

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**207999Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

**Errata to the Clinical Pharmacology Review for NDA 207999 in DAARTS  
dated 03/02/2016**

**Erratum:** ‘Original version’ of Table 26 of the Clinical Pharmacology Review (page 69) needs to be replaced by the ‘Corrected version’ as shown below.

**Original version:**

Table 26: Statistical comparison of AUC<sub>0-t</sub> and C<sub>max</sub> (747-103)

| Comparison         | Parameters       | OCA  |            | Glyco-OCA |            | Tauro-OCA |             | Total OCA |            |
|--------------------|------------------|------|------------|-----------|------------|-----------|-------------|-----------|------------|
|                    |                  | GMR  | 90% CI     | GMR       | 90% CI     | GMR       | 90% CI      | GMR       | 90% CI     |
| Mild vs Normal     | AUC              | 1.38 | 72.8 - 261 | 1.27      | 64.7 - 250 | 7.09      | 29.6 – 170  | 1.13      | 56.5 – 225 |
|                    | C <sub>max</sub> | 1.35 | 79.8 - 228 | 1.43      | 79.5 - 256 | 8.72      | 40.4 – 188  | 1.49      | 86.3 – 256 |
| Moderate vs Normal | AUC              | 2.41 | 127 - 456  | 3.33      | 169 – 654  | 6.86      | 286 – 1640  | 4.20      | 211 – 838  |
|                    | C <sub>max</sub> | 1.91 | 113 - 323  | 3.73      | 208 - 670  | 5.63      | 261 – 1220  | 3.76      | 218 – 647  |
| Severe vs Normal   | AUC              | 7.03 | 372 - 1330 | 11.40     | 579 - 2240 | 36.80     | 1540 – 8830 | 17.30     | 867 – 3440 |
|                    | C <sub>max</sub> | 4.70 | 278 - 796  | 8.12      | 452 - 1460 | 21.40     | 991 - 4630  | 9.75      | 566 - 1680 |

**Corrected version:**

Table 26: Statistical comparison of AUC<sub>0-t</sub> and C<sub>max</sub> of OCA and its conjugates in hepatic impairment (747-103)

| Comparison         | Parameters       | OCA  |              | Glyco-OCA |              | Tauro-OCA |               | Total OCA |              |
|--------------------|------------------|------|--------------|-----------|--------------|-----------|---------------|-----------|--------------|
|                    |                  | GMR* | 90% CI       | GMR       | 90% CI       | GMR       | 90% CI        | GMR       | 90% CI       |
| Mild vs Normal     | AUC              | 1.38 | 0.73 – 2.61  | 1.27      | 0.65 – 2.50  | 0.71      | 0.30 – 1.70   | 1.13      | 0.57 – 2.25  |
|                    | C <sub>max</sub> | 1.35 | 0.80 – 2.28  | 1.43      | 0.80 – 2.56  | 0.87      | 0.40 – 1.88   | 1.49      | 0.86 – 2.56  |
| Moderate vs Normal | AUC              | 2.41 | 1.27 – 4.56  | 3.33      | 1.69 – 6.54  | 6.86      | 2.86 – 16.43  | 4.20      | 2.11 – 8.38  |
|                    | C <sub>max</sub> | 1.91 | 1.13 – 3.23  | 3.73      | 2.08 – 6.70  | 5.63      | 2.61 – 12.17  | 3.76      | 2.18 – 6.47  |
| Severe vs Normal   | AUC              | 7.03 | 3.72 – 13.30 | 11.38     | 5.79 – 22.36 | 36.84     | 15.37 – 88.30 | 17.28     | 8.67 – 34.44 |
|                    | C <sub>max</sub> | 4.70 | 2.78 – 7.96  | 8.12      | 4.52 – 14.58 | 21.42     | 9.91 – 46.27  | 9.75      | 5.66 – 16.80 |

\*GMR= Geometric mean ratio

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/s/  
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DHANANJAY D MARATHE  
05/03/2016

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## Clinical Pharmacology Review

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|---|--|
| <b>NDA</b>                                | 207999 / SDN 2, 6, 8, 11, 12, 14, 15, 16, 20, 23, 26, 28, 37, 39, 40, 42, 43, 44, 45, 46, 52   |
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| <b>Brand Name:</b>                        | Ocaliva <sup>®</sup>   |
| <b>Generic Name:</b>                      | Obeticholic acid   |
| <b>Formulation:</b>                       | Oral tablet  |
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| <b>OND Division:</b>                      | Division of Gastroenterology and Inborn Errors Products  |
| <b>Sponsor:</b>                           | Intercept  |
| <b>Submission Type:</b>                   | Original NDA; NME; Priority Review with Major Amendment  |
| <b>Sponsor's Proposed Dosing regimen:</b> | Starting dose of 5 mg once daily with option of up titration to 10 mg at 3 months based on response and tolerability   |
| <b>Indication:</b>                        | Treatment of primary biliary cirrhosis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA   |

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## 1 EXECUTIVE SUMMARY

The current submission is the original NDA for obeticholic acid (OCA) for the following indication:

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

Primary biliary cirrhosis is a rare, serious, life-threatening liver disease. It is characterized by cholestasis with progressive impairment of bile flow in the liver that results in increased hepatocellular bile acid concentrations. Bile acids at high hepatocellular concentrations can cause hepatocellular injury, which results in a local inflammatory response. It is identified by the secretion of alkaline phosphatase (ALP). In the absence of adequate therapy, the disease progresses to hepatic fibrosis and eventual cirrhosis. This is followed by hepatic decompensation and death if the liver transplant is not done. OCA is a selective agonist for farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing synthesis, increasing transport of bile acids out of the hepatocytes, suppressing transport of bile acids into the hepatocytes, and decreasing bile acid re-absorption by suppressing ASBT transport in enterocytes thus reducing hepatic exposure to bile acids.

Ursodeoxycholic acid (UDCA) is the only drug currently approved to treat PBC.

The Sponsor is proposing a starting dose of 5 mg once daily, which should be increased after 3 months, if tolerated, to 10 mg once daily to improve response.

The to-be-marketed formulation is OCA tablets 5 mg and 10 mg.

To support the approval of this NDA, the Sponsor conducted an array of clinical pharmacology-related studies including 16 in vitro studies using human biomaterials. The phase 1 studies evaluated OCA pharmacokinetics (PK) and short term safety, pharmacodynamics (PD), clinical DDIs, QT prolongation potential (thorough QT study), absolute bioavailability, relative bioavailability, hepatic impairment, food-effect, and agent altering gastric pH on OCA PK. In addition, population PK, exposure-response for efficacy and safety, and physiological PK (PBPK) modeling and simulations were also performed.

The clinical studies conducted in patients with PBC consist of two Phase 2 and one pivotal Phase 3 studies. The phase 2 studies evaluated dosing of 10, 25 and 50 mg QD dosing. The Phase 3 study evaluated 10 mg QD and a titration arm (5 mg QD for 6 months followed by up-titration to 10 mg QD based on efficacy and tolerability). For efficacy, the Phase 3 study demonstrated that both 10 mg arm and titration arm were superior to placebo in terms of responders defined by a composite primary endpoint based on changes in ALP and bilirubin levels.

OCA is not metabolized by CYP enzymes. Major active metabolites (glyco-OCA and tauro-OCA) in human plasma are amino acid conjugates. After oral administration of 25 mg [<sup>14</sup>C]-OCA, about 87% is excreted in feces. Urinary excretion is less than 3%.

The key questions raised during the review of this NDA are given below along with the OCP review team's recommendations:

1. Are the assay methods used for ALP and total bilirubin adequate to measure the changes of

these primary surrogate endpoints in Phase 3 trial?

Yes, the assay methods used to measure ALP and bilirubin in the Phase 3 trial are adequate. ALP and total bilirubin are routine clinical lab tests. The Sponsor used commercially available assay kits for ALP and total bilirubin. In addition, the Sponsor used three labs instead of using one central lab for measuring these endpoints. These labs are accredited by their respective national authorities. In US, it is CLIA-certified. One of the three labs was used as a reference lab as it had better precision and accuracy. The measurements in the other two labs were harmonized to the reference lab by applying harmonization factors. The majority (~92%) of patients enrolled in phase 3 study had normal bilirubin at baseline and at the end of the treatment. Thus, the difference between corrected and uncorrected values is less critical. For ALP, the difference between corrected and uncorrected values is < 10%. Only 10 measurements had difference > 10% with the highest of 20%. The Sponsor also conducted primary efficacy analysis with uncorrected values and found that the conclusion remained the same. Thus, using commercially available assay kits for ALP and total bilirubin in this NDA is acceptable.

It is recommended that the sponsor use uncorrected values of ALP and total bilirubin for the primary efficacy analysis as some of the total bilirubin data were not corrected in the database.

2. Is the proposed starting dose of 5 mg QD with titration to 10 mg QD at 3 months appropriate for overall population?

Yes, based on the dose dependent increase in incidences of pruritus (refer section 2.3.4.3) and better tolerability profile with time with a lower starting dose, Sponsor's proposal to start dosing at 5 mg QD (once daily) is appropriate. Although, patients in the phase 3 trial were up-titrated at 6 months, the proposal of up-titration of dose at 3 months is supported by the clinical data that showed that the trend of reduction in ALP saturated at 3 months upon 5 mg once daily dosing and there was minimal further decrease in ALP from 3 months to 6 months and beyond with the same dose at the population level (refer section 1.3.4, Figure 1A, C, D). Further, the median time to onset of severe pruritus was < 2 weeks and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months (refer section 2.3.4.3). Thus, the duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability. The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12 (refer Table 9). Also there were some subjects who were responders at month 6, but became non-responders by month 12, possibly due to disease progression, with continued dosing of 5 mg QD. These patients might also benefit from up-titration to 10 mg QD. The physicians should continue to evaluate biochemical response (reduction in ALP) longitudinally and utilize the up-titration rule at  $\geq 3$  months from the treatment initiation.

3. Are dose adjustments required for patients with hepatic impairment?

Yes, given that the hepatic impairment (moderate and severe) resulted in several fold (4- to 17-fold) increase in plasma exposures of OCA as compared to healthy volunteers in the dedicated study with a single 10 mg dose, the following dosing schema is recommended: Given the signal of dose-response for pruritus in PBC patients (refer section 2.3.4.3), we propose an alternative dosing regimen of 5 mg QW (once weekly) as the starting dose to target comparable initial plasma exposures to subjects with no or mild hepatic impairment. This could be followed by subsequent dose up-titrations based on efficacy and tolerability to 5 mg BIW (twice weekly) followed by further increase to 10 mg BIW (twice weekly) in order to mitigate the potential risk of early discontinuations and gain requisite efficacy. It is worth noting that the Sponsor had

proposed no dose adjustment for hepatic impairment citing that despite higher systemic plasma exposure levels of OCA in patients with hepatic impairment, liver exposure was predicted to be similar (~2-fold) to healthy controls based on their physiologic pharmacokinetic model.

4. Is there evidence for approval of OCA as a monotherapy in adult subjects unable to tolerate UDCA?

Yes, there is evidence of activity of OCA to support its approval in a monotherapy setting for adult subjects unable to tolerate UDCA. Evidence for monotherapy was evaluated based on the response at 3 months in a pooled dataset consisting of two Phase 2 studies and the Phase 3 study. The pooled data showed good responder rate (38%) for monotherapy at 3 months and this responder rate was comparable to that achieved with combination therapy with UDCA (Table 12). Also there was marked reduction in ALP biomarker with monotherapy and this change was statistically significant ( $p < 0.0001$ ) (Figure 14). Based on this evidence, use of OCA as a monotherapy for subjects who are unable to tolerate UDCA seems reasonable.

5. Should there be consideration for discontinuation of OCALIVA for lack of efficacy and, if yes, when?

Possibly, the consideration could be given for discontinuation of OCALIVA for the subjects who do not show response of reduction in alkaline phosphatase if the benefit-risk is unfavorable. Currently there is not enough evidence to show how the long term efficacy of transplant-free survival and overall survival would transpire for subjects who do not show response of reduction in alkaline phosphatase with OCALIVA. This uncertainty in long term efficacy should be weighed against the possible unfavorable lipid profile (decrease in HDL) and its relation to possible cardiovascular risk due to continued treatment with OCALIVA. Based on the evidence from Phase 3 study, the reviewers propose that the physicians could consider possible discontinuation of drug if there is a lack of clinically meaningful response (reduction in ALP) after the subject is on a stable dose of OCALIVA for  $\geq 6$  months. There is currently an ongoing Phase 3 extension trial with continued dosing of OCALIVA for subjects with PBC and with composite efficacy endpoint consisting of death, liver transplant, MELD (Model for End-stage Liver Disease) score  $>15$ , hospitalization for variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and hepatocellular carcinoma. The protocol for this extension trial does not stipulate discontinuation based on lack of efficacy. The evidence from this study could be taken into consideration to possibly weigh the anti-fibrotic beneficial effect of OCALIVA in order to consider continuation of therapy in the absence of ALP response. This issue will be discussed at the GIDAC (Advisory Committee) meeting and the discussion at the meeting will be considered for informing our final recommendations.

6. Is there potential for OCA to affect the pharmacokinetics of drugs that are CYP1A2 substrates?

Yes, there appears to be potential for OCA to increase the systemic exposure to drugs that are CYP1A2 substrates based on the in vitro and in vivo findings. Although in vitro studies did not show CYP1A2 inhibition, down regulation of CYP1A2 expression by OCA was suggested. Further, in an in vivo study, the effect of 10 mg OCA on CYP1A2 substrate caffeine showed that systemic exposure to caffeine increased by 42% while the exposure of metabolite paraxanthine was unaltered. Similarly, the systemic exposure to caffeine increased by 65% following 25 mg OCA without change in systemic exposure to paraxanthine. Unaltered paraxanthine exposure could be due to the fact that this metabolite is partially metabolized by CYP1A2. Based on the

overall findings, there appears to be potential for OCA to modulate CYP1A2 expression and affect the systemic exposure to co-administered drugs that are CYP1A2 substrates. These findings will be reflected in the label.

APPEARS THIS WAY ON ORIGINAL

## 1.1 RECOMMENDATIONS

The acceptability of specific drug information is provided below:

| Decision                              | Acceptable to OCP?   | Comment   |
|---------------------------------------|--|---|
| Overall                               | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |   |
| Evidence of effectiveness             | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A |   |
| Proposed dose for general population  | <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> N/A | The Sponsor's proposed dose for the overall population is acceptable.   |
| Proposed dose for specific population | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> N/A | For subjects with moderate and severe hepatic impairment, the Sponsor's proposal of no adjustment in dosing regimen is unacceptable. In this subpopulation, the starting dose of OCA should be 5 mg QW (once a week), followed by up-titration to 5 mg BIW (twice weekly) and subsequently to 10 mg BIW depending on tolerability and efficacy. |

## 1.2 PHASE IV REQUIREMENTS/COMMITMENTS

None.

**Signatures:**

|   |   |
|---|---|
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DD - V Sinha  
OCP Director – I Zineh

## 1.3 CLINICAL PHARMACOLOGY SUMMARY

### 1.3.1 Dose Recommendations

#### Starting Dosage

The recommended starting dosage of OCALIVA is 5 mg orally once daily in adult patients who

(b) (4)

#### Dosage Titration

If an adequate reduction in alkaline phosphatase has not been achieved after 3 months of OCALIVA 5 mg once daily, and the patient is tolerating the drug, increase the dose of OCALIVA to 10 mg once daily.

For patients

(b) (4)

- Reduce the dosage:
  - 5 mg every other day, for patients intolerant to 5 mg once daily
  - 5 mg once daily, for patients intolerant to 10 mg once daily

(b) (4)

#### Administration Instructions

Take OCALIVA with or without food.

(b) (4)

#### Use in Renal Impairment

No dose adjustment is needed when OCA is used in patients with serum creatinine clearance > 50 mL/min/1.73m<sup>2</sup>. No data is available as how severe impairment would impact the systemic exposure to OCA and its conjugates.

#### Dosage Adjustment in Hepatic Impairment

The recommended starting dose of OCALIVA for moderate and severe hepatic impairment (Child-Pugh B and C) is 5 mg once weekly. If an adequate reduction in alkaline phosphatase has not been achieved after 3 months of OCALIVA 5 mg once weekly, and the patient is tolerating the drug, increase the dose of OCALIVA to 5 mg twice weekly and then subsequently to 10 mg twice weekly depending on response and tolerability.

#### Rationale for Dosing Recommendations

Based on the dose dependent increase in incidences of pruritus (refer section 2.3.4.3) and better tolerability profile with time with a lower starting dose, 5 mg QD (once daily) is a more appropriate starting dose over 10 mg QD dosing. This is consistent with sponsor's proposal and is acceptable to the OCP review team.

The up-titration of dose at 3 months was proposed by the Sponsor even though the Phase 3 study evaluated up-titration of dose (from 5 mg to 10 mg once daily) at 6 months. This dosing strategy was supported by the clinical data that showed that the trend of reduction in ALP saturated at 3 months upon 5 mg once daily dosing and there was minimal further decrease in ALP from 3 months to 6 months at the population level (refer section 1.3.4, Figure 1A, C, D). Further, the median time to onset of severe pruritus was < 2 weeks and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months (refer section 2.3.4.3). Thus, the duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability. The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12 (refer Table 9). Also there were some subjects who were responders at month 6, but became non-responders by month 12, possibly due to disease progression, with continued dosing of 5 mg QD. These patients might also benefit from up-titration to 10 mg QD. The physicians should continue to evaluate biochemical response (reduction in ALP) longitudinally and utilize the up-titration rule at  $\geq 3$  months from the treatment initiation. This titration strategy is acceptable to the OCP review team.

(b) (4)

Food effect study showed that plasma exposure of OCA and glyco-OCA were ~15% higher and tauro-OCA was ~5% lower in fed condition as compared to the fasting condition (refer section 2.6.4). These differences in exposure are not clinically meaningful and thus OCALIVA can be administered without regard to meals.

Regarding bile acid binding resins (bile acid sequestrants; BAS), since the BAS can bind to and reduce the bioavailability of OCA, the Phase 3 study protocol specified that subjects taking a BAS should stagger their dosing of OCALIVA (and UDCA) and BAS by at least 4 hours. With these dosing instructions, modestly lower trough concentrations of OCA were observed at Month 6 and Month 12 in subjects taking BAS (refer section 2.5.2.6). This was associated with a modest attenuation of efficacy for the 5 mg dose group but no meaningful effect for the 10 mg dose group. Thus, the same approach of staggered dosing of BAS is acceptable to us.

Hepatic impairment (moderate and severe) resulted in several fold (4- to 17-fold) increase in plasma exposures of OCA as compared to healthy volunteers. Given the signal of dose-response for pruritus in PBC patients (refer section 2.3.4.3), we arrived at an alternative dosing regimen of 5 mg QW (once weekly) as the starting dose based on plasma exposure matching to subjects with no or mild hepatic impairment using simulations with physiologic PK model. Further dose up-titrations based on efficacy and tolerability can be allowed in order to mitigate the potential risk of intolerability and discontinuations while gaining more efficacy.

### 1.3.2 Exposure-response findings:

#### Efficacy

The sponsor conducted the exposure-response (E-R) relationship of reduction in ALP in PBC subjects that indicated that a 5 mg QD and 10 mg QD dose of OCA, with average total OCA trough concentrations >40 ng/mL (dosing ~2.5-5 mg QD), is predicted to cause at least on average a 30% decrease in ALP and there is plateauing of reduction in ALP with higher concentrations (Figure 6). Doses greater than 10 mg are predicted to not result in additional meaningful benefit in ALP reduction. In addition, the E-R relationship of C4, a marker of FXR activation and bile acid synthesis, showed that C4 levels in healthy subjects decreased with increasing total OCA exposure and plateaued at total OCA concentrations ~50 ng/ml (Figure 7).

