0	-0.2 (-1.2, 0.8)	0.5	0.5	0.0 (-1.1, 1.1)
12	-0.8	-0.2	-0.6 (-1.5, 0.3)	-0.1	-0.0	0.0 (-1.0, 1.0)

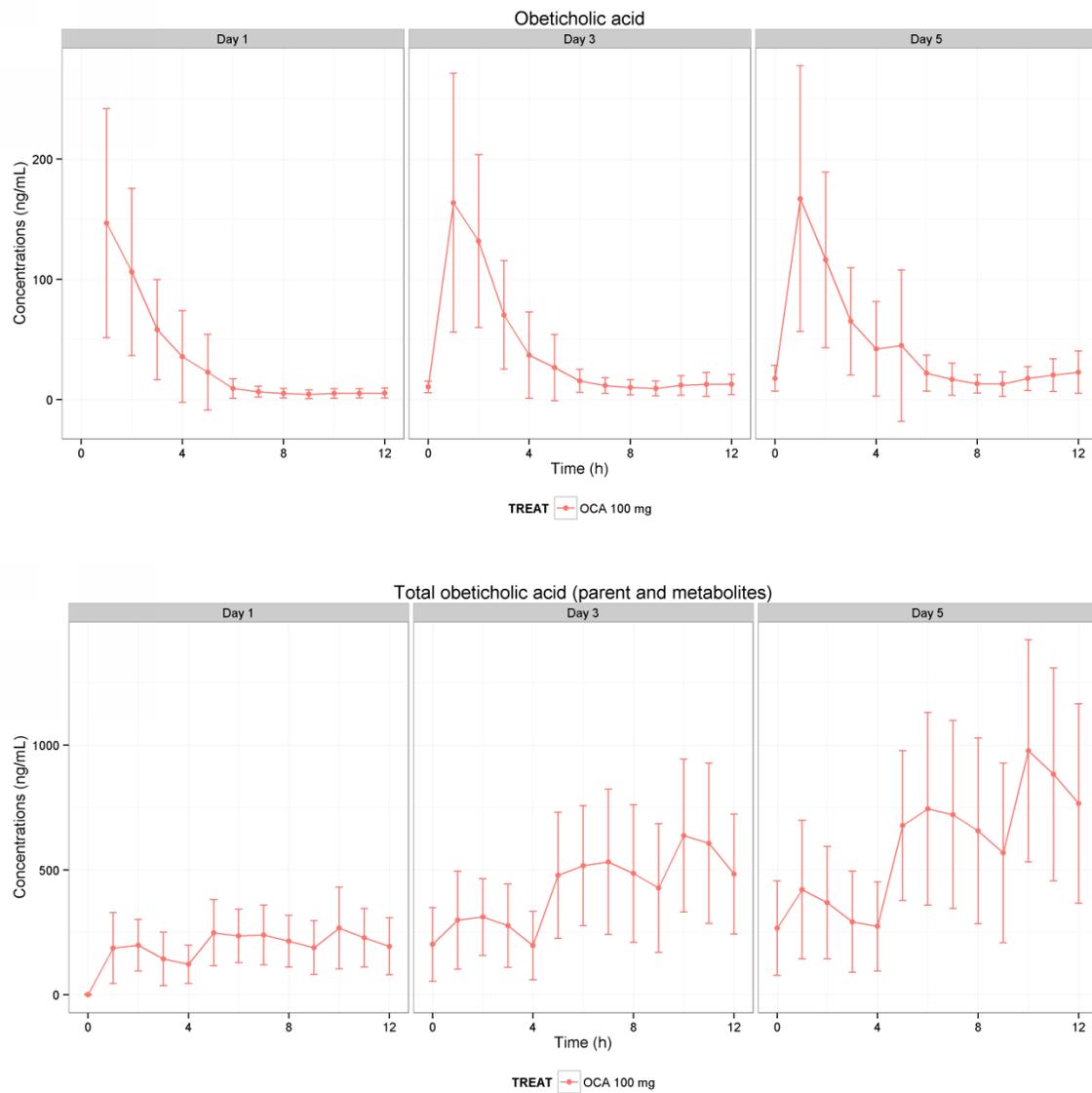
**Table 17: Categorical Analysis for QRS**