#### Safety

Pruritus was the most common adverse event with OCA treatment. Evidence from various Phase 2 studies showed a clear trend of dose-response relationship for pruritus as well as discontinuations due to pruritus, with more events at higher doses (Table 8). Phase 3 study also showed a dose-response relationship for pruritus related discontinuations. During the conduct of clinical studies, the PK samples were collected much later in the trial, e.g. at the end of 6 months and 12 months in Phase 3 study, while the discontinuations happened at earlier times. Thus E-R for pruritus and discontinuations would be biased if these PK measurements were to be used as exposure metric. Hence, evaluation of E-R relationship for pruritus and discontinuations was not carried out.

### 1.3.3 Pharmacokinetics

Like bile acids, OCA and its conjugates also undergo extensive enterohepatic recirculation. Therefore, the PK profiles exhibit multiple peaks within a day following once daily dosing as meals will affect the bile secretion into the intestine.

Total OCA (sum of OCA, glyco- and tauro-OCA) is used in exposure-response analysis for efficacy as OCA and these conjugates have similar potency in FXR activation.

#### Absorption

Following multiple oral doses of OCA 10 mg once daily, peak plasma concentrations ( $C_{max}$ ) of OCA occurring at a median time ( $T_{max}$ ) of approximately 1.5 hours. Median  $T_{max}$  for glyco-OCA and tauro-OCA is 10 hours.

Systemic exposures ( $AUC_{0-24h}$ ) to OCA, glyco-OCA and tauro-OCA are 2.1-, 6.4-, and 9.4-fold higher, respectively, compared to single dose administration.

Food does not have a clinically relevant effect on the PK of 10 mg OCA.

#### Distribution

OCA and its conjugates are highly bound to human plasma proteins (> 99.0%). After intravenous (IV) administration of 0.1 mg OCA, the volume of distribution of OCA was 618 L. Liver concentration is predicted to be much higher (~20-fold) than the plasma concentration in healthy subjects based upon a PBPK model.

#### Metabolism and Elimination

OCA is not metabolized by CYP enzymes. Major active metabolites, glyco-OCA and tauro-

OCA, are present in the plasma at much higher concentrations (~14- and ~12-fold, respectively) compared to the parent drug.

Following an oral administration of 25 mg [<sup>14</sup>C]-OCA, about 87% of the dose is excreted in feces through biliary secretion. Less than 3% of the dose is excreted in the urine with no detection of OCA.

The effective half-life of OCA is about 24 hours.

### **Specific Populations**

Gender, age, and race had no impact on the pharmacokinetics of OCA based on the pop-PK analysis.

Body weight was a significant predictor of OCA pharmacokinetics, with lower OCA exposure expected with higher body weight. The median AUC for a 40 kg subject is expected to be 50% higher and median AUC for a 134 kg subject is expected to be 43% lower compared to the AUC for a typical 67 kg subject. The body weight effect is not expected to cause a meaningful impact on efficacy as concentrations of total OCA are predicted to be above the estimated IC<sub>50</sub> for efficacy (reduction in ALP) after daily administration of OCA at 5 mg and 10 mg doses. Also in the Phase 3 study, for the subjects with 5 mg QD starting dose, there was no trend of up-titration occurring preferably in higher body weight subjects (associated with lower concentration) over lower body weight subjects with titrations based on response and tolerability. Thus, the impact of body weight is not clinically meaningful to suggest dose recommendation based on body weight. Our analysis based on the body mass index (BMI) showed an initial lower response at week 2 in high BMI group with 5 mg QD starting dose vis-à-vis 10 mg QD starting dose, but this difference vanished by 6 months (Table 23). Since there is no clinical urgency to get a more rapid response and dose discontinuation due to pruritus is a major concern with a potential higher starting dose, the review team does not recommend a higher starting dose based on a higher body weight or high BMI criteria.

### **Renal Impairment**

Renal excretions of OCA and conjugates are low (<3% in the mass balance study). Population PK analysis did not identify renal function (eGFR) as a significant covariate for OCA clearance/exposure for patients with renal impairment (eGFR ranged from 52 to 433 mL/min/1.73 m<sup>2</sup>). However, patients with eGFR <50 mL/min/1.73 m<sup>2</sup> were not enrolled in the study. The effect of severe renal impairment on the systemic exposure to total OCA is unknown.

### **Hepatic Impairment**

The systemic exposure (AUC<sub>0-9 days</sub>) to total OCA is 1.1-, 4.2-, and 17.3-fold in patients with mild, moderate and severe hepatic impairment, respectively, when compared to healthy controls after a single dose of 10 mg OCA.

There was no apparent association of change of free fraction (%Fu) of OCA and tauro-OCA with the increased degree of hepatic impairment. Mean %Fu of glyco-OCA increased in patients with severe hepatic impairment.

Based on the consideration of tolerability, the review team proposed dose adjustment for PBC patients with moderate and severe hepatic impairment (refer section 1.3.1).

## DRUG-DRUG INTERACTIONS

Because OCA and its conjugates are FXR agonists, additional effect on transporters and certain CYP enzymes can occur. For example, FXR activation is known to induce BSEP, MRP2/3, and MDR3 and down regulate OATPs, which may impact the pharmacokinetics of other drugs. Additional relevant information is given in details below. Also refer to 2.5.2.5, Table 47 for details.

### *In vitro drug-drug interaction potential*

**Effect of other drug on OCA:** Because OCA is not a substrate for CYP enzymes, CYP enzyme inhibition/induction by other drugs will not affect the PK of OCA.

### **Effect of OCA on other drugs:**

**CYP inhibition:** Clinical relevant inhibition of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 by OCA, glyco-OCA, or tauro-OCA at the systemic level is not anticipated, but a potential in-vivo drug interaction via inhibition of CYP3A4 in the gut cannot be ruled out.

**CYP induction:** There is low potential for induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 enzymes by OCA, glyco-OCA, or tauro-OCA. However, mRNA down-regulation was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by OCA, glyco-OCA, and tauro-OCA.

**Substrate for transporters:** OCA, glyco-OCA, and tauro-OCA are weak substrates for P-gp. Glyco-OCA and tauro-OCA are substrates for ASBT, NTCP, OAT3, OATP1B1, and OATP1B3. Tauro OCA is also a substrate for BSEP.

**Transporter inhibition:** There is potential for OCA and its conjugates to inhibit OATP1B1 and OATP1B3, but not other transporters.

**Resin binding agents:** Bile acid sequestrants, colestevlam and cholestyramine, bind to OCA, glyco-OCA, and tauro-OCA.

### *In vivo Drug-drug interactions*

#### **Effect on midazolam, a CYP3A substrate**

Following multiple doses of OCA 10 mg QD, systemic exposures to midazolam and alpha-hydroxy-midazolam was the same as those without OCA. However, multiple doses of OCA 25 mg QD did result in increase of AUC (26%) and C<sub>max</sub> (17%) of midazolam. Dose adjustment of CYP3A substrates is not needed when co-administering OCA 10 mg with a CYP3A substrate.

#### **Effect on caffeine, a CYP1A2 substrate**

Following multiple doses of OCA 10 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of caffeine increased by 42% and 6%, respectively. Systemic exposures to paraxanthine were minimally decreased. Further increase in systemic exposure to caffeine was noted when multiple doses of 25 mg QD were co-administered with caffeine. The interaction may be due to CYP1A2 down regulation by OCA, thus, therapeutic monitoring and dose adjustment of CYP1A2 substrates may be needed when co-administering OCA with a CYP1A2 substrate (e.g. theophylline) that has a narrow therapeutic index.

#### **Effect on warfarin, a CYP2C9 substrate**

Co-administration of warfarin with multiple doses of OCA 10 mg and 25 mg QD resulted in 13 % and 18% increase in systemic exposure to S-warfarin, respectively. However, the maximum INR is decreased by 11.1% (10 mg QD). Monitoring INR when warfarin is co-administered with OCA 10 mg QD and adjusting dose of warfarin accordingly is recommended.

Effect on omeprazole, a CYP2C19 substrate

Following multiple doses of OCA 10 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of omeprazole increased by 33%. Systemic exposure to hydroxyl-omeprazole is also increased. Similar effect was found at OCA 25 mg QD. The mechanism for this increase is unknown. Dose adjustment of CYP2C19 substrate is not needed when co-administering OCA 10 mg with a CYP2C19 substrate.

Effect on dextromethorphan, a CYP2D6 substrate

Following multiple doses of OCA 10 mg and 25 mg QD, no significant effect on systemic exposure to dextromethorphan or dextropropranolol was found.

Effect on digoxin, a P-gp substrate

Following multiple doses of OCA 10 mg and 25 mg QD, no significant effect on systemic exposure to digoxin was observed. Renal clearance of digoxin remained the same.

Effect on rosuvastatin, a substrate for OATP1B1, OATP1B3, and BCRP

Following multiple doses of OCA 10 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of RSV increased by 22% and 27%, respectively. AUC<sub>inf</sub> of N-desmethyl-RSV increased by 1.1% while C<sub>max</sub> of N-desmethyl-RSV decreased by 1.3%. Similar effect was found at OCA 25 mg QD.

Although in vitro study and the known effect of FXR activation point to potential increased exposure to OATP substrates, only a small increase in exposure to rosuvastatin was observed.

Effect of bile acid binding agents on resins (bile acid sequestrants; BAS)

In the Phase 3 study, subjects taking a BAS were to stagger their dosing of OCA and UDCA by at least 4 hours. Modestly lower trough concentrations of OCA were observed at Month 6 and Month 12 in subjects taking BAS. This was associated with a modest attenuation of efficacy for the 5 mg dose group but no meaningful effect for the 10 mg dose group. Thus, the same approach of staggered dosing of BAS is acceptable.

Effect of gastric acid reducing agent on OCA

Administration of 10 mg OCA with omeprazole 20 mg QD for 4 days resulted in 19% increase in steady-state C<sub>max</sub> and AUC of OCA. C<sub>max</sub> and AUC of glyco-OCA increased by 20% and 16%, respectively. C<sub>max</sub> and AUC of tauro-OCA increased by 15% and 13%, respectively.

Similar effect was found for OCA 25 mg. This is likely due to the increased absorption of OCA as a result of elevated gastric pH. The magnitude of increase in systemic exposure to OCA and its conjugates does not have a significant clinical impact. No dose adjustment is needed when OCA is co-administered with omeprazole 20 mg QD.

The Sponsor did not study the effect of omeprazole 40 mg on the systemic exposure to OCA and its metabolites.

### **1.3.4 Efficacy and Safety**

#### **Efficacy**

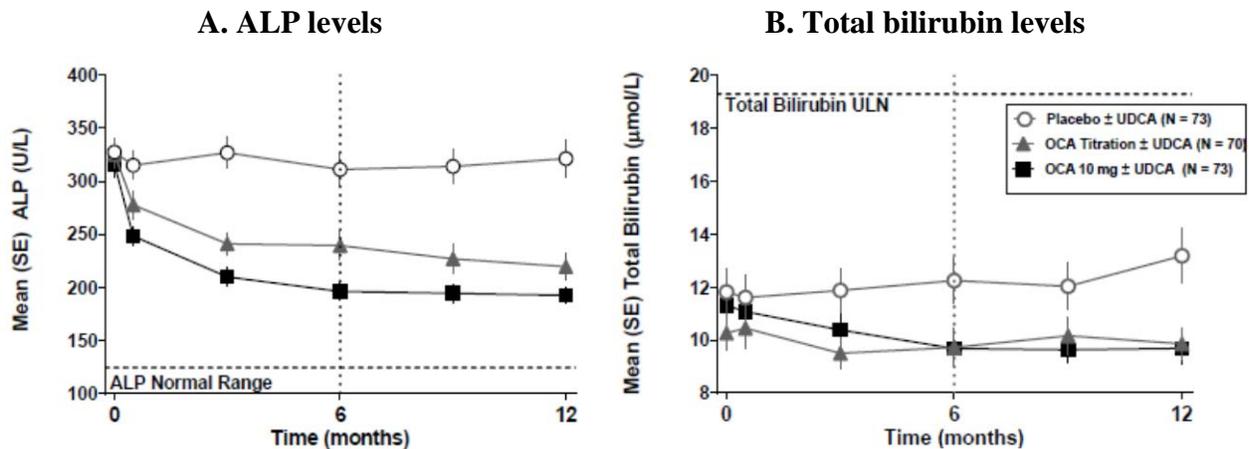
The clinical efficacy result from the Phase 3 study is shown in Table 1. The primary efficacy endpoint in the Phase 3 study was the percentage of subjects reaching specific biochemical criteria for ALP and bilirubin after 1 year of treatment (ALP <1.67x ULN [with a ≥15% reduction] and bilirubin ≤ULN). The study demonstrated that a statistical significance in the primary efficacy endpoints was achieved for both 10 mg QD arm and titration arm (5 mg QD with possible up-titration to 10 mg QD) at 6 months and at 12 months. OCA treatment showed improvement in ALP levels as early as 2 weeks and resulted in statistically significant improvement versus placebo ( $p \leq 0.0001$ ) in ALP levels at month 6 and 12 (Figure 1A). Over the 12 month treatment period, there was an increase in mean total bilirubin levels in placebo group, while the levels were maintained in the OCA treatment groups (Figure 1B). For the subjects in OCA titration arm, who were up-titrated to 10 mg QD, there was further decrease in ALP levels from month 6 to month 12, with mean ALP at baseline, month 6 and month 12 being 348 U/L, 256 U/L and 222 U/L respectively (Figure 1C-D).

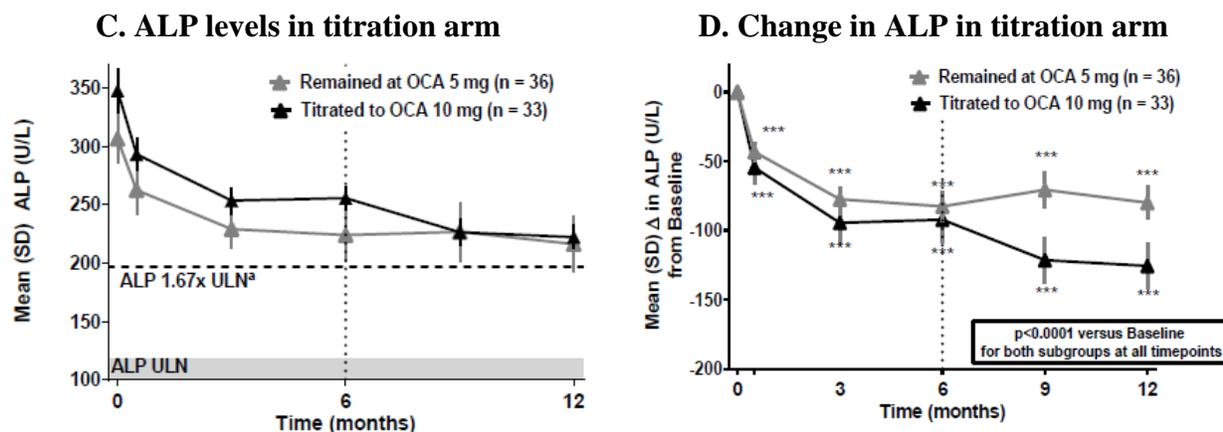
Table 1: Summary of clinical efficacy results in patients treated with OCA (Phase 3 study 747-301)

| Time     | Responders, % (n/N) |                           |                |
|----------|---------------------|---------------------------|----------------|
|          | Placebo             | OCA Titration (5 - 10 mg) | OCA 10 mg      |
| Month 6  | 7%<br>(5/73)        | 34%<br>(24/70)            | 51%<br>(37/73) |
| Month 12 | 10%<br>(7/73)       | 46%<br>(32/70)            | 47%<br>(34/73) |

OCA treatments ( $\pm$ UDCA) at both 6 and 12 month statistically significant over placebo ( $\pm$ UDCA),  $p < 0.0001$

Figure 1: Time profiles of mean ALP and total bilirubin levels in the ITT population for Phase 3 study 747-301 across the three randomized arms (panel A-B) and ALP levels within the titration arm for subjects remaining at 5 mg vs. those titrated to 10 mg OCA at month 6 (panel C-D)





Source Data: Section 2.5, Figure 11 and CSR 747-301, Figure 24

## Safety

Table 2 shows the comparison of adverse drug reactions for placebo and the two OCA treatment arms. Pruritus was the most prominent safety event of concern. For details, refer to the clinical review by Dr. Ruby Mehta, Medical Officer of DGIEP.

Table 2: Summary of adverse drug reactions in safety population (Phase 3 study 747-301)

| ADRs <sup>a</sup><br>Category              | Placebo<br>(N=73) | Titration<br>(N=70) | OCA 10mg<br>(N=73) |
|--|-------------------|---------------------|--------------------|
| Pruritus/Skin eruptions <sup>b</sup>       | 28 (38.4)         | 39 (55.7)           | 51 (69.9)          |
| Fatigue/Tiredness <sup>c</sup>             | 11 (15.1)         | 13 (18.6)           | 18 (24.7)          |
| Abdominal pain and discomfort <sup>d</sup> | 10 (13.7)         | 13 (18.6)           | 7 (9.6)            |
| Oropharyngeal pain                         | 1 (1.4)           | 5 (7.1)             | 6 (8.2)            |
| Arthralgia                                 | 3 (4.1)           | 4 (5.7)             | 7 (9.6)            |
| Procedural pain                            | 1 (1.4)           | 4 (5.7)             | 1 (1.4)            |
| Oedema peripheral                          | 2 (2.7)           | 2 (2.9)             | 5 (6.8)            |
| Palpitations                               | 1 (1.4)           | 2 (2.9)             | 5 (6.8)            |
| Eczema                                     | 0 (0.0)           | 4 (5.7)             | 2 (2.7)            |
| Pyrexia                                    | 1 (1.4)           | 0 (0.0)             | 5 (6.8)            |

<sup>a</sup> ADRs were defined as AEs that occurred in  $\geq 5\%$  in any OCA treatment group and at a rate that was at least 3% greater than that observed in the placebo treatment group.

<sup>b</sup> Includes prurigo, pruritus, pruritus generalised, eye pruritus, anal pruritus, vulvovaginal pruritus, and rash pruritic

<sup>c</sup> Includes PTs of Fatigue and Asthenia

<sup>d</sup> Includes PTs Abdominal Pain Upper, Abdominal Pain, Abdominal Discomfort, Abdominal Pain Lower, Abdominal Tenderness, and Gastrointestinal Pain

Source Data: Section 2.5, Table 16

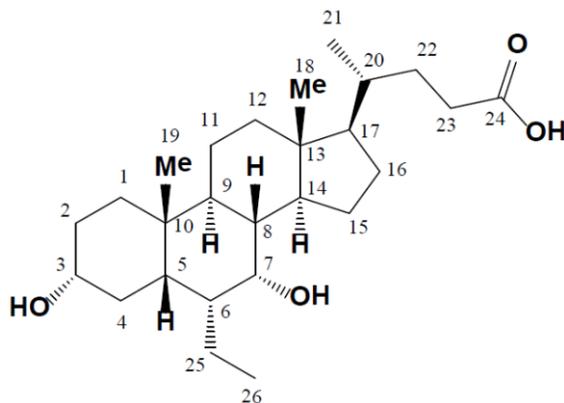
## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Physico-chemical properties:

1. Structural formula: C<sub>26</sub>H<sub>44</sub>O<sub>4</sub>.



2. Established name: Obeticholic acid
3. Other names: 6 $\alpha$ -ethyl chenodeoxycholic acid (6-ECDCA); INT-747; or DSP-1747
4. Molecular Weight: 420.63 g/mol

Obeticholic acid is a Biopharmaceutics Classification System (BCS) Class II drug. See 2.6.1 for the review on permeability data.

#### 2.1.2 What are the proposed mechanism of action and therapeutic indications?

Obeticholic acid is an agonist for FXR, a nuclear receptor expressed at high levels in the liver and intestine, with EC<sub>50</sub> values ~100-fold lower than the natural FXR agonist chenodeoxycholic acid (CDCA) (see Pharmacology/Toxicology review). 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, thus reducing hepatic exposure to bile acids.

The proposed indication is indicated for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

#### 2.1.3 What is the Sponsor's proposed dosage and route of administration?

The Sponsor's proposed starting dose is 5 mg once daily given orally. Based on the assessment of efficacy and tolerability after 3 months, the dose may be increased to 10 mg once daily, to improve biochemical response.

### 2.2 What is the regulatory history of this product?

OCA is considered as a new molecular entity (NME) for the purposes of FDA review. The NDA 207999 Obeticholic acid (Ocaliva) Clinical Pharmacology Review

clinical pharmacology related regulatory history is shown below.

Table 3: Regulatory timeline

| Type of submission  | Date       | Recommendations   |
|---|------------|---|
| PIND  | 10/27/2004 |   |
| Open IND  | 1/27/2006  |   |
| EOP2  | 10/11/2011 | DCP3 recommended the Sponsor study an additional lower dosage in Phase 3 program due to dose-related AE (pruritus).                         |
| Type C Written Response to Clinical Pharmacology Development Plan | 2/27/2014  | address effect of gastric acid reducing agents<br>address effects on CYP2B6 and 2C8<br>address mass balance/ADME<br>Evaluate impact of ESRD |
| Grant Fast Track  | 5/27/2014  |   |
| Type C meeting on formulation bridging strategy                   | 6/24/2014  | Recommended an additional bridging study  |
| Type C meeting on Phase 3 trial design                            | 7/22/2014  | Recommended to collect sparse PK samples to facilitate exposure-response analyses for efficacy and safety                                   |
| Pre-NDA meeting   | 11/18/2014 | Requested submitting analytical reports, and pH-solubility data to aid in the evaluation of the effect of gastric acid reducing agents      |
| Grant rolling review  | 11/18/2014 |   |
| DCP3: Division of Clinical Pharmacology 3                         |            |   |

## 2.3 GENERAL CLINICAL PHARMACOLOGY

### 2.3.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The clinical development program for OCA consists of seventeen clinical pharmacology Phase 1 studies; two double-blind, placebo-controlled, 3-month Phase 2 studies; one double-blind, placebo-controlled Phase 3 study; and the open-label, long-term safety extension phases for the Phase 2 and Phase 3 studies. There were additional two Phase 2 studies, one for the treatment of portal hypertension and another to investigate the effect of OCA on lipoprotein metabolism in subjects with PBC. The clinical studies supporting the NDA are listed in Table 4.

#### Clinical Pharmacology Studies

Refer to Table 4 for a brief description of study design for Phase 1 studies.

#### Clinical Efficacy/Safety Studies

Refer to Table 4 for a brief description of the two Phase 2 studies and one Phase 3 study for efficacy and safety of OCA in subjects with PBC. All these three studies were randomized, double-blind, placebo-controlled studies. The duration of treatment in the two Phase 2 studies was 3 months. The dosing regimen of OCA employed in study 747-201 was 10 mg or 50 mg QD and it was a monotherapy study. The dosing regimen of OCA employed in study 747-202 was 10 mg, 25 mg or 50 mg QD and there was concomitant dosing of UDCA. The duration of treatment in the Phase 3 study was 12 months. The Phase 3 study evaluated two dosing regimen: i) 10 mg QD for 12 months and ii) 5 mg QD for 6 months followed by up-titration to 10 mg QD for next 6 months based on efficacy and tolerability. A schematic of Phase 3 study design is provided in Figure 2.

Population PK analysis was performed using the PK data for OCA, glyco-OCA and tauro-OCA from following Phase 1 and Phase 2 studies (16 studies): 747-101, 747-102, 747-103, 747-104, 747-105, 747-107, 747-108, 747-109, 747-110, 747-111, 747-112, 747-114, 747-115, 747-116, 747-204, 747-205.

Exposure-response analyses were carried out with the data from Phase 3 study 747-301 with observed trough concentrations as exposure metric.

PBPK analysis was performed based upon PK data from following Phase 1 and Phase 2 studies: 747-103, 747-105, 747-115, 747-116, and 747-204. Review of PBPK analysis can be found in Appendix.

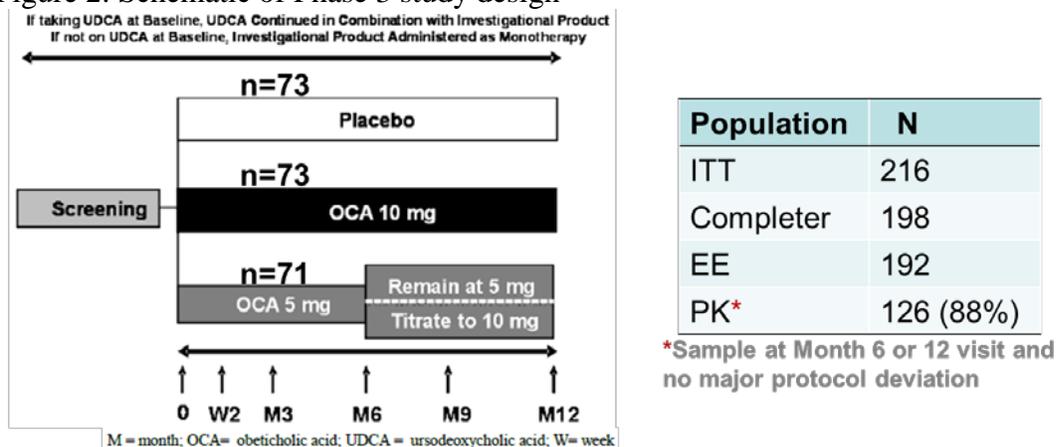
Table 4: Summary of individual clinical studies

| Study Type   | Study No. | OCA Dosing Regimen and Duration   | No. of Subjects in Study |
|--|-----------|---|--------------------------|
| <b>Phase 1 Studies in Healthy Subjects</b>                             |           |   |                          |
| Absolute bioavailability   | 747-113   | 25 mg tablets, followed by IV infusion, 5 mL dose (100 µg, NMT (b) (4))           | 5                        |
|  |           | [ <sup>14</sup> C] capsule, 25 mg (containing NMT (b) (4))                        | 8                        |
| Food effect  | 747-104   | 10 and 25 mg single dose (2 period, 2 sequence, crossover)                        | 32                       |
| Biocomparability   | 747-115   | 10 mg tablet (commercial image and clinical development)                          | 160                      |
| Biocomparability   | 747-116   | 10 mg tablet (commercial image) 10 mg capsule (Phase 2 formulation)               | 160                      |
| PK/Tolerability  | 747-102   | 25, 50, 100, or 250 mg QD multiple doses (Day 1-12)                               | 50                       |
| PK (single and multiple doses)   | 747-105   | 5, 10 or 25 mg single dose (Day 1)<br>5, 10 or 25 mg multiple QD doses (Day 4-17) | 24                       |
| Thorough QT/QTc  | 747-108   | 100 mg multiple QD doses (Day 1-5)  | 192                      |
| Midazolam (CYP3A4 substrate) and Caffeine (CYP1A2 substrate)           | 747-109   | 10 or 25 mg QD multiple doses (Day 5-23)  | 48                       |
| Racemic warfarin   | 747-110   | 10 or 25 mg QD multiple doses (Day 8-27)  | 44                       |
| Rosuvastatin   | 747-111   | 10 or 25 mg QD multiple doses (Day 6-23)  | 48                       |
| Dextromethorphan (CYP2D6 substrate) and Omeprazole (CYP2C19 substrate) | 747-112   | 10 or 25 mg QD multiple doses (Day 5-28)  | 48                       |
| Digoxin  | 747-114   | 10 or 25 mg QD multiple doses (Day 6-23)  | 48                       |
| Hepatic impairment   | 747-103   | 10 mg single dose   | 32                       |
| PK   | 747-107   | 100 mg QD for 5 days  | 8                        |
| PK/Tolerability  | 747-101   | 50, 100, 250, 500 mg single dose  | 24                       |

|  |          |  |          |
|--|----------|--|----------|
| PK/Safety in Japanese healthy volunteers                                   | D8601002 | 5, 10 or 25 mg single dose;<br>50 mg QD multiple dose (Day 1, Day 4-10)  | 42<br>12 |
| PD (FGF-19 levels) /Safety/Efficacy  | OBADIAH1 | 25 mg QD for 15 days   | 25       |
| <b>Phase 2 and Phase 3 Studies in PBC Patients</b>                         |          |  |          |
| Phase 2 randomized, double-blind, placebo-controlled study                 | 747-201  | Monotherapy study<br>10 and 50 mg QD multiple doses (Day 1-85)   | 59       |
|  | 747-202  | Study with concomitant UDCA<br>10, 25 and 50 mg QD multiple doses (Day 1-85)   | 165      |
| Phase 3 randomized, double-blind, placebo controlled efficacy/safety study | 747-301  | 10 mg QD for 12 months<br>or 5 mg QD for 6 months followed by titration to 10 mg QD for next 6 months based on efficacy/tolerability | 217      |
| <b>Additional Phase 2 Studies</b>  |          |  |          |
| Safety/tolerability/efficacy for treatment of portal hypertension          | 747-204  | 10 and 25 mg QD multiple doses (7 days)  | 34       |
| Effects of OCA on lipoprotein metabolism in subjects with PBC              | 747-205  | 10 mg QD multiple doses (8 weeks)  | 27       |

Source Data: Section 2.7.6, Table 1

Figure 2: Schematic of Phase 3 study design



**Inclusion criteria:** At least 1 of the following qualifying biochemistry values:

(1) ALP level  $\geq 1.67 \times \text{ULN}$ , (2) Total bilirubin  $> \text{ULN}$  but  $< 2 \times \text{ULN}$

**Responders:** Subjects who have ALP  $< 1.67 \times \text{ULN}$  and total bilirubin  $\leq \text{ULN}$  and ALP decrease of  $\geq 15\%$

## 2.3.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

### Endpoints

The primary efficacy endpoint in the Phase 3 double-blind and placebo-controlled trial was the percentage of subjects reaching specific biochemical criteria for ALP and bilirubin after 1 year of treatment (ALP <1.67x ULN [with a  $\geq$ 15% reduction] and bilirubin  $\leq$ ULN). ALP is considered to be a marker of cholestasis and is a key component of diagnosis of PBC in American and European guidelines. Bilirubin was the regulatory endpoint used for initial approval of UDCA in the EU and US. Thus, it is already considered as an independent predictor of PBC prognosis. The slow rate of disease progression and being a rare disease, registration trials based on clinical outcome such as transplant-free survival are challenging. Thus, the changes in ALP and bilirubin are hypothesized as surrogate markers for potential clinical benefit in this program. The combination of changes in ALP and bilirubin has been investigated for their prognostic ability in small cohorts although it has never been investigated on a large enough size to be deemed suitable per the regulatory guidance. The table below shows various such response criteria that have been evaluated (Table 5).

Table 5: Response criteria of predictive laboratory markers for progression of PBC

|                           |         |   |
|---------------------------|---------|---|
| Barcelona (Pares 2006)    | N = 192 | ALP reduction $\geq$ 40% from baseline or normalization                 |
| Paris I (Corpechot 2008)  | N = 292 | ALP $\leq$ 3x ULN and AST $\leq$ 2xULN and Bilirubin $\leq$ 1 mg/dL     |
| Paris II (Corpechot 2011) | N = 165 | ALP $\leq$ 1.5x ULN and AST $\leq$ 1.5xULN and Bilirubin $\leq$ 1 mg/dL |
| Toronto I (Kumagi 2010a)  | N = 165 | ALP $\leq$ 1.67x ULN  |
| Toronto II (Kumagi 2010b) | N = 69  | ALP <1.76x ULN  |
| Rotterdam (Kuiper 2009)   | N = 375 | Albumin $\geq$ LLN and Bilirubin $\leq$ ULN                             |

Source Data: Section 2.5, Table 2

A number of these response criteria considered that ALP has prognostic value in the range of 1.5x- to 2.0x- Upper Limit of Normal (ULN) of ALP. Since elevated circulating bilirubin is a marker of hepatocellular damage and thus the intensity of disease progression, the combination of bilirubin with ALP is hypothesized to increase the prognostic or predictive value towards assessing OCA efficacy.

The minimum 15% reduction in ALP was recommended by (b) (4) (an internationally recognized PBC expert) to be added to the composite endpoint for additional rigor in the study design. This ensured that subjects who initiated the study with an ALP close to the 1.67x- ULN threshold inclusion criteria had a clinically meaningful ALP response to be considered to have met the primary endpoint.

The Sponsor provided validation of value of primary composite endpoint by evidence from analysis of two large independent databases for PBC patients (Global PBC Group and UK-PBC Group). The analyses of these databases showed that reductions in serum ALP and bilirubin levels were strongly associated with increased transplant-free survival and that the composite endpoint in Phase 3 study 747-301 was predictive of clinical outcomes in patients with PBC

(Table 6).

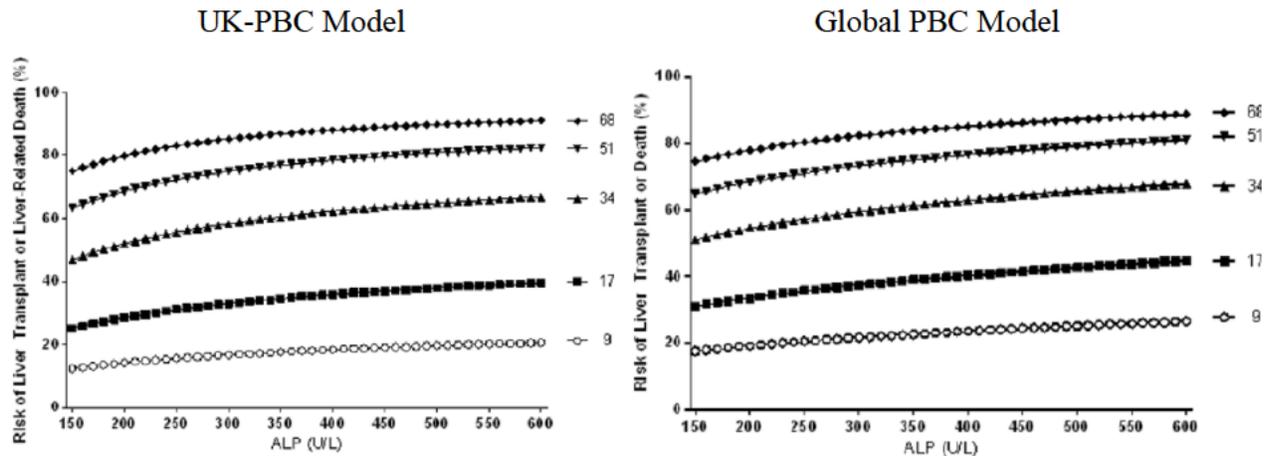
Table 6: Summary of hazard ratios calculated for biochemical endpoints

|  | UK-PBC Cohort<br>(N = 4022) | Global PBC Group<br>(N = 4845) |
|--|-----------------------------|--------------------------------|
| Parameter  | Hazard Ratio (± 95%)        | Hazard Ratio (± 95%)           |
| Abnormal vs Normal Bilirubin   | 14.6 (11.5-18.6)            | 5.1 (4.3-5.9)                  |
| ALP >1.67 versus ≤1.67   | 4.8 (3.5-6.3)               | 2.2 (1.9-2.5)                  |
| ALP <1.67x ULN [with a >15% reduction] and bilirubin <ULN); Phase 3 Endpoint | 7.5 (5.0-11.2)              | 2.12 (1.42-3.44)               |

Source Data: Section 2.5, Table 3

Multivariate analyses done by both groups indicate that ALP and bilirubin were significant predictors of risk. Based on the model scores produced by both groups, survival curves associated with a range of ALP values at given levels of bilirubin (9 µmol/L [0.5x ULN] to 68 µmol/L [4x ULN]) were evaluated (Figure 3). Both sets of results indicate the predictive utility of ALP and bilirubin in assessing risk in patients with PBC and improvements in survival were seen across the range of ALP values.

Figure 3: Risk of liver transplant or mortality by bilirubin and ALP levels from the Global PBC and UK-PBC models



Source Data: Section 2.5, Figure 5

The Global PBC study group dataset that comprised subjects with placebo and UDCA treatment followed for >10 years for their clinical outcome has been under review to confirm evidence about the value of the surrogate endpoint evaluated in Phase 3. Please refer to clinical and statistical reviews for further insights regarding this issue.

### Biomarkers

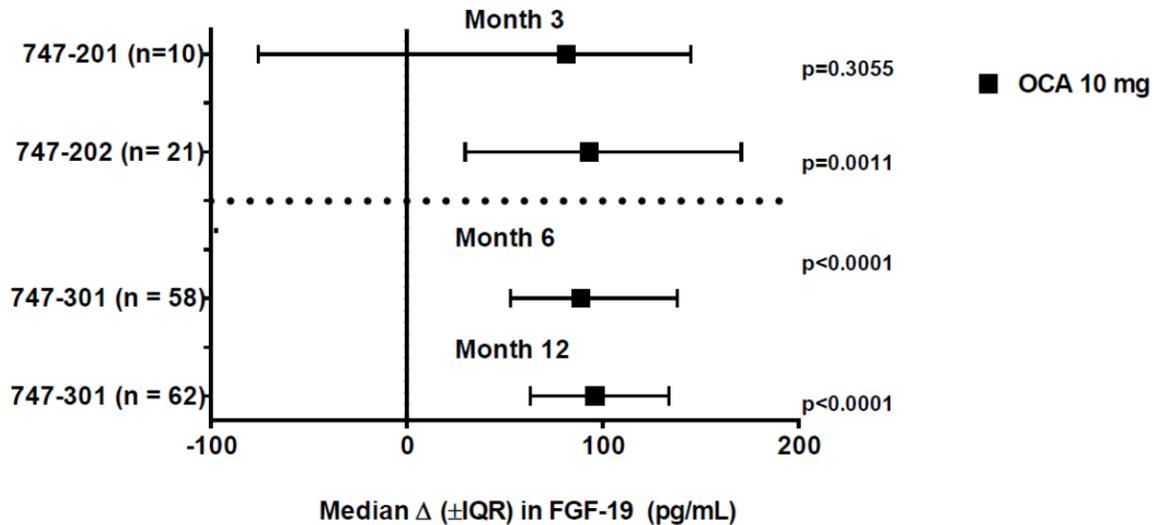
Besides ALP and total bilirubin which are discussed under the section on clinical endpoints above, several biomarkers including fibroblast growth factor-19 (FGF-19), 7-alpha-hydroxy-4-cholesten-3-one (C4), endogenous bile acids [cholic acid (CA), CDCA, deoxycholic acid (DCA), lithocholic acid (LCA)], were explored during the clinical development of this drug. As C4 and FGF-19 are related to the mechanism of action, the findings on plasma C4 and FGF-19 were

reviewed and summarized below.

As part of the clinical development program for OCA, plasma FGF-19 and C4 concentrations were measured as a marker of OCA pharmacological activity.

OCA increased FGF-19 levels in 2 Phase 2 studies and 1 Phase 3 study (Studies 747-201, 202, and 301). Consistent with FXR agonist effects, statistically significant increases in FGF-19 from Baseline to Month 3 were observed in Study 747-202 and at Month 6 and Month 12 in Study 747-301 for OCA compared with placebo. The increase observed in Study 747-201 was not statistically significant. The median difference (95% CI) for OCA 10 mg compared with placebo for each individual study is summarized in Figure 4. In Phase 2 Study 747-202 which evaluated a range of doses (10 mg, 25mg and 50 mg), the increase in levels of FGF-19 was dose dependent (Figure 5).