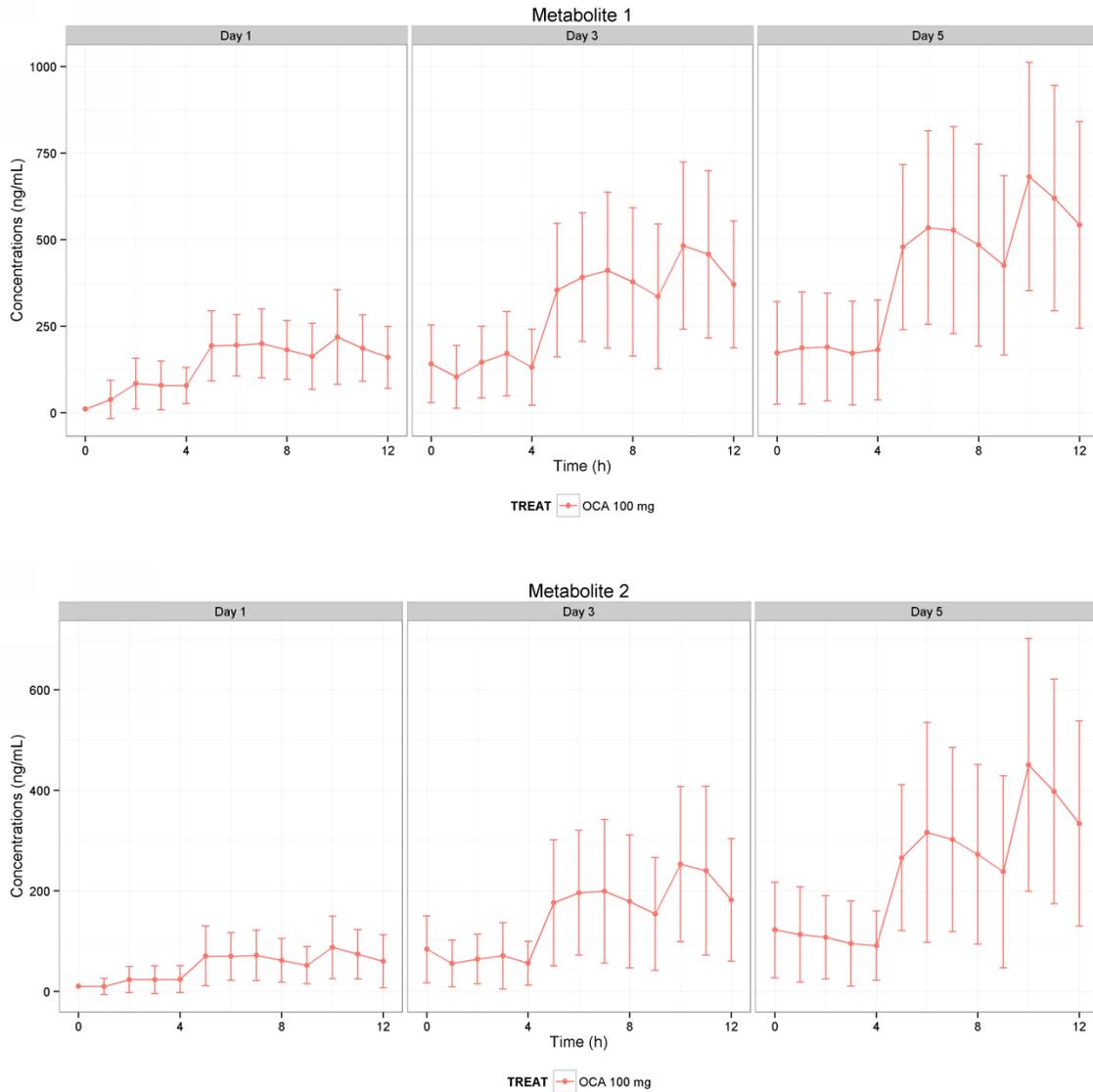
Treatment Group	Total N		QRS $\leq$ 110 ms		QRS $>$ 110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline & Predose	188	2632	173 (92.0%)	2527 (96.0%)	15 (8.0%)	105 (4.0%)
Placebo	63	2394	59 (93.7%)	2339 (97.7%)	4 (6.3%)	55 (2.3%)
Moxifloxacin Arm Pre-Dose Admin.	63	1638	59 (93.7%)	1607 (98.1%)	4 (6.3%)	31 (1.9%)
Moxifloxacin 400 mg	63	756	61 (96.8%)	743 (98.3%)	2 (3.2%)	13 (1.7%)
OCA 100 mg	62	2356	53 (85.5%)	2184 (92.7%)	9 (14.5%)	172 (7.3%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 3 (only concentration data with matched ECG measurement were included).

**Figure 3: Mean Obeticholic Acid, Total Obeticholic Acid, Glyco-Obeticholic Acid, and Tauro-Obeticholic Acid Concentration-Time Profiles**





The relationship between  $\Delta QTcF$  and obeticholic acid, total obeticholic acid, glyco-obeticholic acid, and tauro-obeticholic acid concentration, exposure was analyzed separately using a linear mixed effects models, with the general form:

$$\Delta QTcF = \mu_l + p_t + qC_{l,k,t} + W_k + D_k + \varepsilon_{l,k,t}$$

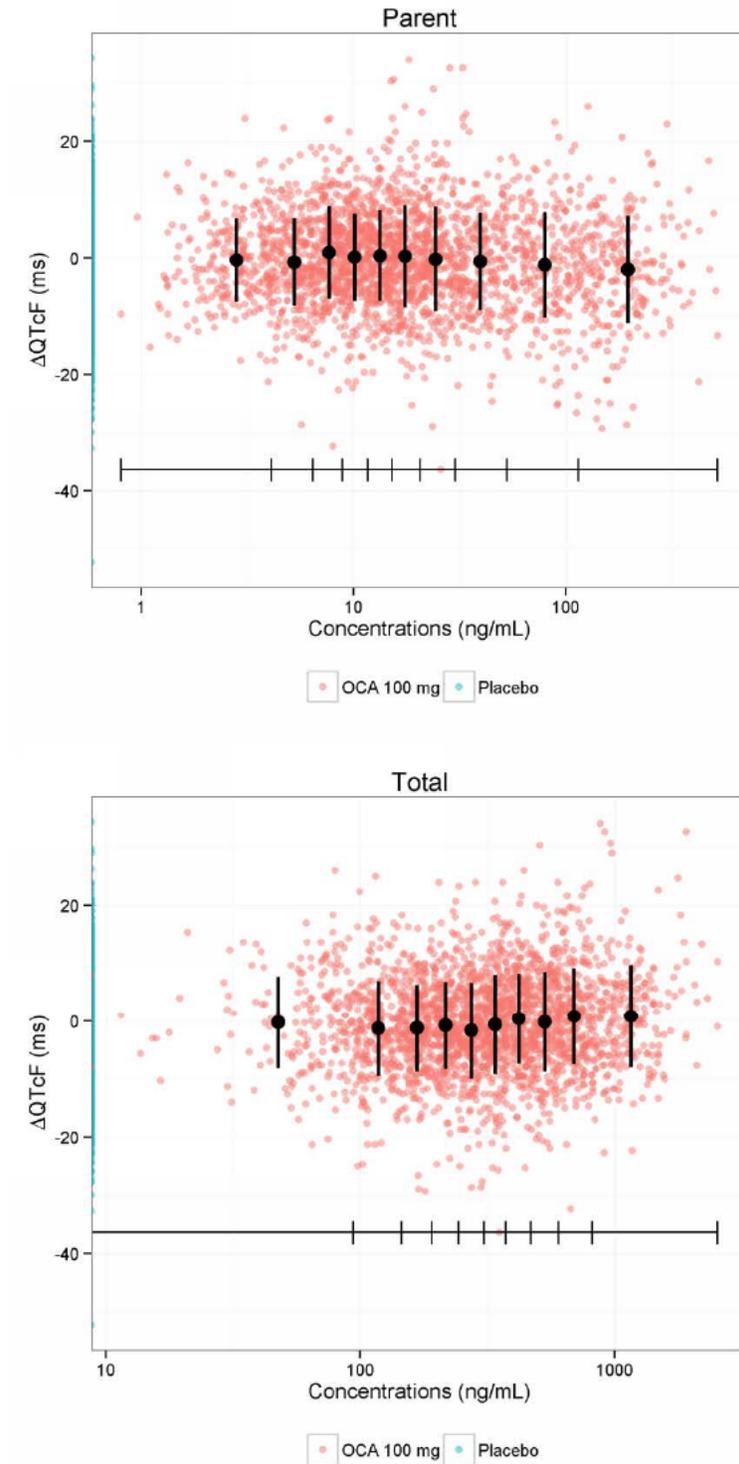
- $\mu_l = \text{Fixed effect, treatment specific } (l) \text{ intercept (active, placebo)}$
- $p_t = \text{Fixed effect, time } (t) \text{ specific intercept (as factor)}$
- $q = \text{Fixed effect, slope parameter}$

- $C_{l,k,t}$  = *Independent variable*, Concentration for time point ( $t$ ), treatment ( $l$ ), and subject ( $k$ )
- $W_k$  = *Random effect*, random subject level ( $k$ ) effect on intercept ( $\mu$ )
- $D_k$  = *Random effect*, random subject level ( $k$ ) effect on slope ( $q$ )
- $\epsilon_{l,k,t}$  = *Random effect*, residual error for time point ( $t$ ), treatment ( $l$ ), and subject ( $k$ )

No significant exposure response relationship was estimated for any of the moieties.

The relationship between  $\Delta$ QTcF and log obeticholic acid concentrations and log total obeticholic acid concentration is visualized in Figure 4 with no evident exposure-response relationship.

**Figure 4:  $\Delta$ QTcF vs. Obeticholic Acid and Total Obeticholic Acid Concentration**



#### 5.4 CLINICAL ASSESSMENTS

#### **5.4.1 Safety assessments**

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred on study drug in this study.

#### **5.4.2 ECG assessments**

Overall ECG acquisition and interpretation in this study appears acceptable.