Figure 4: Median difference (95% IQR) in plasma FGF-19

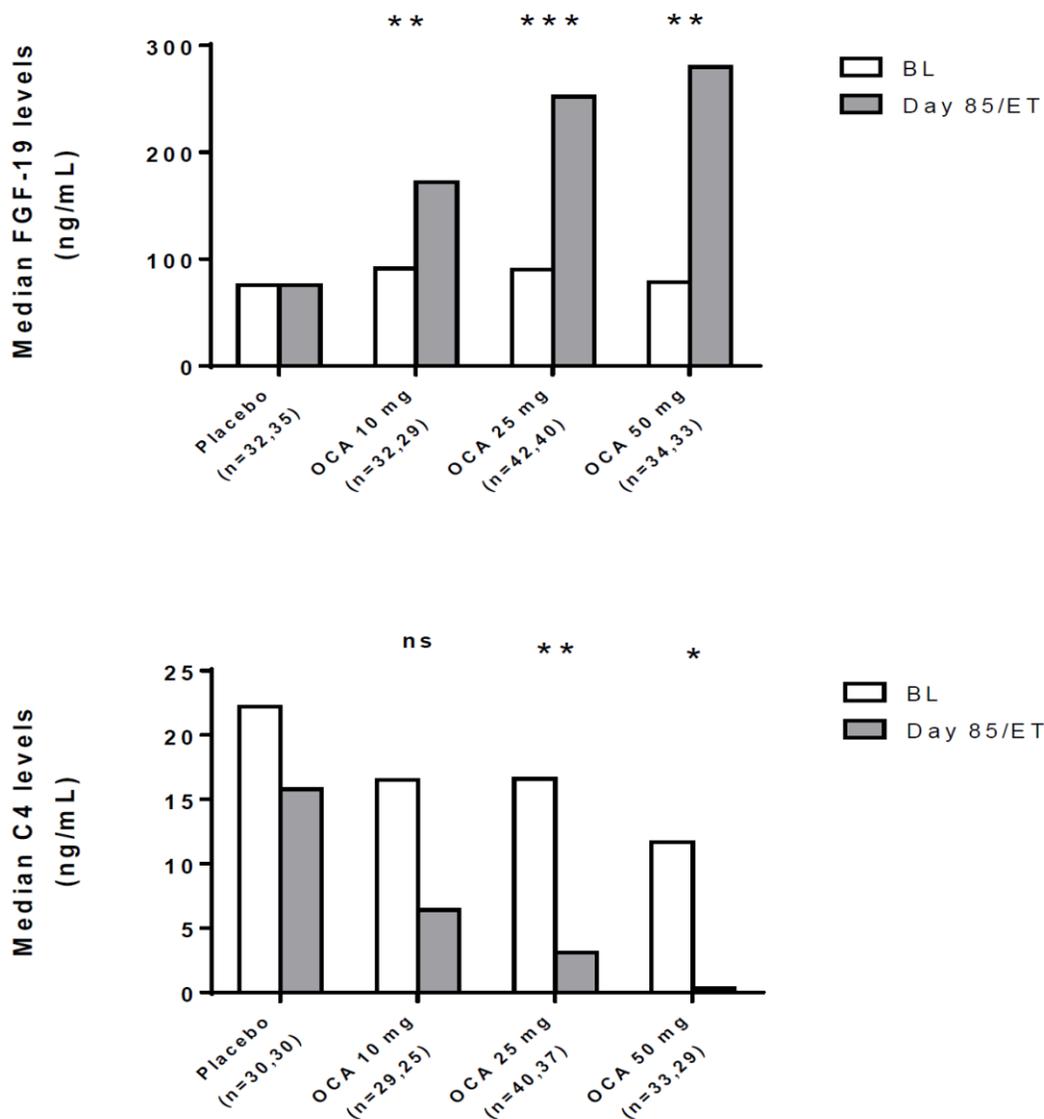


FGF-19 = fibroblast growth factor-19; ITT = intent-to-treat; LLN = lower limit of normal; OCA = obeticholic acid  
p-value for comparing active treatments to placebo were obtained using the Wilcoxon rank-sum test.  
Hodges-Lehmann estimates for the median difference (OCA - Placebo).  
For Studies 747-201 and 747-202 the LLN = 31 pg/mL and the ULN = 554 pg/mL. For Study 747-301, the LLN = 157 pg/mL and the ULN = 229 pg/mL.  
Source: Module 5.3.5.3, ISE, SDS 3.11.2.2

Source Data: Section 2.7.2, Figure 14.

FGF-19 activation was associated with a reduction in C4. In Study 747-202, C4 levels decreased with increasing exposure of total OCA consistent with regulation of CYP7A1 by FGF-19 (Figure 5).

Figure 5: FGF-19 and C4 Levels at Baseline and Day 85/ET After Daily Administration of Placebo, 10 mg OCA, 25 mg OCA, and 50 mg OCA: ITT Population (N = 165) (Study 747-202)



Source Data: Section 2.7.2, Figure 15

In Study 747-301, reductions in total endogenous bile acid were observed for subjects receiving OCA titration (-1.41  $\mu\text{mol}$ ; p-value = 0.0553) and OCA 10 mg (-5.72  $\mu\text{mol}$ ; p-value = 0.0035), while an increase from Baseline was observed for subjects receiving placebo (2.24  $\mu\text{mol}$ ; p-value = 0.1212). Statistically significant mean absolute reductions in total endogenous bile acids from Baseline to Month 12 were observed for the OCA titration (-2.86  $\mu\text{mol}$ ; p = 0.0010) and OCA 10 mg (-4.70  $\mu\text{mol}$ ; p = 0.0037).

Overall, the increase in FGF-19 concentration was associated with a reduction in C4 and total

endogenous bile acids in patients receiving OCA which is consistent with the mechanism of action of OCA as an FXR agonist.

**2.3.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess PK parameters and exposure response relationships?**

Yes. Refer to Section 2.3.7.7.

**2.3.4 Exposure-response (E-R)**

**2.3.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?**

**Clinical Marker/Endpoint**

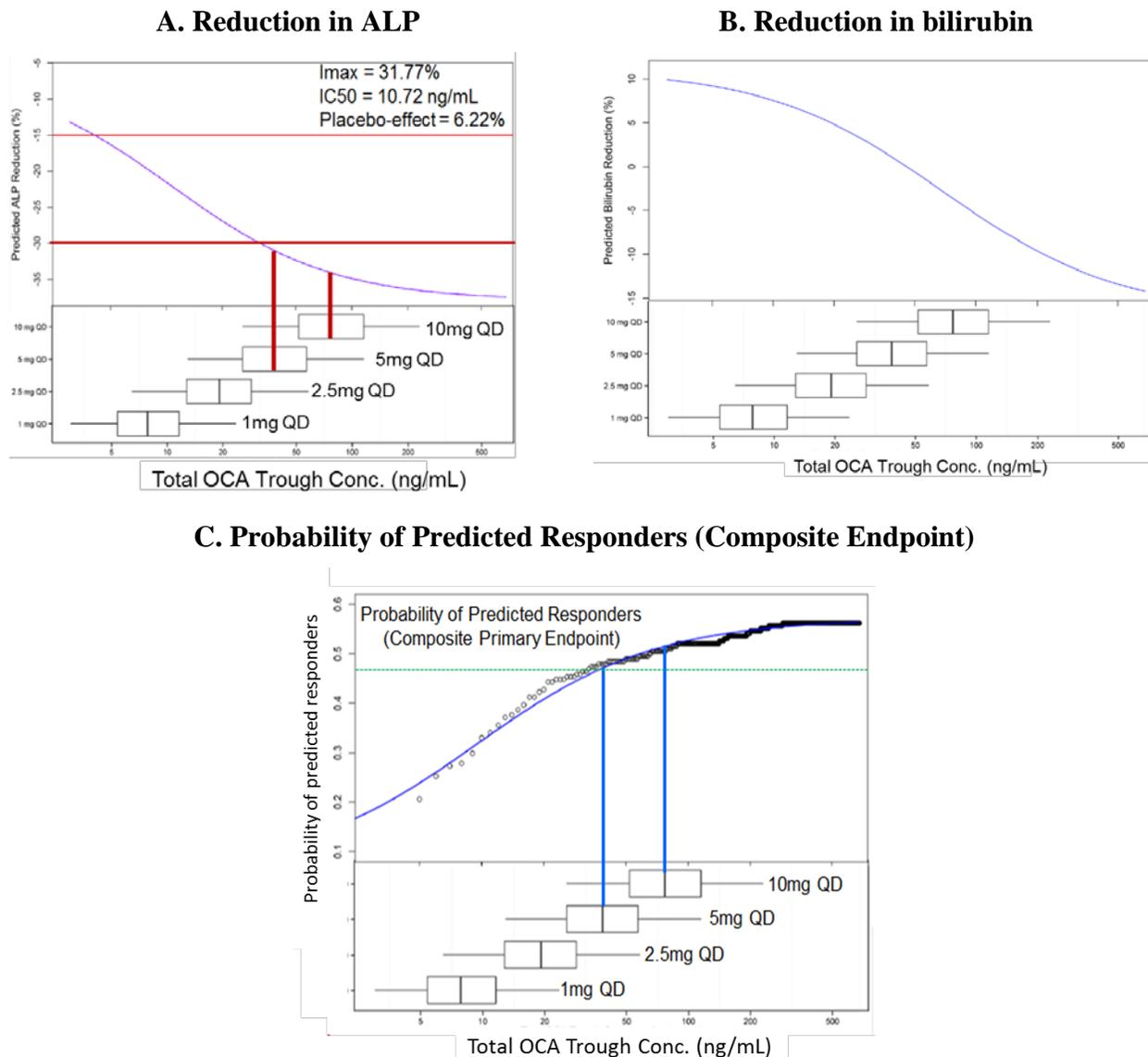
The Sponsor evaluated the exposure-response (E-R) relationship of reduction in ALP and bilirubin (which form the parts of composite efficacy endpoint) as well as the probability of responders in PBC subjects with total OCA concentration as the exposure metric, using data at 6 months for treatment regimens of 5 mg and 10 mg QD OCA in study 747-301 (Figure 6).

For percent change from baseline in ALP, a maximum inhibition model ( $I_{\max}$  model) was fitted.  $I_{\max}$  and  $IC_{50}$  values for the model were 31.8% and 10.7 ng/mL, respectively (Figure 6A). Placebo effect showed a decrease in ALP of 6.2%. These results indicate that a 5 mg and 10 mg dose of OCA, with average concentrations >40 ng/mL, is predicted to cause at least on average a 30% decrease in ALP and there is plateauing of reduction in ALP with higher concentrations. Also doses greater than 10 mg are not predicted to result in additional meaningful benefit in ALP reduction, which was consistent with the Phase 2 data (747-201 and 747-202).

For percent change from baseline in bilirubin, a maximum inhibition model ( $I_{\max}$  model) was fitted.  $I_{\max}$  and  $IC_{50}$  values for the model were 27.9% and 68.9 ng/mL, respectively (Figure 6B). Placebo effect showed an increase in bilirubin by 11.1%.

These exposure-response models for ALP and bilirubin were used to predict the probability of response of achieving composite primary endpoint in Phase 3 study 747-301 (composite primary endpoint → ALP <1.67x ULN, and total bilirubin within the normal range, and ALP decrease ≥15% from baseline). Based on the median value of predicted trough concentrations (calculated from pop-PK models), the average probability of achieving the composite primary endpoint with 5 mg and 10 mg QD dosing of OCA was greater than 40% (Figure 6C).

Figure 6: E-R relationship of reduction in ALP and bilirubin with total OCA concentrations



Boxplots in the above figures represent the predicted trough exposure levels of total OCA based on the final population PK model.

Symbols represent composite endpoint predicted based on prediction of ALP and bilirubin.

Blue lines represent simple  $I_{max}$  or  $E_{max}$  fit.

For predicted ALP reduction:  $IC_{50}=10.72 \text{ ng/mL}$ ,  $I_0$  (placebo effect) = -6.22%,  $I_{max} = 31.77\%$ .

For predicted bilirubin reduction:  $IC_{50}=68.92 \text{ ng/mL}$ ,  $I_0$  (placebo effect) = 11.1%,  $I_{max} = 27.87\%$ .

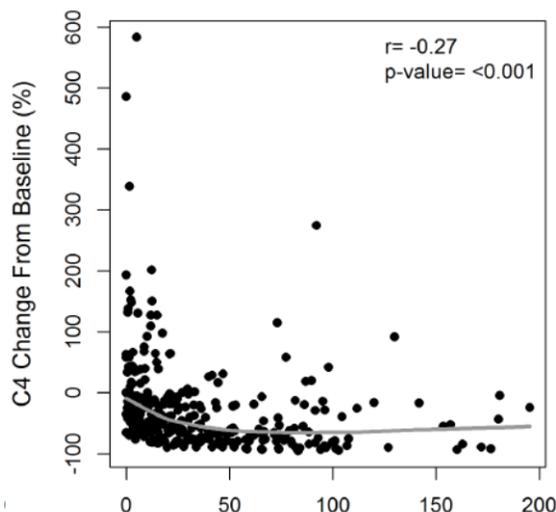
For probability of predicted responders:  $EC_{50}=8.33 \text{ ng/mL}$ ,  $E_{max} = 57.0\%$ . Probability of responder predicted based on ALP and bilirubin predictions at concentrations within 1 and 4 ng/mL was 0 (not shown in figure).

Source Data: Sponsor's Population PK/PD and Simulation Report, Adapted from Figures 10.1, 10.2, 10.4

## Biomarker

The Sponsor evaluated the exposure-response (E-R) relationship of C4, a marker of FXR activation, in healthy subjects with data from Study 747-105 (Figure 7). Average values of C4 over the assessment period were used in the analysis. The analysis showed that C4 levels, which are the marker of bile acid synthesis, decreased with increasing total OCA exposure. Reduction in C4 seems to plateau at total OCA concentrations ~50 ng/ml.

Figure 7: E-R relationship of change in C4 from baseline with total OCA concentrations ( $C_{avg}$ ) in healthy subjects



Source Data: Sponsor's Population PK/PD and Simulation Report, Figure 9.1

### 2.3.4.2 Does this drug prolong the QT or QTc interval?

No significant QTc prolongation effect of obeticholic acid (OCA 100 mg) was detected in the thorough QT 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 (Table 7). 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  $C_{max}$  ratios of total OCA, OCA, glyco-OCA and tauro-OCA relative to the steady-state exposure after a 10-mg dose (therapeutic 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.

Table 7: 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

| Treatment            | Day | Time (hour) | $\Delta\Delta QTcF$ (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.

Source: QT-IRT review in DARRTS

### 2.3.4.3 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

#### Safety Events

Pruritus was the most common adverse event with OCA treatment and there were multiple instances of discontinuations from the study that were attributed to pruritus in the Phase 2/3 studies. During the conduct of clinical studies, the PK samples were collected at longer times, e.g. at the end of 6 months and 12 months in Phase 3 study, while the discontinuations happened at earlier times. Thus E-R for pruritus and discontinuations would be biased if these PK measurements were to be used as exposure metric. Hence, evaluation of E-R relationship for pruritus and discontinuations was not carried out. Instead the evaluation of dose-response was done to infer about these safety signals. Evidence from various Phase 2 studies showed a clear dose-response relationship for pruritus as well as discontinuations due to pruritus with more events at higher doses (Table 8).

Table 8: Dose-response relationship for pruritus and discontinuations due to pruritus in Phase 2 studies

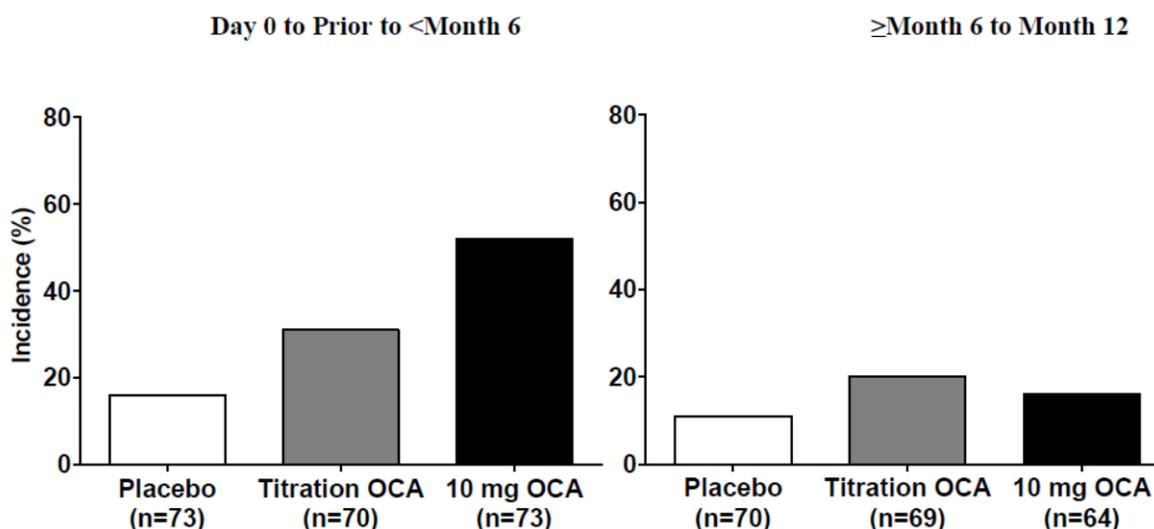
| Population/AE   | Placebo   | OCA 10 mg  | OCA 25 mg  | OCA 50 mg   |
|---|-----------|------------|------------|-------------|
| <b>Alcoholic cirrhotic portal hypertension (Study 204: OCA dosed for ~7 days)</b> |           |            |            |             |
| All grade pruritus  |           | 10% (2/20) | 31% (4/13) |             |
| <b>PBC subjects (Study 202: Phase 2, + UDCA, OCA dosed for 3 months)</b>          |           |            |            |             |
| Related TEAE pruritus   | 45%       | 47%        | 81%        | 80%         |
| Discont. due to pruritus  | 0% (0/38) | 8% (3/38)  | 8% (4/48)  | 24% (10/41) |
| <b>PBC subjects (Study 201: Phase 2, no UDCA, OCA dosed for 3 months)</b>         |           |            |            |             |
| Related TEAE pruritus   | 26%       | 70%        |            | 88%         |
| Discont. due to pruritus  | 0% (0/23) | 15% (3/20) |            | 38% (6/16)  |
| TEAE= Treatment Emergent Adverse Events<br>Discont.=Discontinued                  |           |            |            |             |

Phase 3 study also showed a dose-response relationship for treatment emergent adverse events leading to discontinuations, 3% (2/73) in placebo, 7% (5/70) in OCA titration arm (5 mg QD starting dose with up-titration to 10 mg QD based on efficacy/tolerability) and 11% (8/73) in

OCA 10 mg arm. There was a dose-response relationship for pruritus related discontinuations too, with 0% in placebo, 1% (1/70) in OCA titration arm and 10% (7/73) events in the OCA 10 mg arm. The median time to first onset of severe pruritus in OCA 10 mg arm was 11 days (< 2 weeks) and the range for the time of discontinuations due to pruritus was 6 to 86 days (< 3 months).