#### **5.4.3 PR and QRS Interval**

Neither PR nor QRS are affected to any clinically relevant extent.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	5, 10, (b) (4) mg QD <sup>a</sup>	
Maximum tolerated dose	500 mg after a single dose <sup>b</sup> 100 mg after QD dosing for two weeks <sup>c</sup>	
Principal adverse events	Pruritus	
Maximum dose tested	Single Dose	500 mg <sup>b</sup>
	Multiple Dose	250 mg QD <sup>c</sup>
Exposures Achieved at Maximum Tested Dose	Single Dose	Obeticholic Acid <sup>b</sup> Mean C <sub>max</sub> (%CV): 846 (41%) ng/mL Mean AUC <sub>0-t</sub> (%CV): 2207 (22%) ng·h/mL
	Multiple Dose	Obeticholic Acid <sup>c</sup> Mean C <sub>max</sub> (%CV) on Day 12 (steady state): 575.9 (78%) ng/mL Mean AUC <sub>0-24</sub> (%CV) on Day 12 (steady state): 2783.4 (115%) ng·h/mL
Range of linear PK	Obeticholic Acid <sup>c</sup> 25 mg to 250 mg after a single dose (Day 1) and at steady-state (Day 12)	
Accumulation at steady state	Obeticholic Acid <sup>c</sup> Mean Accumulation Index AUC <sub>0-24</sub> (%CV): 2.17 (29%) at 25 mg QD (Day 12) to 1.33 (64%) at 250 mg QD (Day 12) Mean Accumulation Index C <sub>max</sub> (%CV): 1.40 (63%) at 50 mg QD (Day 12) to 1.10 (65%) at 250 mg QD (Day 12)	
Metabolites	Glyco-obeticholic Acid: EC <sub>50</sub> =24 nM <sup>d</sup> Tauro-obeticholic Acid: EC <sub>50</sub> =85 nM <sup>d</sup>	
Absorption	Absolute/Relative Bioavailability (% CV)	17.1 (17.5) <sup>c</sup>
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Obeticholic Acid<sup>c</sup> Median (range) 25 mg (Day 1): 1.5 (0.3-3.0) h Median (range) 25 mg (Day 12): 1.3 (0.5-3.0) h</li> <li>• Glyco-Obeticholic Acid<sup>c</sup> Median (range) 25 mg (Day 1): 6.0 (5.0-11.0) h Median (range) 25 mg (Day 12): 8.0 (5.0-12.0) h</li> <li>• Tauro-Obeticholic Acid<sup>c</sup> Median (range) 25 mg (Day 1): 5.5 (5.0-10.0) h Median (range) 25 mg (Day 12): 8.0 (5.0-11.0) h</li> </ul>
Distribution	Vd/F or Vd	Mean (SD) OCA V <sub>z</sub> single IV dose <sup>e</sup> 618 (341.9) L
	% bound	<ul style="list-style-type: none"> <li>• Obeticholic Acid Mean (%CV): 99.93% (3%)</li> <li>• Glyco-Obeticholic Acid Mean (%CV): 99.77% (6%)</li> <li>• Tauro-Obeticholic Acid Mean (%CV): 99.78% (6%)</li> </ul>

Elimination	Route	The elimination pathway of obeticholic acid is primarily via hepatic metabolism. <sup>e</sup>															
	Terminal t <sub>1/2</sub>	The PK of OCA is characterized by significant enterohepatic recirculation which makes the determination of terminal half-life difficult. Based on population PK analyses, the predicted terminal half-life of total OCA (OCA and its metabolites) is approximately 4 days.															
	CL/F or CL	Mean (SD) OCA CL single IV dose <sup>e</sup> 25.0 (1.052) L/h															
Intrinsic Factors	Age	No effect on PK based on population PK analysis <sup>f</sup>															
	Sex	No effect on PK based on population PK analysis <sup>f</sup>															
	Race	No effect on PK based on population PK analysis <sup>f</sup>															
	Hepatic & Renal Impairment	<p>Hepatic OCA PK after a Single 10 mg OCA Dose<sup>g</sup></p> <table border="1"> <thead> <tr> <th>Hepatic Function</th> <th>C<sub>max</sub> Mean (SD)</th> <th>AUC<sub>0-t</sub> Mean (SD)</th> </tr> </thead> <tbody> <tr> <td>Normal</td> <td>54.0 (18.9)</td> <td>175 (114)</td> </tr> <tr> <td>Mild Impairment</td> <td>80.0 (49.6)</td> <td>252 (181)</td> </tr> <tr> <td>Moderate Impairment</td> <td>141 (143)</td> <td>563 (645)</td> </tr> <tr> <td>Severe Impairment</td> <td>254 (85)</td> <td>1112 (406)</td> </tr> </tbody> </table> <p>Renal: Not evaluated in renal impairment; Minimal renal elimination (&lt;3%)<sup>e</sup></p>		Hepatic Function	C <sub>max</sub> Mean (SD)	AUC <sub>0-t</sub> Mean (SD)	Normal	54.0 (18.9)	175 (114)	Mild Impairment	80.0 (49.6)	252 (181)	Moderate Impairment	141 (143)	563 (645)	Severe Impairment	254 (85)
Hepatic Function	C <sub>max</sub> Mean (SD)	AUC <sub>0-t</sub> Mean (SD)															
Normal	54.0 (18.9)	175 (114)															
Mild Impairment	80.0 (49.6)	252 (181)															
Moderate Impairment	141 (143)	563 (645)															
Severe Impairment	254 (85)	1112 (406)															