The incidence of new or worsened pruritus was lower in the 6-12 month study period compared to the 0-6 month study period across all treatment arms: 16% versus 11% in the placebo arm, 31% versus 20% in the titration arm, and 52% versus 16% in the 10 mg arm respectively (Figure 8). Thus, based on the incidence of new or worsened pruritus, pruritus improved with continued treatment. *However there is an important caveat that treatment emergent AEs of pruritus that occurred during the 0-6 month period and were ongoing during the 6-12 month period were not counted as events during the latter period. Thus there could be a certain bias introduced in incidences for the 6-12 month period. Nevertheless, at the very least certainly the number of incidences did not increase in the second 6 month period compared to the first 6 month period, which indicates that the hazard of pruritus events was constant or diminishing with time.*

Figure 8: Incidence of new onset or worsened treatment-emergent pruritus events during 0-6 months and during 6-12 months in Phase 3 study



Source Data: CSR 747-301, Figure 39

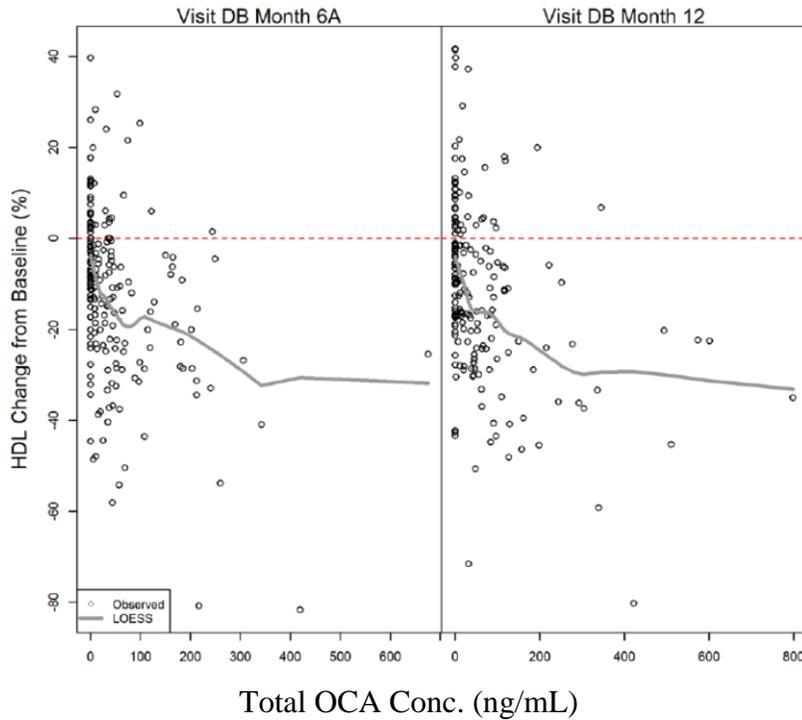
## Biomarkers

A relationship of response of change in HDL and LDL with observed trough concentrations of total OCA was assessed with data from Phase 3 study 747-301. Higher total OCA concentrations were associated with reduction in both LDL and HDL from baseline. The concentration dependent reduction in HDL was observed for the entire concentration range, while the reduction in LDL was observed for concentrations greater than 100 ng/mL (Figure 9).

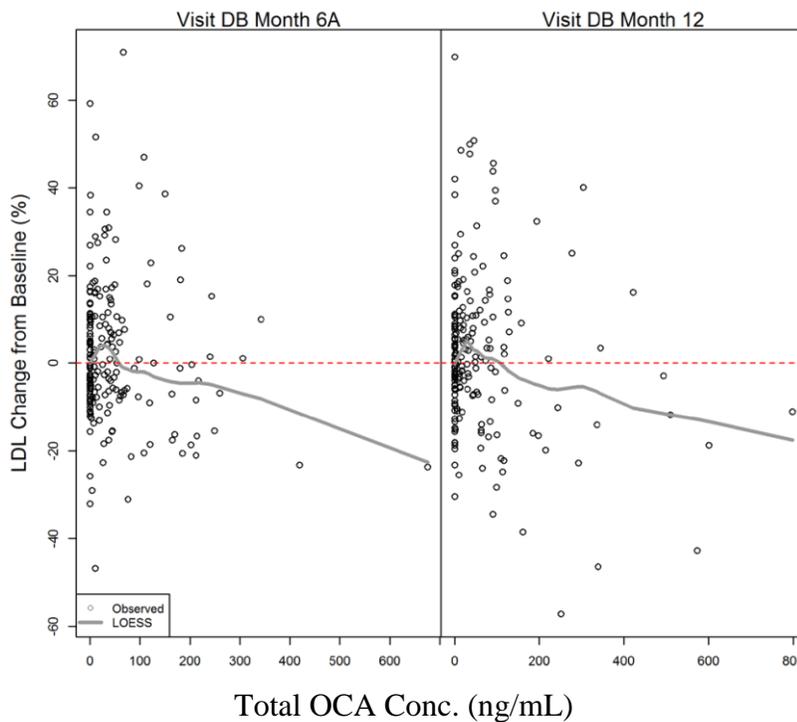
*Reviewer comments: Magnitude of reduction in HDL seems to be higher than the reduction in LDL and the reduction in LDL does not seem to be marked below total OCA concentrations of ~300 ng/mL.*

Figure 9: Relationship of change in HDL and LDL with total OCA concentrations

**A. Change in HDL from baseline**



**B. Change in LDL from baseline**



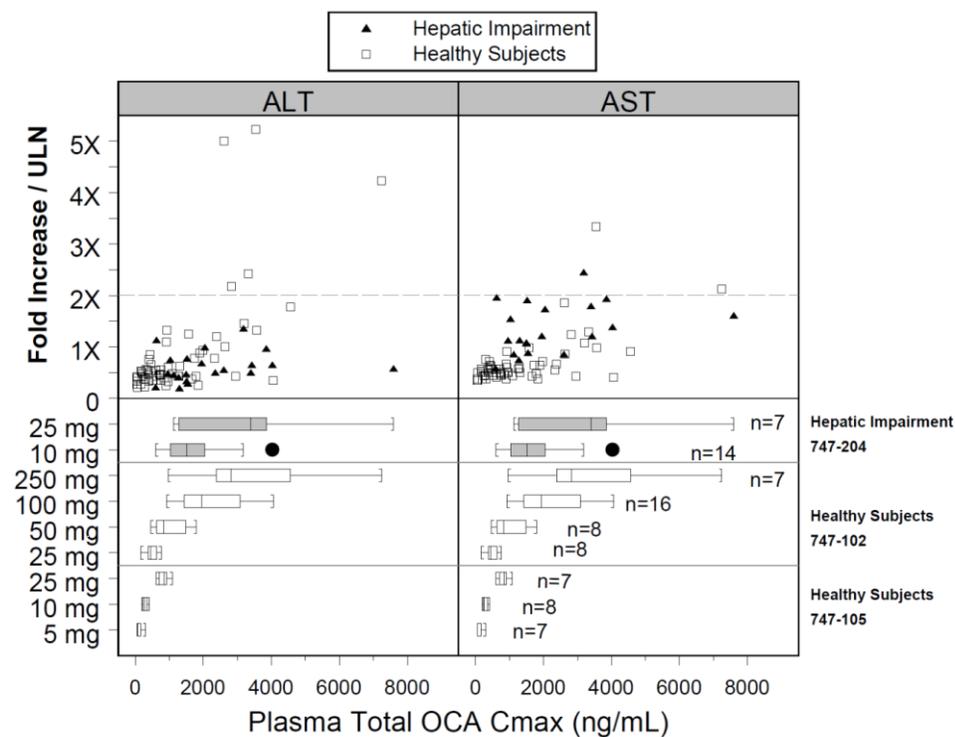
Source Data: Sponsor's Population PK/PD and Simulation Report, Figures 9.4, 9.5

An exploratory E-R analysis of ALT/AST elevation signal with  $C_{max}$  of total OCA was carried

out in healthy subjects (study 747-102) and in subjects with various degrees of hepatic impairment (study 747-204). In study 747-102, ALT/AST elevations had been observed in 4 of 8 subjects receiving 250 mg QD OCA and the signal was considered dose-limiting. While there were incidences of increased ALT and AST levels in healthy subjects occurring at  $C_{max}$  greater than 2000 ng/ml, there was no associated increase in ALT and AST levels in patients with hepatic impairment (cirrhosis) in spite of having systemic OCA levels above 2000 ng/mL in some subjects (Figure 10).

*Reviewer comments: It is worth noting here that OCA was dosed for only 7 days in the subjects with hepatic impairment (portal hypertension) in study 747-204 and emergence of any hepatotoxicity safety signal with continued dosing cannot be ruled out.*

Figure 10: E-R relationship for ALT and AST with QD dosing of OCA at 5, 10, 25, 50, 100 and 250 mg per day



Source Data: Section 2.7.2, Figure 11

#### 2.3.4.4 Is the dose and dosing regimen selected by the Sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The Sponsor's proposed dosing regimen of 5 mg QD starting dose, followed by up-titration to 10 mg QD at 3 months based on response and tolerability for the overall population is acceptable. However, for subjects with moderate and severe hepatic impairment, the Sponsor's proposal of no adjustment in dosing regimen is unacceptable. The reviewers propose a dosing regimen of 5 mg QW (once weekly) as the starting dose, followed by subsequent dose up-titrations at 3 months to 5 mg twice weekly and further to 10 mg twice weekly based on efficacy and

tolerability.

### General Population

Based on the dose dependent increase in incidences of pruritus (refer section 2.3.4.3) and better tolerability profile with time with a lower starting dose, 5 mg QD (once daily) is a more appropriate starting dose over 10 mg QD dosing for the general population. This is consistent with sponsor's proposal and is acceptable to the OCP review team.

The up-titration of dose at 3 months was proposed by the Sponsor even though the Phase 3 study evaluated up-titration of dose (from 5 mg to 10 mg once daily) at 6 months. This dosing strategy was supported by the clinical data that showed that the trend of reduction in ALP saturated at 3 months upon 5 mg once daily dosing and there was minimal further decrease in ALP from 3 months to 6 months at the population level (refer section 1.3.4, Figure 1A, C, D). Further, the median time to onset of severe pruritus was < 2 weeks and all of the discontinuations due to pruritus in the 10 mg QD arm occurred within the first three months (refer section 2.3.4.3). Thus, the duration of 3 months will give fair idea of tolerability of starting dose and identification of subjects with tolerability. The increase in dose from 5 mg to 10 mg QD resulted in additional responders from month 6 to month 12 (Table 9). Also there were some subjects who were responders at month 6, but became non-responders by month 12, possibly due to disease progression, with continued dosing of 5 mg QD. These patients might also benefit from up-titration to 10 mg QD. The physicians should continue to evaluate biochemical response (reduction in ALP) longitudinally and utilize the up-titration rule at  $\geq 3$  months from the treatment initiation. This titration strategy is acceptable to the OCP review team.

Table 9: Categorization of subjects as responders (+) / non-responders (-) based on criteria of achievement of primary endpoint at 6 months and at 12 months for different treatment arms in Phase 3 study

| Treatment         | Primary Endpoint at 6M / 12M |            |           |            |
|-------------------|------------------------------|------------|-----------|------------|
|                   | - / -                        | - / +      | + / -     | + / +      |
| Placebo (N=73)    | 66 (90.4%)                   | 2 (2.7%)   | 0 (0%)    | 5 (6.9%)   |
| 5 mg (N=37)       | 11 (29.7%)                   | 2 (5.4%)   | 7 (18.9%) | 17 (45.9%) |
| 5 mg→10 mg (N=33) | 20 (60.6%)                   | 13 (39.4%) | 0 (0%)    | 0 (0%)     |
| 10 mg (N=73)      | 32 (43.8%)                   | 4 (5.5%)   | 7 (9.6%)  | 30 (41.1%) |

### Special Population: Subjects with moderate/severe hepatic impairment

The dedicated hepatic impairment study with a single dose of 10 mg showed 4- to 17-fold exposures of total OCA in subjects with moderate and severe hepatic impairment as compared to normal healthy volunteers. The Sponsor developed a physiologic PK model to quantify the fold changes in liver concentrations of OCA and its conjugates under hepatic impairment scenario. The details of the physiologic PK model can be found in the PBPK model review in Appendix.

Per the model, the Sponsor contends that even though the plasma exposure is several folds high, the liver exposure is just ~1.7-fold with single dose in case of severe hepatic impairment and thus dose adjustment is not needed in this subpopulation.

Table 10 shows the model predicted steady state  $C_{avg}$  values for plasma and liver concentrations in subjects with normal hepatic function and subjects with mild/moderate/severe hepatic impairment with different dosing regimen. With the dosing regimen of 5 mg QD, the steady state plasma concentrations (plasma  $C_{ss, avg}$ ) in moderate and severe hepatic impairment would be 9- and 17-fold and steady state liver concentrations (liver  $C_{ss, avg}$ ) would be 1.7- and 2.3-fold compared to normal hepatic function.

Table 10: Predicted steady state  $C_{avg}$  values for plasma and liver concentrations of total OCA in subjects with different categories of hepatic impairment under different dosing regimen

| Exposure Parameter   | Hepatic Function | Dose & Dosing Interval  |                      |
|--|------------------|-------------------------|----------------------|
|  |                  | 5 mg QD                 | 5 mg QW              |
| Plasma $C_{ss, avg}$ (ng/mL)<br>Median [5th-95 <sup>th</sup> ] | Normal           | <b>63.3</b> [57-64]     |                      |
|  | Mild HI          | <b>85.9</b> [77-87]     |                      |
|  | Mod. HI          | <b>602</b> [511-608]    | <b>85.9</b> [74-87]  |
|  | Severe HI        | <b>1090</b> [899-1100]  | <b>156</b> [130-157] |
| Liver $C_{ss, avg}$ (ng/mL)<br>Median [5th-95 <sup>th</sup> ]  | Normal           | <b>1260</b> [1140-1270] |                      |
|  | Mild HI          | <b>1410</b> [1300-1430] |                      |
|  | Mod. HI          | <b>2180</b> [1890-2210] | <b>312</b> [274-315] |
|  | Severe HI        | <b>2840</b> [2390-2870] | <b>407</b> [346-410] |

Source Data: Adapted from Sponsor's response to Clinical Pharmacology information request

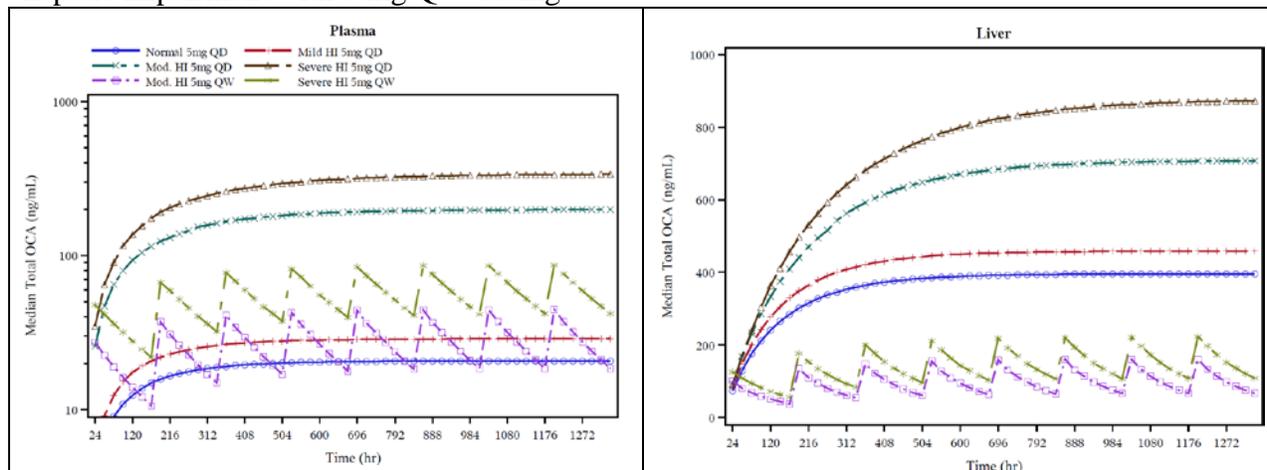
We considered following aspects for this scenario:

- There was a known dose-response relationship for pruritus (refer section 2.3.4.3).
- It is not entirely known whether the pruritus is driven by plasma exposures or liver exposures.
- Even if the pruritus events were to be driven by liver exposures, it is unknown whether there was a shallow or steep E-R relationship of pruritus with liver exposures to consider the 2-fold changes to be problematic or otherwise.

Thus, in the absence of dose adjustment, there is potential for high plasma exposures (and potentially liver exposures) leading to safety/discontinuation issues in case of PBC patients with moderate/severe hepatic impairment (Child Pugh B/C). Since there was no time-dependent worsening of tolerability on same dose/exposure, and 50% of severe pruritus onset occurred within 2 weeks of dose initiation, initial dosing regimen to match exposures to normal (no or mild hepatic impairment) PBC subjects will likely avoid potential safety/discontinuation issues and allow identification of subjects who may qualify up-titration. The dosing regimen of 5 mg QW (once a week) for moderate and severe hepatic impairment in this scenario gives the ability to achieve matching plasma exposures with the no impairment or mild hepatic impairment subjects (Table 10 and Figure 11). Further up-titration to 5 mg BIW and subsequently to 10 mg BIW (twice a week) depending on tolerability and efficacy can then be followed to further

increase the liver concentrations and meet individual efficacy goals.

Figure 11: Predicted plasma and liver concentrations of total OCA in subjects with different categories of hepatic impairment with 5 mg QD dosing and in subjects with moderate/severe hepatic impairment with 5 mg QW dosing



Source Data: Analysis of simulation dataset submitted by the Sponsor in response to Clinical Pharmacology information request

### 2.3.5 Should there be consideration for discontinuation of drug for lack of efficacy and, if yes, when?

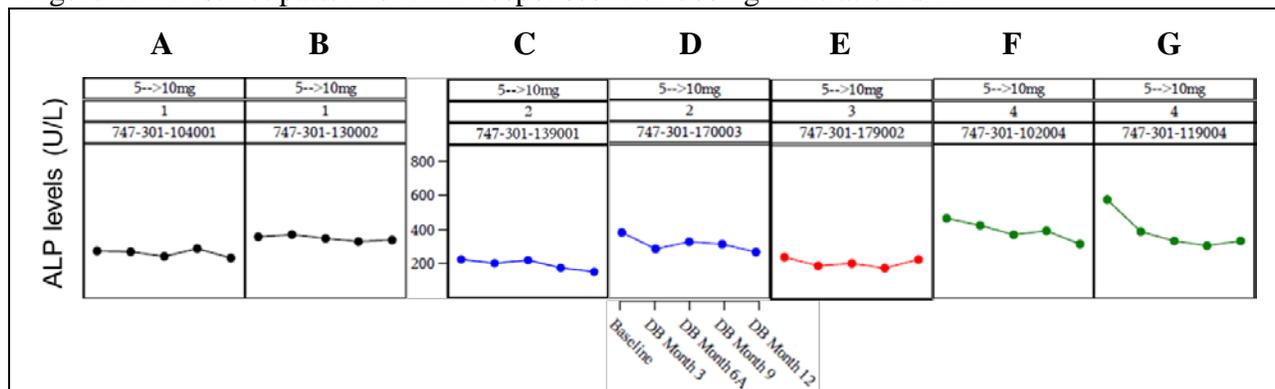
Possibly, the consideration could be given for discontinuation of OCALIVA for the subjects who do not show response of reduction in alkaline phosphatase if the benefit-risk is unfavorable. Currently there is not enough evidence to show how the long term efficacy of transplant-free survival and overall survival would transpire for subjects who do not show response of reduction in alkaline phosphatase with OCALIVA. This uncertainty in long term efficacy should be weighed against the possible unfavorable lipid profile (decrease in HDL) and its relation to possible cardiovascular risk due to continued treatment with OCALIVA. Based on the evidence from Phase 3 study, the reviewers propose that the physicians could consider possible discontinuation of drug if there is a lack of clinically meaningful response (reduction in ALP) after the subject is on a stable dose of OCALIVA for  $\geq 6$  months. There is currently an ongoing Phase 3 extension trial with continued dosing of OCALIVA for subjects with PBC and with composite efficacy endpoint consisting of death, liver transplant, MELD (Model for End-stage Liver Disease) score  $>15$ , hospitalization for variceal bleeding, encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites, and hepatocellular carcinoma. The protocol for this extension trial does not stipulate discontinuation based on lack of efficacy. The evidence from this study could be taken into consideration to possibly weigh the anti-fibrotic beneficial effect of OCALIVA in order to consider continuation of therapy in the absence of ALP response. This issue will be discussed at the GIDAC (Advisory Committee) meeting and the discussion at the meeting will be considered for informing our final recommendations.

The data in the Phase 3 study was analyzed to evaluate the pattern of gain or loss of efficacy in subjects at different time points (esp. 3, 6, 9 and 12 months) during the treatment period. The analysis of individual profiles suggested that there is a huge variability in pattern of response

with either the continued same dosing or up titration to a higher dose in the treatment period. For example, within the titration arm where subjects were dosed at 5 mg QD for the first six months, followed by up-titration to 10 mg QD for the next six months for a part of those subjects depending upon efficacy and tolerability, there were following distinct patterns of responses (Figure 12):

- Some subjects did not have reduction in ALP within first six months and continue to not have any reduction in ALP in the next six months even after dose up titration to 10 mg (panel A-B)
- Some subjects do not have reduction in ALP within the first six months, but show reduction in ALP upon dose up-titration in the next six months (panel C)
- Some subjects do show reduction in ALP within the first 3-6 months on 5 mg dose, but do not show further reduction in ALP upon up titration to 10 mg (panel D)
- Some subjects show reduction in ALP with 5 mg dose, but there is reversal of this reduction in the next six months while they are up-titrated to 10 mg (panel E)
- Some subjects show reduction in ALP in the first six months and achieve 15% reduction in ALP by 6 months and continue to show further reduction in ALP when they are up titrated to 10 mg dose (panel F)
- Some subjects show reduction in ALP in the first six months and achieve 15% reduction in ALP by 6 months but do not show further reduction in ALP upon up titration to 10 mg (panel G).

Figure 12: Distinct pattern of ALP responses with dosing in titration arm



Based on these different patterns, we can categorize subjects as responder/non-responder at 6 months (6M) and at 12 months (12M) for response criteria such as 15% reduction in ALP (Table 11) or achievement of primary endpoint (Table 9).

Table 11: Categorization of subjects as responders (+) / non-responders (-) based on criteria of 15% reduction in ALP from baseline at 6 months and at 12 months for different treatment arms in Phase 3 study

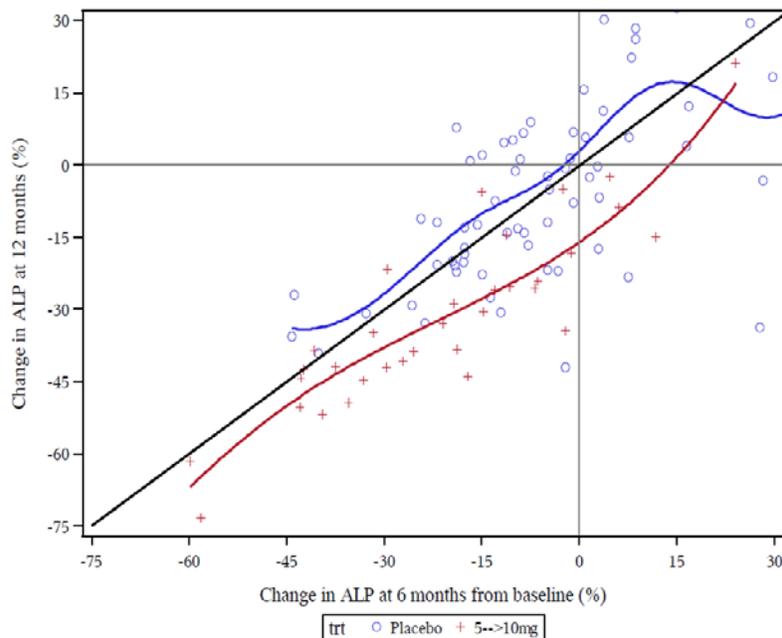
| Treatment         | ALP 15% reduction at 6M / 12M |           |           |            |
|-------------------|-------------------------------|-----------|-----------|------------|
|                   | - / -                         | - / +     | + / -     | + / +      |
| Placebo (N=73)    | 47 (64.4%)                    | 8 (11%)   | 5 (6.9%)  | 13 (17.8%) |
| 5 mg (N=37)       | 3 (8.1%)                      | 4 (10.8%) | 7 (18.9%) | 23 (62.2%) |
| 5 mg→10 mg (N=33) | 5 (15.2%)                     | 8 (24.2%) | 1 (3.0%)  | 19 (57.6%) |
| 10 mg (N=73)      | 13 (17.8%)                    | 2 (2.7%)  | 4 (5.5%)  | 54 (74.0%) |

The

Table 9 shows that a substantial number of subjects that did not achieve responder criteria at 6 months, but with the up-titration (5 mg→10 mg), they were able to achieve responder status by 12 months (13 subjects for primary endpoint criteria). Also some of the subjects did become responders by 6 months, but lost their responder status by 12 months even in spite of continuing on the same dose that they achieved the response on (7 subjects for primary endpoint criteria). Thus, there may be value in affording the up-titration to those individuals who may have achieved responder status at short time, and thus did not get up-titrated, but lost their efficacy due to may be disease progression or lack of sustained response.

Furthermore, on a population level, there was an increase in ALP response as seen by further reduction in ALP levels from 6 months to 12 months in treatment arm where subjects were up-titrated from 5 mg to 10 mg at six months (Figure 13). This is evidenced by the majority of points lying below the line of identity in the plot of reduction in ALP at 12 months vs. reduction in ALP at 6 months. Conversely, majority of points in the placebo arm remain above the line of identity, indicating that the placebo response of reduction in ALP did not sustain from month 6 to month 12. Based on this plot, depending on the threshold of reduction in ALP that can be deemed to be clinical significant and distinguishable from placebo response, an appropriate criteria can be suggested (e.g. minimum 15% reduction in ALP from baseline) to determine whom to discontinue because of lack of efficacy (lack of clinically relevant reduction in ALP) after they are titrated to 10 mg dose and evaluated for ≥6 month duration on this dose.

Figure 13: Change in ALP at 6 and 12 months after treatment



### 2.3.6 Is there evidence for approval of OCA as a monotherapy in adult subjects unable to tolerate UDCA?

Yes, there is evidence of ALP reduction when considering pooled data from phase 2 and 3 trials that supports approval of OCA as a monotherapy in adult subjects unable to tolerate UDCA.

Phase 3 study had only ~7.5% subjects treated with OCA as a monotherapy. So the evidence for monotherapy was evaluated based on response at 3 months in a pooled dataset consisting of two Phase 2 studies (747-201, 747-202) and the Phase 3 study (747-301). The pooled data showed good responder rate (38%) for monotherapy at 3 months and this responder rate was comparable to that achieved with combination therapy with UDCA (Table 12). Also the data showed marked change in ALP biomarker with monotherapy and this change was statistically highly significant ( $p < 0.0001$ ) (Figure 14). The baseline values of ALP were higher in monotherapy as compared to combination therapy, while the ALP values after treatment were similar at 3 months. Based on this evidence, use of OCA as a monotherapy for subjects who are unable to tolerate UDCA seems reasonable.

Table 12: Efficacy results for OCA monotherapy and combination therapy with UDCA based on pooled data from study 747-201, study 747-202 and Phase 3 study 747-301

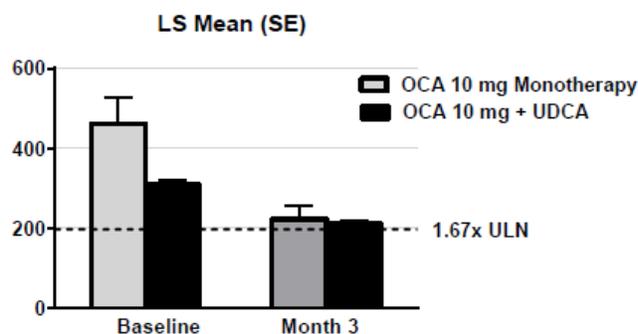
| Month 3                     | Composite Endpoint: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Baseline |                          |
|-----------------------------|---|--------------------------|
|                             | Responder   | CMH p-value <sup>a</sup> |
| <b>Monotherapy</b>          |   |                          |
| Placebo (N = 28)            | 1 (4)   | NA                       |
| OCA 10 mg (N = 26)          | 10 (38)   | <b>0.0010</b>            |
| <b>Combination (+ UDCA)</b> |   |                          |
| Placebo (N = 106)           | 5 (5)   | NA                       |
| OCA 10 mg (N = 105)         | 43 (41)   | <b>&lt;0.0001</b>        |

Baseline is defined as the mean of all available evaluations prior to double-blind treatment. Subjects with missing values are considered non-responders.

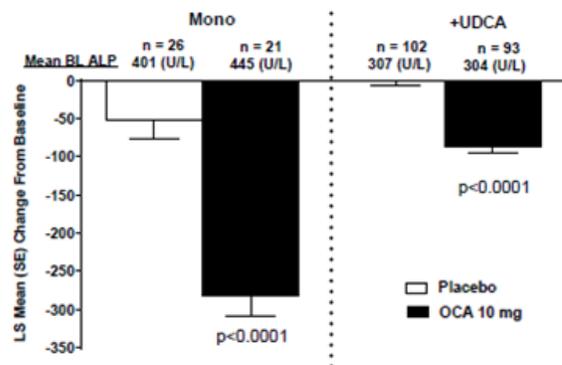
Source Data: Section 2.5, Table 13

Figure 14: ALP levels (panel A) and change in ALP from baseline (panel B) with OCA monotherapy and combination therapy with UDCA, based on pooled data from study 747-201, study 747-202 and Phase 3 study 747-301

**A. LS Mean ALP (U/L) Values at Baseline and Month 3**



**B. LS Mean Change in ALP (U/L) From Baseline to Month 3**



Source Data: Section 2.5, Figures 12, 13

**2.3.7 PK characteristics of the drug and its major metabolites**

**Note:** In this NDA, the Sponsor may lump the systemic exposure to OCA itself with those to the conjugates and refers to the sum as the systemic exposure to total OCA (or total OCA-equivalents). This is because a) the potency (EC<sub>50</sub>) of glyco-OCA (24 nM) and tauro-OCA (84 nM) are similar to that of OCA (45 nM) in activating FXR (refer to Pharmacology/toxicology review); and b) the systemic exposure (AUC<sub>tau</sub>) to Glyco-OCA and tauro-OCA are higher than OCA with metabolite to parent ratios of 13.8 and 12.3 following 10 mg QD dosing, respectively.

For the OCA conjugates, the systemic concentration is adjusted for the molecular weight

difference to obtain the OCA-equivalent concentrations, i.e.,

Glyco-OCA (adjusted) = unadjusted glyco-OCA concentration (ng/mL) × 0.8805

Tauro-OCA (adjusted) = unadjusted tauro-OCA concentration (ng/mL) × 0.7969

### **2.3.7.1 What are the single dose and multiple dose PK parameters?**

#### **2.3.7.1.1 Healthy subjects**

##### **2.3.7.1.1.1 Single Dose - Plasma**

The single dose PK of OCA in healthy subjects was characterized in three Phase 1 studies: 747-101, 747-102 (Day 1) and 747-105. The sensitivity (LLOQ) of analytical method used in 747-101 was 100 ng/mL for all three analytes (OCA, glyco-, and tauro-OCA), 200 times higher than the most sensitive method used for 747-105 (LLOQ = 0.5 ng/mL for all three analytes). The PK results of 50, 100, 250, 500 mg of OCA from Study 747-101 were not reviewed. The sensitivities of analytical method used in 747-102 were 1, 5, and 1 ng/mL for OCA, glyco- and tauro-OCA, respectively. Since Study 747-102 studied higher doses, the assay sensitivity difference comparing to Study 747-105 is not an issue.

Study 747-105 is a single-dose (Day 1; 5, 10 or 25 mg OCA) and multiple-dose (Days 4-17; 5, 10 or 25 mg OCA once daily) PK study under fasting condition, i.e. subjects were fasted for 10 hours before the dose followed by PK sampling. The mean concentration-time profiles (linear and semi-log) of OCA, glyco-OCA, and tauro-OCA following single oral dose administration are presented in Figure 15, and the PK parameters are summarized in Table 13. Note that the single dose PK sampling time in this study was up to 60 hours, which was not long enough to estimate terminal T<sub>1/2</sub>. Thus, the only AUC parameter presented in the table is AUC<sub>0-24h</sub>. The Sponsor reported Metabolite-to-Parent Ratio of C<sub>max</sub> (MRC<sub>max</sub>), however, more weight should be given to Metabolite-to-Parent Ratio of AUC (MRAUC) provided in the table below.

Table 13: Mean (CV%) of single dose plasma PK parameters by dose level (Study 747-105)

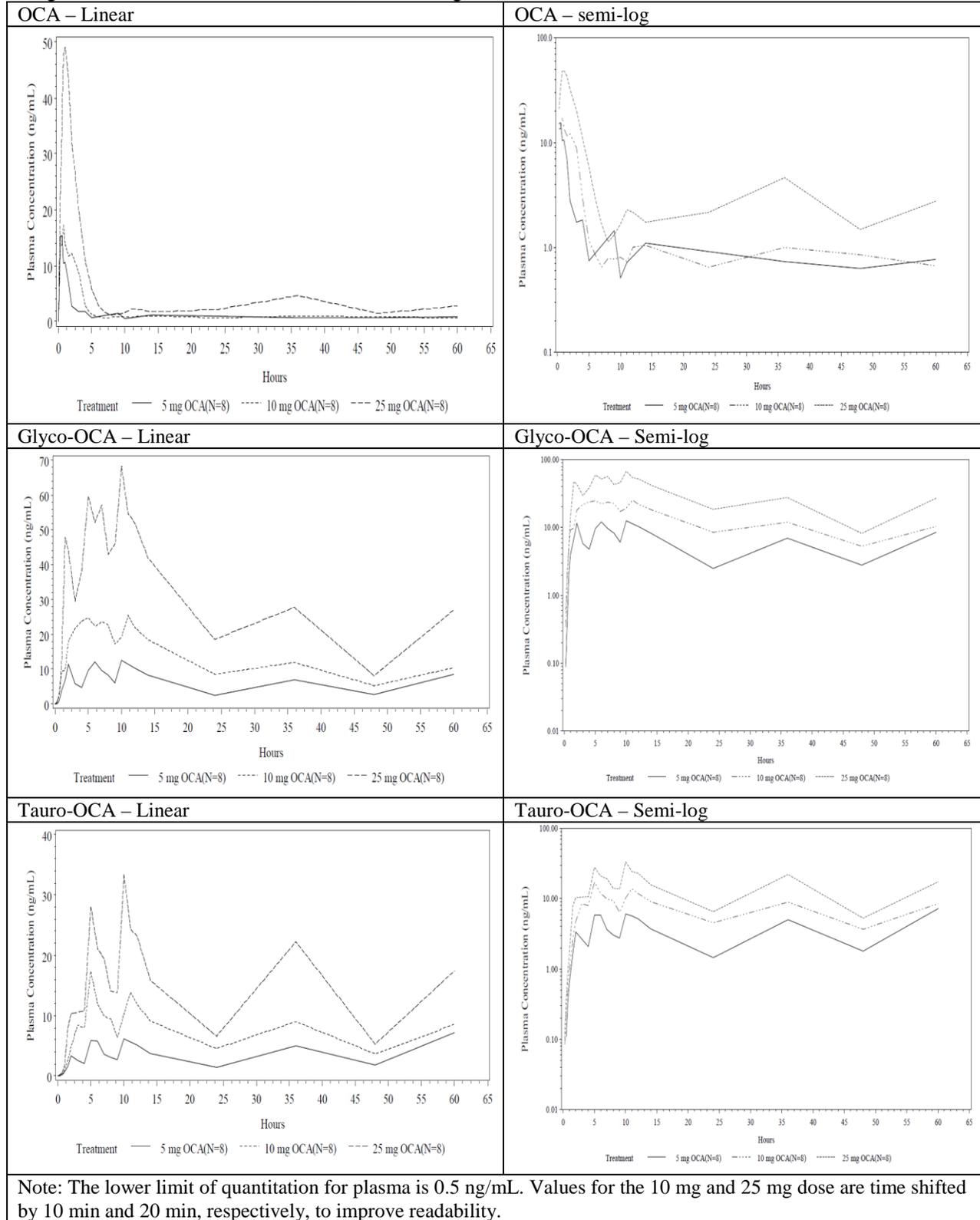
| Analyte<br>PK Parameter           | n | 5-mg OCA<br>(N = 8) | n | 10-mg OCA<br>(N = 8) | n | 25-mg OCA<br>(N = 8) |
|-----------------------------------|---|---------------------|---|----------------------|---|----------------------|
| <b>OCA</b>                        |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 8 | 18.6 (51.1)         | 8 | 29.7 (69.9)          | 8 | 78.6 (56.7)          |
| t <sub>max</sub> (h) <sup>a</sup> | 8 | 0.5 (0.3-1.5)       | 8 | 1.8 (0.3-3.0)        | 8 | 0.9 (0.3-4.0)        |
| AUC <sub>t</sub> (ng·h/mL)        | 8 | 36.5 (70.7)         | 8 | 68.5 (54.7)          | 8 | 263 (33.7)           |
| AUC <sub>0-24</sub> (ng·h/mL)     | 6 | 33.2 (45.5)         | 7 | 61.1 (39.5)          | 8 | 162 (34.5)           |
| <b>Glyco-OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 8 | 19.3 (48.2)         | 8 | 37.5 (86.9)          | 8 | 81.9 (55.9)          |
| t <sub>max</sub> (h) <sup>a</sup> | 8 | 5.5 (1.5-60)        | 8 | 4.5 (2.0-10)         | 8 | 10 (1.5-36)          |
| AUC <sub>t</sub> (ng·h/mL)        | 8 | 371 (58.4)          | 8 | 734 (81.0)           | 8 | 1641 (53.6)          |
| AUC <sub>0-24</sub> (ng·h/mL)     | 8 | 173 (59.2)          | 8 | 412 (88.8)           | 8 | 935 (69.4)           |
| MRC <sub>max</sub>                | 8 | 1.1 (52.4)          | 8 | 1.3 (90.3)           | 8 | 0.9 (13.5)           |
| MRAUC <sub>0-24</sub>             | 6 | 5.3 (35.9)          | 7 | 6.4 (59.9)           | 8 | 4.7 (33.9)           |
| <b>Tauro-OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 8 | 10.8 (82.5)         | 8 | 19.8 (54.5)          | 8 | 42.5 (50.5)          |
| t <sub>max</sub> (h) <sup>a</sup> | 8 | 5 (2-60)            | 8 | 8 (3-36)             | 8 | 10 (5-36)            |
| AUC <sub>t</sub> (ng·h/mL)        | 8 | 232 (78.3)          | 8 | 428 (44.8)           | 8 | 827 (33.1)           |
| AUC <sub>0-24</sub> (ng·h/mL)     | 8 | 80.1 (82.0)         | 8 | 197 (53.5)           | 8 | 352 (25.1)           |
| MRC <sub>max</sub>                | 8 | 0.5 (65.1)          | 8 | 0.7 (58.9)           | 8 | 0.6 (77.8)           |
| MRAUC <sub>0-24</sub>             | 6 | 2.2 (40.0)          | 7 | 2.9 (52.4)           | 8 | 1.9 (40.7)           |
| <b>Total OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng-eq/mL)       | 8 | 28.8 (47.9)         | 8 | 53.7 (68.7)          | 8 | 126 (42.8)           |
| t <sub>max</sub> (h) <sup>a</sup> | 8 | 4.5 (0.3-60)        | 8 | 4.5 (0.3-11)         | 8 | 1.8 (1.5-36)         |
| AUC <sub>t</sub> (ng-eq·h/mL)     | 8 | 534 (64.7)          | 8 | 1040 (66.6)          | 8 | 2357 (37.4)          |
| AUC <sub>0-24</sub> (ng-eq·h/mL)  | 8 | 237 (63.5)          | 8 | 568 (72.1)           | 8 | 1260 (51.2)          |

AUC = area under the plasma concentration-time curve; AUC<sub>t</sub> = AUC from time 0 to the last sampling time with measurable analyte concentration; AUC<sub>0-24</sub> = AUC from time 0 to 24 hours; C<sub>max</sub> = maximum concentration (observed); CV% = percent coefficient of variation; glyco-OCA = glycine 6α-ethyl-chenodeoxycholic acid; MRAUC<sub>0-24</sub> = ratio of conjugate to OCA for AUC<sub>0-24</sub>; MRC<sub>max</sub> = ratio of conjugate to OCA for C<sub>max</sub>; ng-eq = nanogram equivalents; OCA = obeticholic acid; tauro-OCA = taurine 6α-ethyl-chenodeoxycholic acid; t<sub>max</sub> = time to C<sub>max</sub>

<sup>a</sup> Median and range

Source: CSR 747-105, Section 14, [Table 14.2.3.1](#), [Table 14.2.3.3](#), [Table 14.2.3.5](#), and [Table 14.2.3.7](#)

Figure 15: Mean concentration-time profiles for OCA and its metabolites in plasma following single oral administration of 5, 10, and 25 mg



The Day 1 single dose PK of OCA, glyco-, and tauro-OCA following single dose of 25, 50, 100,

and 250 mg are summarized in Table 14. Note the Sponsor only collected PK samples in the first 24 hours after first dose. Thus, the concentration-time profiles are not presented in this review.