Extrinsic Factors	Drug interactions	The effects of OCA after a 10 mg daily dose on selected drug metabolizing enzymes and transporters are summarized below.		
		Probe Substrate	LSM Ratio (90% CI)	
			$C_{max}$	$AUC_{0-t}$
		CYP1A2 <sup>n</sup>		
		Caffeine	1.06 (1.01-1.11)	1.41 (1.35-1.48)
		CYP2C9 <sup>i</sup>		
		S-Warfarin	1.12 (1.05-1.19)	1.11 (1.08-1.14)
		R-Warfarin	1.11 (1.04-1.18)	1.15 (1.12-1.19)
		CYP2C19 <sup>j</sup>		
		Omeprazole	1.33 (1.17 - 1.51)	1.34 (1.21 - 1.49)
		CYP2D6 <sup>l</sup>		
		Dextromethorphan	0.879 (0.725 - 1.07)	0.810 (0.652 - 1.01)
		CYP3A4 <sup>h</sup>		
		Midazolam	1.02 (0.919-1.13)	1.02 (0.937-1.12)
		P-gp <sup>k</sup>		
Digoxin	0.967 (0.869 - 1.08)	1.03 (0.969 - 1.09)		
BCRP/OATP1B1/OATP1B3 <sup>o</sup>				
Rosuvastatin	1.27 (1.15-1.41)	1.24 (1.14-1.35)		
	Food Effects	<p>There was a modest increase in the exposure of OCA when administered with food relative to fasting.</p> <p>The geometric least square mean (90% CI) of OCA (fed versus fasted)<sup>m</sup></p> <ul style="list-style-type: none"> <li>• <math>C_{max}</math> 104% (74.2%-146%)</li> <li>• <math>AUC_{0-t}</math> 111% (88.0%-140%)</li> </ul>		
Expected High Clinical Exposure Scenario	The highest exposure of obeticholic acid and its conjugates (glyco-OCA and tauro-OCA) is expected after a meal.			
Preclinical Cardiac Safety	<p>In vitro studies</p> <p>Study 070927.JPQ; Design: A GLP patch-clamp assay was performed using HEK293 cells transfected with hERG. Vehicle or OCA at target concentrations of 10 <math>\mu</math>M, 100 <math>\mu</math>M, and 300 <math>\mu</math>M were tested at 35°C±2°C. Results: Patch clamp recordings were disrupted by OCA and not obtained at the target concentration of 300 <math>\mu</math>M. At 82.8 and 8.3 <math>\mu</math>M OCA, IKr was reduced 10.1% 5.1%, respectively, compared to 83.9% with 60 nM terfenadine. OCA at concentrations ≤82.8 <math>\mu</math>M had no clear effect on cloned hERG channel currents in HEK293 cells.</p> <p>Study hERG-001; Design: A non-GLP study was performed using the Predictor™ hERG Fluorescence Polarization assay (Invitrogen) in membrane fractions from CHO cells overexpressing the hERG channel protein. Results: OCA did not compete with tracer binding to hERG and no IC50 was calculable for OCA at concentrations up to 30 <math>\mu</math>M compared with positive control values for tamoxifen (1.5<math>\mu</math>M) and E-4301 (15 nM).</p> <p>In vivo studies</p> <p>Study 7654-100; Design: The cardiovascular safety of OCA was evaluated in a 4-dose crossover design in telemetered beagle dogs (N = 4 male). Each dog was given a single dose of OCA by oral gavage of 0 (vehicle), 2, 10, or 20 mg/kg OCA on Days 1, 4, 8, and 11. Electrocardiographs (ECGs) were recorded for at least 60 minutes before dosing, continuously for at least 6 hours after dosing, and then hourly through approximately 24 hours postdose. Seven ECG intervals</p>			