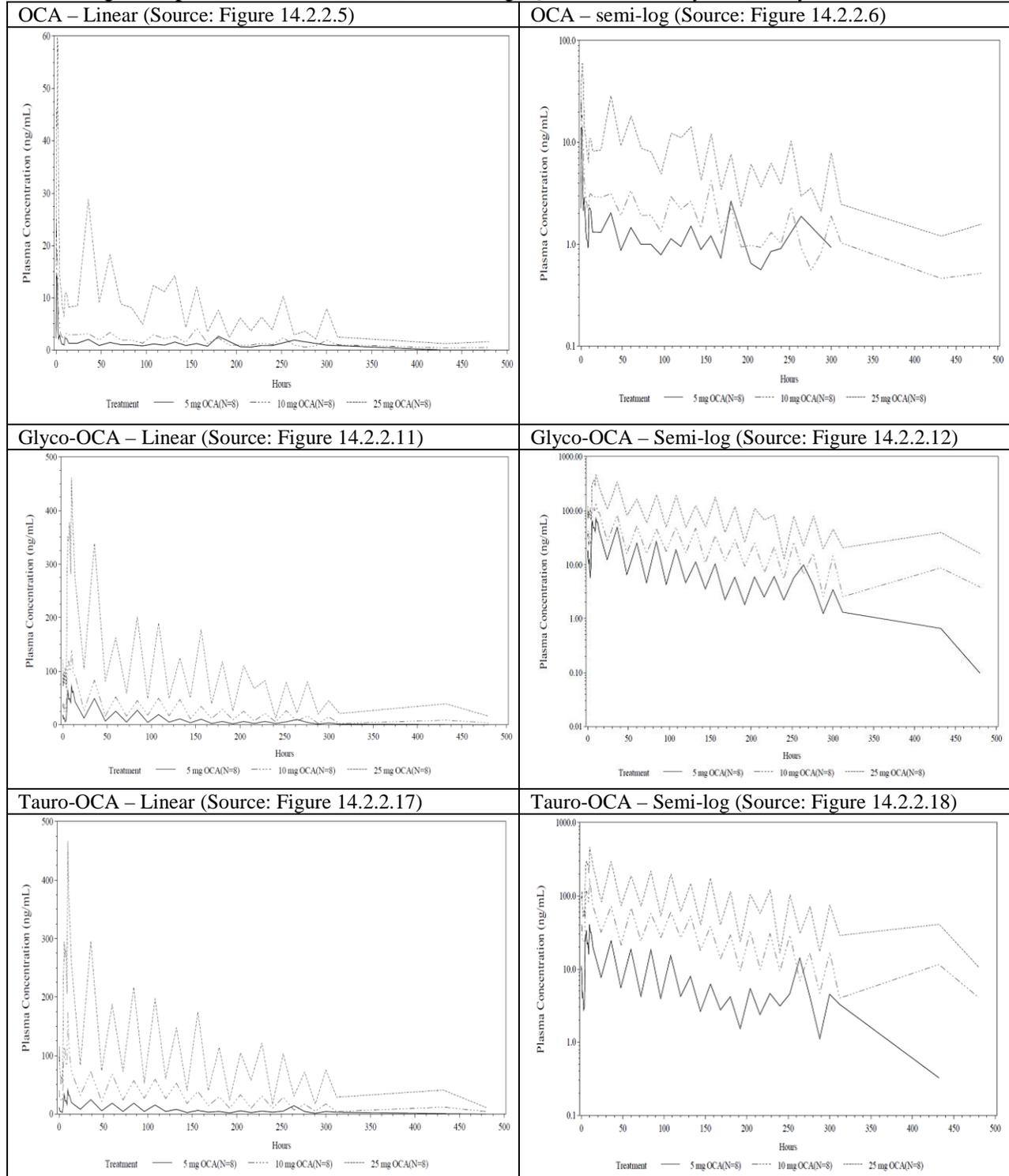
Table 14: Mean (CV%) of plasma PK parameters of OCA and its metabolites after single oral dose of 25, 50, 100, and 250 mg in healthy subjects on Day 1 (Study 747-102)

| Dose (mg)  | 25                 | 50                 | 100                | 250                |
|--|--------------------|--------------------|--------------------|--------------------|
| <b>OCA</b>   |                    |                    |                    |                    |
| N  | 8                  | 8                  | 16                 | 8                  |
| Cmax (ng/mL)   | 71.9 (61)          | 129.2 (52)         | 274.4 (40)         | 541.9(41)          |
| AUC(0-24)<br>(ng·h/mL)   | 130.2 (53)         | 303.1 (53)         | 622.6 (29)         | 1750.8 (40)        |
| Median Tmax (h)<br>(min, max)  | 1.5<br>(0.3, 3.0)  | 1.8<br>(0.5, 3.1)  | 1.5<br>(1.0, 3.0)  | 2.0<br>(1.0, 5.0)  |
| <b>Glyco-OCA</b>   |                    |                    |                    |                    |
| N  | 8                  | 8                  | 16                 | 7                  |
| Cmax (ng/mL)*  | 60.0 (46)          | 153.3 (41)         | 361.9 (33)         | 936.3 (70)         |
| AUC(0-24)<br>(ng·h/mL)*  | 685.5 (44)         | 1702.3 (45)        | 3816.9 (32)        | 7855.5 (43)        |
| Median Tmax (h)<br>(min, max)  | 6.0<br>(5.0, 11.0) | 6.0<br>(5.0, 20.0) | 5.5<br>(5.0, 11.0) | 5.5<br>(5.0, 11.0) |
| M:P ratio AUC(0-24)  | 5.65 (48)          | 6.13 (28)          | 6.32 (29)          | 4.55 (31)          |
| <b>Tauro-OCA</b>   |                    |                    |                    |                    |
| N  | 8                  | 8                  | 16                 | 8                  |
| Cmax (ng/mL)*  | 15.8 (30)          | 28.0 (33)          | 86.5 (92)          | 150.4 (65)         |
| AUC(0-24)<br>(ng·h/mL)*  | 168.8 (35)         | 319.9 (40)         | 786.6 (57)         | 1537.0 (80)        |
| Median Tmax (h)<br>(min, max)  | 5.5<br>(5.0, 10.0) | 6.0<br>(5.0, 6.0)  | 6.0<br>(5.0, 24.0) | 6.0<br>(5.0, 11.0) |
| M:P ratio AUC(0-24)  | 1.58 (55)          | 1.18 (44)          | 1.26 (52)          | 0.86 (54)          |
| M:P = metabolite-to-parent   |                    |                    |                    |                    |
| * The PK results for glyco-OCA and tauro-OCA are presented in nanogram equivalents of OCA (ng-eq OCA). |                    |                    |                    |                    |

### 2.3.7.1.1.2 Multiple doses - plasma

The multiple-dose PK of OCA in healthy subjects was characterized in two Phase 1 studies: 747-102 and 747-105. The mean concentration-time profiles of OCA, glyco-OCA, and tauro-OCA following 5, 10, and 25 mg QD OCA are presented in Figure 16.

Figure 16: Mean concentration-time profiles for OCA, glyco-OCA, and tauro-OCA in Plasma following multiple oral doses of 5, 10, and 25 mg QD OCA, on Day 17 (Study 747-105)



The multiple-dose PK of OCA, glyco-, and tauro-OCA following 5, 10, and 25 mg QD for 14 days are summarized in Table 15. Note that in this study, the multiple doses started 4 days after

the subjects received a single dose of OCA.

In the multiple-dose period, the sampling time after the last dose was up to 528 hours post-dose. However, all the subjects had plasma concentrations of OCA and its conjugates below LLOQ at Hour 480 and beyond. Due to extensive enterohepatic recirculation, the terminal T1/2, and CL/F of glyco- and tauro-OCA were not estimable.

Table 15: Mean (CV%) of multiple doses plasma PK parameters by dose level (Study 747-105)

| Analyte<br>PK Parameter           | n | 5-mg OCA<br>(N = 8) | n | 10-mg OCA<br>(N = 8) | n | 25-mg OCA<br>(N = 8) |
|-----------------------------------|---|---------------------|---|----------------------|---|----------------------|
| <b>OCA</b>                        |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 7 | 21.9 (47.2)         | 8 | 38.0 (47.5)          | 7 | 104 (36.3)           |
| t <sub>max</sub> (h) <sup>a</sup> | 7 | 1.0 (0.3-4.0)       | 8 | 1.5 (0.3-3.0)        | 7 | 1.5 (0.5-3.0)        |
| AUC <sub>0-24</sub> (ng·h/mL)     | 7 | 58.9 (39.1)         | 8 | 111 (15.4)           | 7 | 340 (35.5)           |
| Rac AUC <sub>0-24</sub>           | 5 | 1.9 (15.4)          | 7 | 2.1 (33.9)           | 7 | 2.0 (13.0)           |
| Rac C <sub>max</sub>              | 7 | 1.3 (51.1)          | 8 | 1.6 (59.7)           | 7 | 1.5 (36.1)           |
| <b>Glyco-OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 7 | 79.8 (82.5)         | 8 | 157 (32.5)           | 7 | 506 (29.0)           |
| t <sub>max</sub> (h) <sup>a</sup> | 7 | 10 (6-12)           | 8 | 10 (6-11)            | 7 | 10 (5-11)            |
| AUC <sub>0-24</sub> (ng·h/mL)     | 7 | 839 (86.6)          | 8 | 1755 (36.7)          | 7 | 5579 (39.0)          |
| Rac AUC <sub>0-24</sub>           | 7 | 4.5 (25.7)          | 8 | 6.4 (67.7)           | 7 | 6.8 (35.4)           |
| Rac C <sub>max</sub>              | 7 | 3.6 (34.1)          | 8 | 6.4 (68.8)           | 7 | 6.8 (36.1)           |
| MRAUC <sub>0-24</sub>             | 7 | 11.1 (43.3)         | 8 | 13.8 (27.3)          | 7 | 14.5 (16.7)          |
| MRC <sub>max</sub>                | 7 | 3.0 (34.6)          | 8 | 4.1 (41.1)           | 7 | 4.5 (29.8)           |
| <b>Tauro-OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng/mL)          | 7 | 45.1 (108.6)        | 8 | 182 (38.3)           | 7 | 484 (36.8)           |
| t <sub>max</sub> (h) <sup>a</sup> | 7 | 10 (6-12)           | 8 | 10 (6-11)            | 7 | 10 (8-11)            |
| AUC <sub>0-24</sub> (ng·h/mL)     | 7 | 415 (111.7)         | 8 | 1651 (32.4)          | 7 | 4910 (33.6)          |
| Rac AUC <sub>0-24</sub>           | 7 | 4.3 (40.2)          | 8 | 9.4 (28.3)           | 7 | 13.6 (30.6)          |
| Rac C <sub>max</sub>              | 7 | 4.3 (51.5)          | 8 | 10.1 (28.3)          | 7 | 11.4 (25.5)          |
| MRAUC <sub>0-24</sub>             | 7 | 4.6 (71.9)          | 8 | 12.3 (38.2)          | 7 | 13.1 (52.5)          |
| MRC <sub>max</sub>                | 7 | 1.4 (58.7)          | 8 | 4.7 (52.1)           | 7 | 4.4 (61.7)           |
| <b>Total OCA</b>                  |   |                     |   |                      |   |                      |
| C <sub>max</sub> (ng·eq/mL)       | 7 | 108 (90.3)          | 8 | 285 (27.7)           | 7 | 836 (18.7)           |
| t <sub>max</sub> (h) <sup>a</sup> | 7 | 10 (6-12)           | 8 | 10 (6-11)            | 7 | 10 (5-11)            |
| AUC <sub>0-24</sub> (ng·eq·h/mL)  | 7 | 1128 (91.4)         | 8 | 2972 (28.6)          | 7 | 9165 (26.3)          |
| Rac AUC <sub>0-24</sub>           | 7 | 4.2 (23.6)          | 8 | 6.6 (42.5)           | 7 | 7.8 (32.7)           |
| Rac C <sub>max</sub>              | 7 | 3.4 (50.3)          | 8 | 6.9 (45.0)           | 7 | 7.0 (34.1)           |

AUC<sub>0-24</sub> = area under the plasma concentration-time curve from time 0 to 24 hours; C<sub>max</sub> = maximum concentration (observed); C<sub>min</sub> = minimum concentration over a 24-hour dosing interval; CV% = percent coefficient of variation; glyco-OCA = glycine 6 $\alpha$ -ethyl-chenodeoxycholic acid; MRAUC<sub>0-24</sub> = ratio of conjugate to OCA for AUC<sub>0-24</sub>; MRC<sub>max</sub> = ratio of conjugate to OCA for C<sub>max</sub>; ng·eq = nanogram-equivalents; OCA = obeticholic acid; Rac = accumulation ratio; tauro-OCA = taurine 6 $\alpha$ -ethyl-chenodeoxycholic acid; t<sub>max</sub> = time to C<sub>max</sub>

<sup>a</sup> Median and range

Source: CSR 747-105, Section 14, [Table 14.2.3.2](#), [Table 14.2.3.4](#), [Table 14.2.3.6](#), and [Table 14.2.3.8](#)

The multiple-dose PK of OCA, glyco-, and tauro-OCA following 25, 50, 100, and 250 mg QD for 12 days are summarized in Table 16. The sampling time after the last dose was up to 120 hours post-dose. It is not long enough to estimate terminal T1/2, AUCinf, and CL/F of glyco-OCA and tauro-OCA.

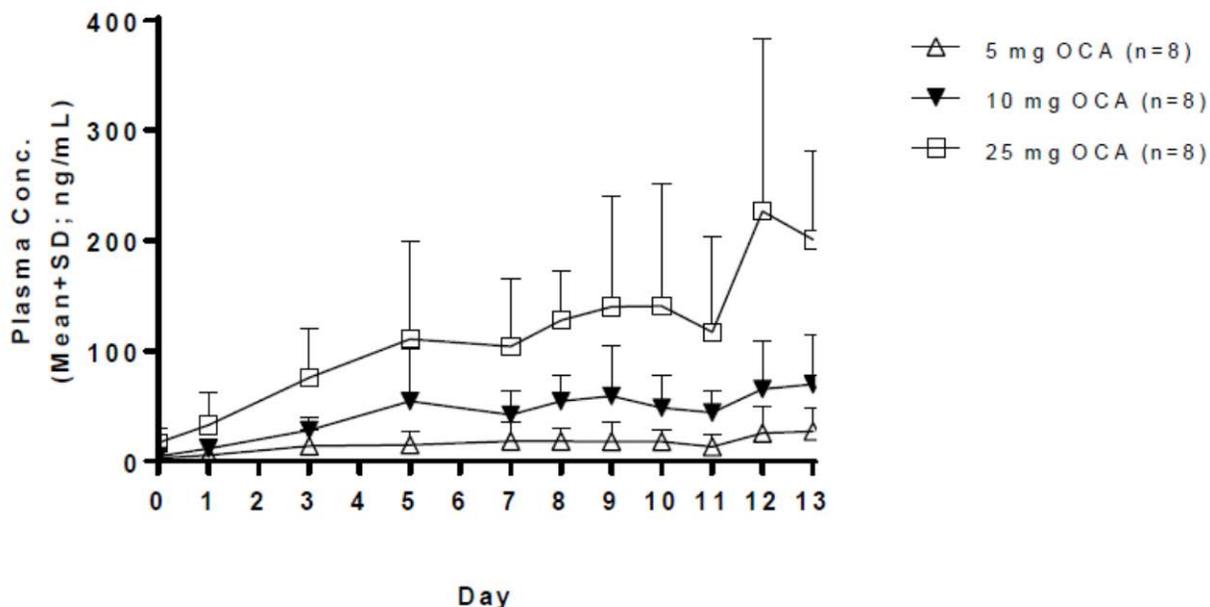
Table 16: Mean (CV%) of plasma PK parameters of OCA and its metabolites after 25, 50, 100, and 250 mg QD in healthy subjects (Study 747-102)

| Dose (mg)   | 25                 | 50                 | 100                | 250                  |
|---|--------------------|--------------------|--------------------|----------------------|
| <b>OCA</b>  |                    |                    |                    |                      |
| N   | 8                  | 8                  | 16                 | 7                    |
| Cmax (ng/mL)  | 68.9 (35)          | 135.3 (40)         | 294.0 (48)         | 575.9 (78)           |
| AUC(0-24) (ng·h/mL)   | 277.4 (52)         | 612.1 (56)         | 1322.4 (48)        | 2783.4 (115)         |
| Median Tmax (h)<br>(min, max)   | 1.3<br>(0.5, 3.0)  | 1.8<br>(0.5, 4.0)  | 1.5<br>(1.0, 30)   | 3.0<br>(1.5, 16.0)   |
| Rac Cmax  | 1.24 (58)          | 1.40 (63)          | 1.12 (45)          | 1.10 (65)            |
| Rac AUC(0-24)   | 2.17 (29)          | 2.11 (32)          | 2.09 (30)          | 1.33 (64)            |
| <b>Glyco-OCA</b>  |                    |                    |                    |                      |
| N   | 8                  | 8                  | 16                 | 7                    |
| Cmax (ng/mL)*   | 273.7 (40)         | 521.9 (45)         | 1482.6 (40)        | 2521.3 (63)          |
| AUC(0-24) (ng·h/mL)*  | 3231.6 (36)        | 7310.5 (66)        | 16004.6 (40)       | 28082.4 (49)         |
| Median Tmax (h)<br>(min, max)   | 8.0<br>(5.0, 12.0) | 6.0<br>(5.0, 20.0) | 6.0<br>(5.0, 11.0) | 11.0<br>(6.0, 12.0)  |
| Rac Cmax  | 5.00 (37)          | 3.51 (33)          | 4.26 (46)          | 2.64 (40)            |
| Rac AUC(0-24)   | 5.01 (21)          | 4.22 (34)          | 4.23 (31)          | 3.29 (17)            |
| M:P ratio AUC(0-24)   | 12.7 (41)          | 12.02 (27)         | 13.24 (42)         | 14.39 (46)           |
| <b>Tauro-OCA</b>  |                    |                    |                    |                      |
| N   | 8                  | 8                  | 16                 | 7                    |
| Cmax (ng/mL)*   | 193.4 (55)         | 467.1 (60)         | 724.8 (75)         | 887.2 (52)           |
| AUC(0-24) (ng·h/mL)*  | 1927.1 (56)        | 4634.1 (74)        | 8160.3 (75)        | 10070.8 (51)         |
| Median Tmax (h)<br>(min, max)   | 8.0<br>(5.0, 11.0) | 6.0<br>(5.0, 12.0) | 6.0<br>(1.5, 12.0) | 11.0<br>(11.0, 12.0) |
| Rac Cmax  | 12.77 (59)         | 17.88 (53)         | 10.38 (62)         | 6.00 (33)            |
| Rac AUC(0-24)   | 11.24 (48)         | 13.83 (44)         | 11.24 (58)         | 7.06 (40)            |
| M:P ratio AUC(0-24)   | 7.75 (48)          | 7.16 (23)          | 6.78 (71)          | 5.50 (75)            |
| Rac = accumulation ratio; M:P = metabolite-to-parent  |                    |                    |                    |                      |
| *The PK results for glyco-OCA and tauro-OCA are presented in nanogram equivalents of OCA (ng-eq OCA). |                    |                    |                    |                      |

### Time to steady-state

Based upon the visual inspection of trough concentration-time profile from Day 4 to Day 17 (Figure 17) in Study 747-105, OCA reaches SS by Day 9 (5-day of QD dosing), while total OCA appears to be close to SS by Day 13 (9 days of QD dosing) for the lower doses.