	<p>were evaluated per day of dosing. At each day of dosing, heart rate and pressure measurements (systolic, diastolic, mean arterial, and pulse pressures) were taken predose, for a 5-minute average every 30 minutes through 6 hours postdose, and every hour afterwards through 24 hours postdose. Results: No test article-related findings were noted for ECG (including QTc [Fredericia's method]), heart rate and systolic, diastolic, mean arterial, or pulse pressures. Although significant changes were observed at a few time points during the recording interval changes were small in magnitude and were not preceded or followed in time by similar direction changes. No qualitative or quantitative findings in the ECG data were considered related to test article. The NOEL for OCA on effects on the cardiovascular system occurred at the highest dose tested (20 mg/kg).</p>
<p>Clinical Cardiac Safety</p>	<p>A total of 1507 subjects were exposed to at least a single dose of OCA in 27 completed clinical studies. This includes subjects from studies from non-Intercept sponsored studies in other indications. A total of 1325 subjects were exposed to at least a single dose of OCA on Intercept sponsored studies in patients with PBC and healthy volunteers. The number of subjects at each drug exposure levels in these Intercept sponsored studies is presented in Table 2 below.</p> <p>A thorough QT study (747-108) designed according to the FDA E14 guidance was performed in healthy subjects, whereby the potential effects of OCA and its active conjugates (glyco-OCA and tauro-OCA) on the QT interval at both therapeutic and supratherapeutic concentrations was assessed. The upper limit of the 2-sided 95% CI for the LS mean difference between OCA and placebo in the change in QTc from baseline was well below the +10 msec threshold of regulatory concern for this parameter, including at concentrations up to 4 fold higher than steady state plasma concentrations typically achieved following a 10-mg dose.</p> <p>Cardiac rhythm safety was also assessed in clinical studies of OCA in patients with PBC and in healthy subjects participating in clinical pharmacology studies, including an evaluation of the incidence of events included in the MedDRA 15.0 SMQ of Torsade de pointes/QT prolongation. A similar rate of events were observed in the OCA and placebo treatment arms as demonstrated in Table 3 below, with an overall incidence consistent with that expected in this patient population (Electrocardiogram abnormalities reportedly occur more frequently in patients with advanced liver disease compared to controls [Josefsson et al BMC Gastroenterology 2014]).</p> <p>Adverse event data related to ventricular arrhythmias from OCA studies in subjects with other indications (NAFLD, NASH, and alcoholic cirrhosis similarly revealed no clinically relevant events. 6 subjects experienced events of syncope (2 OCA-treated subjects and 4 placebo-treated subjects). One subject in the NIDDK-sponsored FLINT study of subjects with NASH experienced a treatment-emergent adverse event of QT prolongation which was assessed to be unrelated to OCA treatment. A brief narrative of the event is provided below.</p> <p>Subject 8392  A 23 year old white female subject with a medical history of drug allergies, polycystic ovary syndrome, major depression, severe anxiety or personality disorder, migraines and palpitations was randomized to receive 25 mg OCA daily. The subject was scheduled to initiate treatment with an unidentified medication known to be associated with palpitations. For this reason, the physician obtained a baseline ECG tracing before starting the new medication and an incidental finding of prolonged QT interval was noted and assessed as probably not related to OCA treatment. The subject underwent additional investigations including a 30-day holter monitor observation and stress echocardiogram. No change in QTc or T wave inversion were noted and the subject was released by the cardiologist. The subject completed the 72 week treatment period and the subsequent 24 week drug free follow up period.</p> <p>Overall, no clinically meaningful difference was observed in the incidence of adverse events representative of ventricular arrhythmias when comparing OCA treated subjects with those treated with placebo or when comparing to the rate of such events in the published literature. These observations further support the negative findings in non-clinical and tQT studies and provide additional evidence of the cardiac safety of OCA.</p>

<sup>a</sup>QD: Once Daily Dosing; <sup>b</sup>Study 747-101; <sup>c</sup>Study 747-102; <sup>d</sup>Determined using Amplified Luminescent Proximity Homogeneous Assay (AlphaScreen) technology. Obeticholic Acid EC50=45 nM (Report Number: NRS-003); <sup>e</sup>Study 747-113; <sup>f</sup>Error! Reference source not found; <sup>g</sup>Study D8601002

<sup>h</sup>Population PK/PD and Simulation Report; <sup>i</sup>Study 747-103; <sup>j</sup>Study 747-109; <sup>k</sup>Study 747-110; <sup>l</sup>Study 747-112; <sup>m</sup>Study 747-114; <sup>n</sup>Study 747-111; <sup>o</sup>Study 747-104

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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HUIFANG CHEN  
10/21/2015

QIANYU DANG  
10/21/2015

DINKO REKIC  
10/21/2015

JIANG LIU  
10/21/2015

MICHAEL Y LI  
10/21/2015

NORMAN L STOCKBRIDGE  
10/21/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 207999 BLA# n/a	NDA Supplement #: S- n/a BLA Supplement #: S- n/a	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: INT-747 Established/Proper Name: obeticholic acid Dosage Form: tablets Strengths: 5 mg and 10 mg		
Applicant: Intercept Pharmaceuticals, Inc. Agent for Applicant (if applicable): n/a		
Date of Application: June 27, 2015 Date of Receipt: June 29, 2015 Date clock started after UN: June 29, 2015		
PDUFA/BsUFA Goal Date: February 29, 2016	Action Goal Date (if different): n/a	
Filing Date: August 28, 2015	Date of Filing Meeting: July 29, 2015	
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(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 UCDA.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

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Type of BLA <i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
Review Classification:  <i>The application will be a priority review if:</i> <ul style="list-style-type: none"> <li>• A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</li> <li>• The product is a Qualified Infectious Disease Product (QIDP)</li> <li>• A Tropical Disease Priority Review Voucher was submitted</li> <li>• A Pediatric Rare Disease Priority Review Voucher was submitted</li> </ul>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority  <input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher

Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
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Part 3 Combination Product? <input type="checkbox"/>  <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
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<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input checked="" type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 063307

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, explain in comment column.</i>				
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Submitted in the December 19, 2014 rolling submission
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a>:</i> ) <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

<b>(NDAs/NDA Efficacy Supplements only)</b>				
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form, cover letter, and annotated labeling</i> ). <b>If yes, answer the bulleted questions below:</b>		<input type="checkbox"/>	<input checked="" type="checkbox"/>	
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>	X
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>	X
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>	X
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>				
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? <i>Check the Electronic Orange Book at: <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></i>		<input type="checkbox"/>	<input type="checkbox"/>	X
<b>If yes, please list below:</b>				
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration	
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>				
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a></i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?  <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?  <b>If yes, # years requested:</b> 7 years	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, did the applicant:</b> (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</b>				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission, does it follow the eCTD guidance?</b> <sup>1</sup> <b>If not, explain (e.g., waiver granted).</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

(BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> navigable hyperlinks (electronic submissions only)  <b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?  <b>If yes, BLA #</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?  <i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <b>both</b> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>				
<i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>				
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Submission was electronic and included a Filed Copy Certification signed by applicant.
<i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>				
<i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>				
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, date consult sent to the Controlled Substance Staff:</i>				
<u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>				
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b>				
Does the application trigger PREA?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Received orphan designation in 2008 for the proposed indication
<i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i>				

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 3/20/2014

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<i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<b><u>BPCA:</u></b>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>				
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	However, DRISK will be a part of the discussions.
<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
<b>Prescription Labeling</b>	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

3

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Version: 3/20/2014

8

Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Application submitted on June 29, 2015; however, the PI was submitted in PLLR format
<b>If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Placed in DARRTS on 7/7/15
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

5

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent: Division of Pediatric and Maternal Health, 7/8/15</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b> 9/1/2010	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 11/24/14	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> 10/6/11 for SPA 1 and SPA 2	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 29, 2015

**BACKGROUND:**

Intercept Pharmaceuticals, Inc. (Intercept) submitted a new drug application, INT- 747 (obeticholic acid) (OCA), under 21CFR314 (Subpart H Accelerated Approval regulations), 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 UCDA. This has been classified as a new molecular entity (NME).

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist. 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 and Rolling Review for NDA on November 18, 2014. The initial submission, nonclinical data, was submitted on December 19, 2014 and the completed and final was submitted on June 27, 2015.

As part of the clinical development program for OCA, two phase 2 clinical studies and a pivotal phase 3 study were completed.

**REVIEW TEAM:**

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	CDR Anissa Davis-Williams	y
	CPMS/TL:	Brian Strongin	Y
Cross-Discipline Team Leader (CDTL)	Lara Dimick-Santos		Y
Division Director/Deputy	Donna Griebel		N
	Andrew Mulberg		Y
Office Director/Deputy	Julie Beitz		Y
Clinical	Reviewer:	Ruby Mehta	Y
	TL:	Lara Dimick-Santos	Y
Social Scientist Review ( <i>for OTC products</i> )	Reviewer:	n/a	n/a
	TL:	n/a	n/a
OTC Labeling Review ( <i>for OTC</i> )	Reviewer:	n/a	n/a

<i>products)</i>	TL:	n/a	n/a
	Reviewer:	n/a	n/a
Clinical Microbiology ( <i>for antimicrobial products)</i> )	TL:	n/a	n/a
	Reviewer:	n/a	n/a
Clinical Pharmacology	TL:	Sue Chih Lee	Y
	Reviewer:	Elizabeth Shang	Y
Biostatistics	TL:	Yeh-Fong Chen	Y
	Reviewer:	BenjaminVali	N

Nonclinical (Pharmacology/Toxicology)	TL:	Sushanta Chakder	Y
	Reviewer:	Tracy Behrsing	Y
Statistics (carcinogenicity)	TL:	n/a	n/a
	Reviewer:	n/a	n/a
Immunogenicity (assay/assay validation) ( <i>for protein/peptide products only</i> )	TL:	n/a	n/a
	Reviewer:	n/a	n/a
Product Quality (CMC)	TL:	Danuta Gromek-Woods	Y
	Reviewer:	Hitesh Shroff	N
Biopharmaceutics	TL:	Albert Chen	Y
	Reviewer:	Peng Duan	Y
Quality Microbiology	TL:	Celia Cruz	N
	Reviewer:	Vaikunth Prabhu	Y
CMC Labeling Review	TL:	Danuta Gromek-Woods	Y
	Reviewer:	Hitesh Shroff	N
Facility Review/Inspection	TL:	Grace McNally	N
	Reviewer:	Marisa Heayn	N
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Matthew Barlow	Y

	TL:	Kendra Worthy	N
OSE/DRISK (REMS)	Reviewer:	Erin Hachey	Y
	TL:	Jamie Wilkins	N
OC/OSI/DSC/PMSB (REMS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a

Bioresearch Monitoring (OSI)	Reviewer:	Susan Leibenhaut	Y
	TL:	Susan Thompson	N
Controlled Substance Staff (CSS)	Reviewer:	n/a	n/a
	TL:	n/a	n/a
Other reviewers/disciplines	Reviewer:	DPMH-Christos Mastroiannis	Y
		Orphan – Jeff Fritsch	Y
		Rare Disease- Kathryn O’Connell	Y
		DEPI-Kira Leishear	Y
		Pharmacometrics- Dhenanja Marathe	N
	TL:	DPMH-Tamara Johnson	N
		DEPI-Sukhminder Sandhu	Y
		Pharmacometrics-Nitin Mehrotra	Y
Other attendees	Alek Winiarski, Yvette Waples, Benjamin Stevens, Cindy Hong, Joyce Korvick, Denise Johnson-Lyles		Y

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505(b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------	-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Review 8/21/15; no comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input checked="" type="checkbox"/> YES Date if known: 1/13/16 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b>  The dedicated hepatic impairment study showed that the exposure to total OCA in subjects with moderate and severe hepatic impairment are 4 and 7 times higher than that in subjects with normal hepatic impairment. The recommendation of use in these subjects will be a review issue.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input checked="" type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>IMMUNOGENICITY (protein/peptide products only)</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>New Molecular Entity (NDAs only)</b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES

	<input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</li> </ul> <p><b>If no</b>, was a complete EA submitted? <input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>If EA submitted</b>, consulted to EA officer (OPS)? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><b>Comments:</b> Submitted 8/17/15</p>	
<p><b><u>Quality Microbiology</u></b></p> <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization? <input type="checkbox"/> YES <input type="checkbox"/> NO</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</li> </ul> <p><b>Comments:</b></p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility/Microbiology Review (BLAs only)</u></b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>CMC Labeling Review</u></b></p> <p><b>Comments:</b> none</p>	<input type="checkbox"/> Review issues for 74-day letter

<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<p><input type="checkbox"/> N/A</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>none</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

**REGULATORY PROJECT MANAGEMENT**

**Signatory Authority:** Dr. Amy Egan

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): September 29, 2015

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

**Comments:**

<b>Milestone Meetings</b>	
Filing Meeting (30 days post submission)	<b>7/29/15</b>
Planning Meeting	<b>8/11/15</b>
Mid-Cycle Meeting	<b>9/29/15</b>

Post Mid-Cycle w/Applicant (2 weeks post Mid-Cycle)	10/13/15
Pre-Meeting for Late Cycle Meeting (5.25 months)	12/8/15
Late Cycle Meeting w/Applicant- hold 12 days prior to AC or by 9.0 month if no AC (briefing packet to applicant- (12 days prior if no AC; if AC send 20 days before AC)	<i>pending</i>
AC Meeting	1/13/16
PeRC <b>PeRC Paperwork Due:</b>	<b>Not applicable (Orphan Designated Application)</b>
<b>Wrap-up Meeting (5 weeks prior to PDUFA goal date)</b>	<b>1/26/16</b>

#### REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>

#### ACTIONS ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> <li>• notify sponsor in writing by day 60 (see CST for choices)</li> <li>• notify OMPQ (so facility inspections can be scheduled earlier)</li> </ul>
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74

<input type="checkbox"/>	
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRA's completed: September 2014

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

ANISSA A DAVIS  
08/28/2015

BRIAN K STRONGIN  
08/31/2015

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 207999

**Application Type:** New NDA

**Name of Drug/Dosage Form:** INT-747 (obeticholic acid) tablets

**Applicant:** Intercept Pharmaceuticals, Inc.

**Receipt Date:** June 29, 2015

**Goal Date:** February 29, 2016

## 1. Regulatory History and Applicant's Main Proposals

Intercept Pharmaceuticals, Inc. (Intercept) submitted a new drug application, INT- 747 (obeticholic acid) (OCA), under 21CFR314 (Subpart H Accelerated Approval regulations), 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 UCDA.

OCA is a modified bile acid and farnesoid X receptor (FXR) agonist. 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.

As part of the clinical development program for OCA, two phase 2 clinical studies and a pivotal phase 3 study were completed.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

In addition, we remind you of an information request was sent to you via email of July 29, 2015.

All SRPI format deficiencies of the PI and other labeling issues identified above will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by October 1, 2015. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment:

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment:

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required

## Selected Requirements of Prescribing Information

• <b>Product Title</b>	Required
• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

*Comment:*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

*Comment:*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

*Comment:*

#### Product Title in Highlights

- YES** 10. Product title must be **bolded**.

*Comment:*

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

*Comment:* *However, the following format was used: 20xx*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

*Comment:*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and

## Selected Requirements of Prescribing Information

other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

### Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

### Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

## Selected Requirements of Prescribing Information

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

*Comment:* However, the one contraindication listed does not have to have a bullet.

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “To report **SUSPECTED ADVERSE REACTIONS**, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)”.

*Comment:*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “See 17 for **PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “See 17 for **PATIENT COUNSELING INFORMATION and Medication Guide**”

*Comment:*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

*Comment:* However, the following format was used: xxxx 2016

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

**YES** 25. The TOC should be in a two-column format.

Comment:

**YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.

Comment:

**N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.

Comment:

**YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.

Comment:

**YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].

Comment:

**YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.

Comment:

**YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”

Comment:

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

***Comment:***

- NO** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

## Selected Requirements of Prescribing Information

**Comment:** *The use of subheadings were utilized as cross-references at the end of 8.5, 8.6 and 8.7.*

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:**

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:**

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:**

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:**

#### CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

**Comment:**

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:**

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is

## Selected Requirements of Prescribing Information

not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:**

### **PATIENT COUNSELING INFORMATION Section in the FPI**

- N/A** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:**

- N/A** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:**

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

#### WARNING: [SUBJECT OF WARNING]

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

#### 6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

#### 7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

#### 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

#### 10 OVERDOSAGE

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

#### 13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

#### 14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

#### 17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ANISSA A DAVIS  
08/28/2015

BRIAN K STRONGIN  
08/31/2015