Figure 17: Mean (+SD) of trough total OCA plasma concentration versus time profile following 5, 10, and 25 mg QD OCA for two weeks.



Note: Day 0 in the plot is Day 4 in the study

#### 2.3.7.1.1.3 Urine PK

Urine PK parameters could not be calculated following single dose of 5, 10, and 25 mg as most concentrations were below LLOQ (BLQ).

In the 5 mg QD group, urine concentrations of OCA, glyco-, and tauro-OCA were BLQ. In the 10 mg QD group, only one out of 8 subjects had reportable AE(6-12hr) of 645.2 ng for tauro-OCA. The %fe(6-12hr) was 0.0065. In the 25 mg QD group, less than 50% subjects have reportable urine PK parameters. The mean (CV%) of %fe(0-24hr) of glyco-OCA was 0.0039 (44%) (N=3). The %fe(0-24hr) of tauro-OCA was 0.0065 with N=1.

Following multiple doses of 25, 50, 100, 250 mg QD, there was little amount or small percent of the OCA dose recovered in urine as the unchanged OCA and its two conjugated metabolite over the 0-24 hour collection interval on Day 1 or Day 12. On average, there was less than 0.25% of the dose excreted in urine as all 3 analytes on Day 1 (0.13 to 0.25%), and less than 0.9% of the dose excreted in urine as all 3 analytes on Day 12 (0.49 to 0.81%) across dose levels.

### **2.3.7.1.2 Patients with PBC**

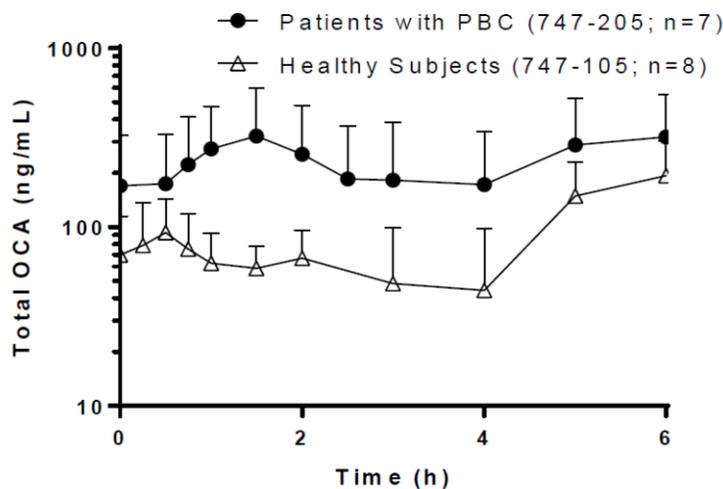
Trough concentrations of OCA and its conjugates in patients with PBC were evaluated in two Phase 2 studies (Studies 747-201 and 747-202) with non-validated analytical methods. Thus, the trough concentrations were not reviewed. OCA and its conjugates concentrations (up to 6 hours) following 10 mg QD for 8 weeks were measured in eight patients with PBC (Study 747-205) with a validated analytical method. Due to extensive enterohepatic recirculation, 6 hours PK sampling is insufficient to represent true systemic exposure of OCA and its conjugates. Thus, the C<sub>max</sub> and AUC(0-6) are not summarized here. The concentration-time profile at Week 8 is shown in Figure 18.

Trough concentrations of OCA and its conjugates in patients with PBC were evaluated in Month 6 and Month 12 in the pivotal Phase 3 study (Table 17).

### **2.3.7.2 How does the PK of the drug in healthy volunteers compare to that in patients?**

A direct comparison between the PK of OCA in healthy volunteers and patients is not feasible because of the limited PK samples collected in patients with PBC. With this caveat in mind, a cross-study comparison was performed and the mean concentration-time profiles of first 6 hours between patients with PBC (Study 747-205) and healthy subjects (Study 747-105) were shown in Figure 18. Study 747-105 evaluated healthy subjects dosed with 10 mg QD OCA for 14 days. Study 747-205 evaluated PK profiles over the first 6 hours after last dose administration of OCA dosed with 10 mg QD OCA for 8 weeks in PBC patients. Study 747-301 evaluated trough PK concentrations for PBC patients dosed for 24 weeks (6 months). The comparative data from study 747-205 and study 747-105 showed an overall similar profile, but with modestly higher systemic exposure for PBC patients compared to healthy volunteers. However, the limited number of subjects in these studies and the high variability in the systemic exposures limits the interpretation of these results. In this comparison, the difference in C<sub>max</sub> of total OCA between patients (mean/SD of 409/299 eq-ng/mL) and healthy subjects (mean /SD of 285/27.7 eq-ng/mL) was two-fold.

Figure 18: Mean (SD) Steady-State Plasma Concentration-Time Profile of Total OCA in Subjects with Primary Biliary Cirrhosis (Study 747-205) and Healthy Subjects (Study 747-105) After Daily Administration of 10 mg OCA (Semi-log)



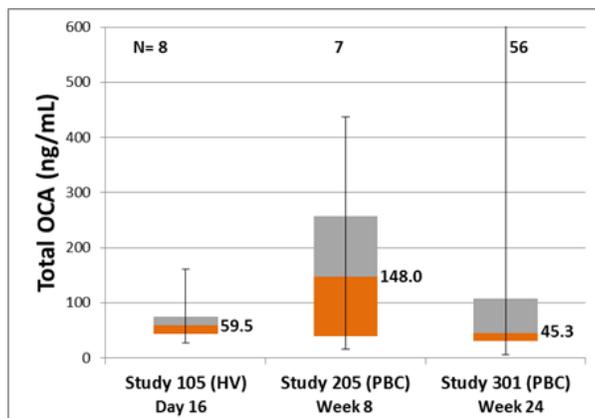
Source data: Figure 7, Section 2.7.2

Table 17: Descriptive statistics of OCA and its conjugates trough concentrations (ng/mL) at Month 6 (Study 747-301), and Day 14 (Study 747-105) by treatment

|                   | OCA          | Glyco-OCA   | Tauro-OCA   | Total OCA   |
|-------------------|--------------|-------------|-------------|-------------|
| Month 6, Patients |              |             |             |             |
| 5 mg (N=63)       | 3.73 (4.62)  | 39.2 (43.0) | 31.8 (44.7) | 63.6 (70.1) |
| 10 mg (N=57)      | 4.90 (4.96)  | 50.7 (60.9) | 42.5 (103)  | 83.4 (114)  |
| Day 14, Healthy   |              |             |             |             |
| 5 mg (N=7)        | 1.30 (0.398) | 12.4 (11.2) | 7.70 (8.18) | 18.4 (16.7) |
| 10 mg (N=8)       | 2.91 (0.811) | 26.4 (15.3) | 31.8 (11.0) | 51.5 (20.7) |

Study 747-301 evaluated trough PK concentrations for PBC patients dosed for 24 weeks (6 months) with 5 mg and 10 mg QD OCA. The mean trough concentrations of total OCA in patients from Study 747-301 were 1.6 fold than healthy subjects (Study 747-105) after 10 mg QD, while the median trough concentrations were similar between these two populations (Figure 19). Overall, there was substantial overlap between the concentrations in the two populations. The inter-subject variability seems to be greater in patients than that in healthy subjects.

Figure 19: Boxplot of trough concentration of total OCA in study 747-105 (healthy volunteers), study 747-105 (PBC patients) and Phase 3 study 747-301 (PBC patients) after daily administration of 10 mg OCA for 14 days, 8 weeks and 24 weeks respectively.



### 2.3.7.3 What is the inter-subject and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

#### Inter-subject variability

Table 18 shows that the inter-subject variability of systemic exposure (AUC<sub>tau</sub>) following multiple doses administration of OCA. The larger inter-subject variability is likely due to the extensive hepatic recirculation. The number of subjects in the study is small affecting the variability assessment.

Table 18: Inter-subject variability (N) of OCA systemic exposures (C<sub>max</sub> and AUC<sub>tau</sub>) after multiple oral doses of 5, 10, 25, 50, 100, and 250 mg QD in healthy subjects.

| Analyte   | Dose (mg)        | Study 747-105 |           |           | Study 747-102 |           |            |            |
|-----------|------------------|---------------|-----------|-----------|---------------|-----------|------------|------------|
|           |                  | 5             | 10        | 25        | 25            | 50        | 100        | 250        |
| OCA       | C <sub>max</sub> | 47<br>(7)     | 48<br>(8) | 36<br>(7) | 35<br>(8)     | 40<br>(8) | 48<br>(16) | 78<br>(7)  |
|           | AUC(0-24)        | 39<br>(7)     | 15<br>(8) | 36<br>(7) | 52<br>(8)     | 56<br>(8) | 48<br>(16) | 115<br>(7) |
| Glyco-OCA | C <sub>max</sub> | 83<br>(7)     | 33<br>(8) | 29<br>(7) | 40<br>(8)     | 45<br>(8) | 40<br>(16) | 63<br>(7)  |
|           | AUC(0-24)        | 87<br>(7)     | 37<br>(8) | 39<br>(7) | 36<br>(8)     | 66<br>(8) | 40<br>(16) | 49<br>(7)  |
| Tauro-OCA | C <sub>max</sub> | 109<br>(7)    | 38<br>(8) | 37<br>(7) | 55<br>(8)     | 60<br>(8) | 75<br>(16) | 52<br>(7)  |
|           | AUC(0-24)        | 112<br>(7)    | 32<br>(8) | 34<br>(7) | 56<br>(8)     | 74<br>(8) | 75<br>(16) | 51<br>(7)  |

### Intra-Subject Variability

No crossover study was conducted following multiple doses in the clinical pharmacology program. For estimating single dose intra-variability, there are three crossover studies (Studies 747-104, 747-115 and 747-116). However, none of them had sufficient sampling time to support estimation of AUC<sub>inf</sub>. Therefore, intra-subject variability is not summarized here.

#### **2.3.7.4 What are the characteristics of drug absorption?**

The mean value of absolute bioavailability (F) for OCA is 17% when the 0.1 mg IV OCA was used as the reference product (Table 19). However, the true absolute bioavailability was indeterminate since the conjugates which are active metabolites were not measured following the IV administration.

Table 19: Mean (SD) C<sub>max</sub> and AUC parameters from single IV dose (Regimen B) and oral dose of OCA (Regimen A)

|       | Dose   | C <sub>max</sub> (ng/mL) | AUC <sub>0-t</sub> (hours*ng/mL) |
|-------|--------|--------------------------|----------------------------------|
| IV    | 0.1 mg | 9.71 (0.3279)            | 3.86 (0.1738)                    |
| PO    | 25 mg  | 80.9 (26.41)             | 144 (21.06)                      |
| F (%) |        |                          | 17.1 (2.993)                     |

#### **2.3.7.5 What are the characteristics of drug distribution?**

The estimated mean (SD) volume of distribution (V<sub>z</sub>) following single IV dose of 0.1 mg OCA was 618 (341.9) L. However, this value may not be the true V<sub>z</sub> as the sampling time was up to 72 hours which is not long enough.

OCA and its glyco- and tauro- conjugates are all extensively bound to human plasma proteins, with the in vitro mean protein bound fraction (%) of 99.93%, 99.77%, and 99.78%, respectively, over the concentration range of 10 to 500 ng/mL.

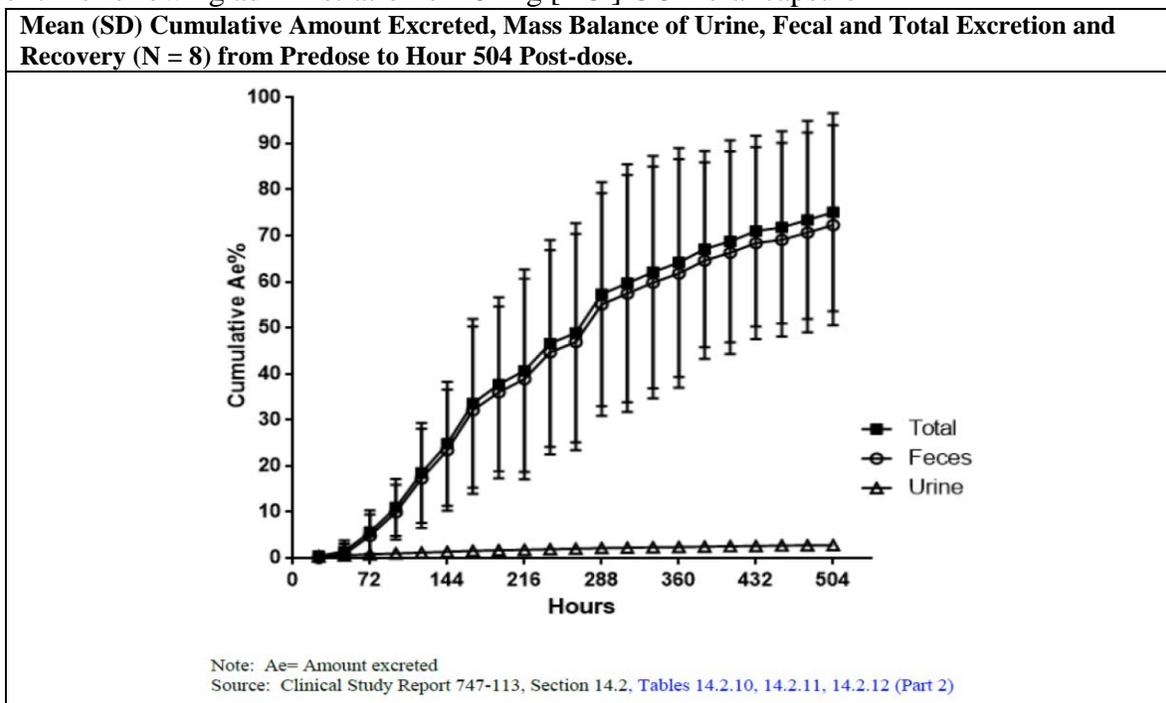
In a separate in vitro protein binding study (b) (4) OCA, glyco-OCA, and tauro-OCA were also found extensively bound to human plasma protein, with the mean protein bound fraction (%) of 99.4%, 97.8%, and 98.6%, respectively, over concentration range of 100-10000 ng/mL. However, significant non-specific binding to the ultrafiltration device was present for all three analytes, which can confound the results.

#### **2.3.7.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?**

Results from the mass balance study showed that OCA is extensively conjugated with glycine or taurine in the liver and secreted into bile. Total recovery in urine on average was 2.83%.

Eight healthy subjects received single oral dose of 25 mg [<sup>14</sup>C]-OCA capsule containing NMT (b) (4). The cumulative excretion of total radioactivity over time following 25 mg [<sup>14</sup>C]-OCA is shown in Figure 20.

Figure 20: Mean (SD) cumulative excretion of total radioactivity in urine, feces, and combined over time following administration of 25-mg [<sup>14</sup>C] OCA oral capsule



**Total recovery:** A mean of 75.1% (range between 28.3% and 97.5%) of the total radioactivity administered was recovered from urine and feces by the end of the inpatient sampling period (504 hours post-dose). A mean of 89.8% of the total radioactivity administered was recovered from urine and feces by 1152 hours post-dose ranging from 76.31% to 111.28% of the administered radioactivity.

**Recovery in Urine:** An average of 2.83% (range 1.57% to 4.00%) of the total radioactivity administered was recovered from the urine. The results from metabolite profiling (Section 2.3.7.7) indicated that OCA was not detected in the urine. No single metabolite in urine accounted for >1% of the dose. The majority of drug-related material in the urine was recovered within the first 312 hours after investigational product administration. No urine samples were collected after hour 504 post-dose.

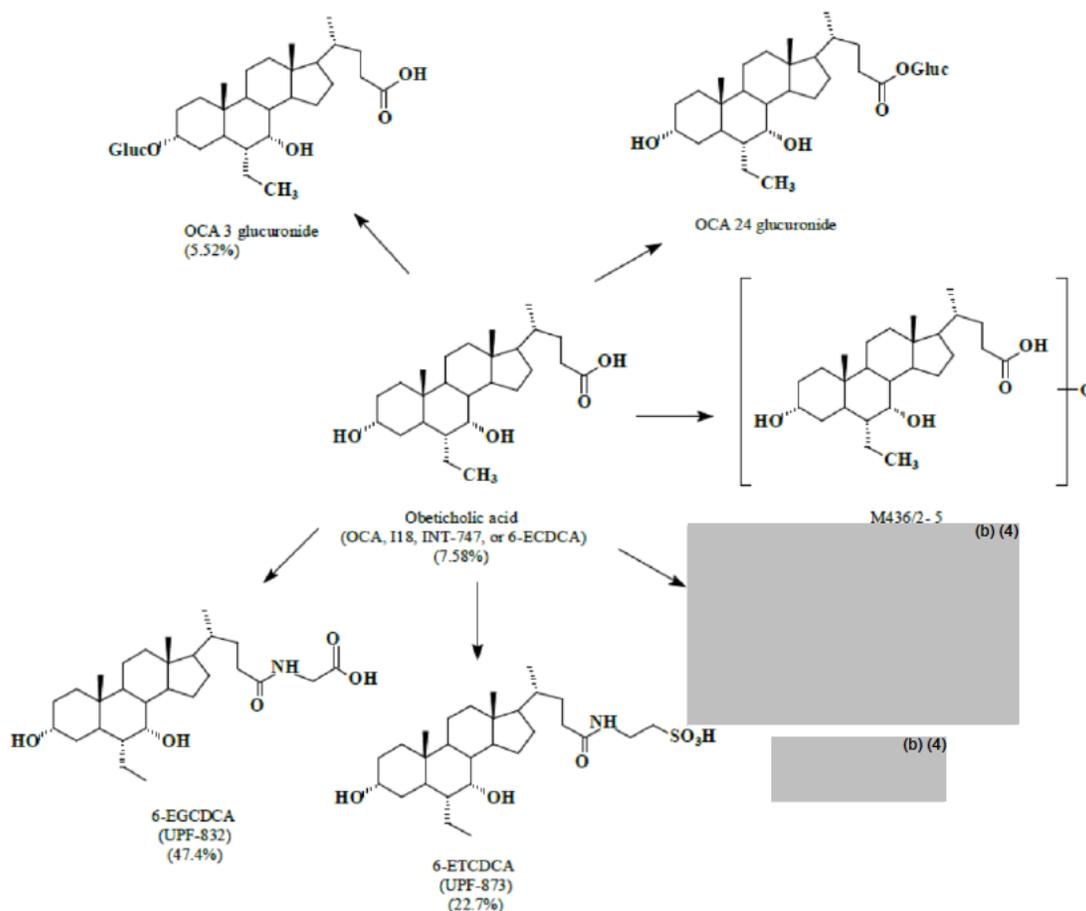
**Recovery in Feces:** An average of 72.3% (range 25.2% to 95.9%) of the total radioactivity administered was recovered from feces by 504 hours post-dose. At 1152 hours, a mean of 87.0% of the total radioactivity administered (range 73.2 to 107%) was recovered from feces. The majority of drug-related material in the feces was recovered within 552 hours of dosing with the investigational product.

### 2.3.7.7 What are the characteristics of drug metabolism?

In vitro study indicated that OCA is not metabolized to any significant extent by CYP450 enzymes (Section 2.5.2.2). The in vivo mass balance study, metabolite profiling (Section 2.3.7.7.1.1 below), single and multiple doses studies in healthy subjects indicated that the major metabolites of OCA in human plasma are amino acid conjugates, i.e., glyco-OCA and tauro-OCA.

The proposed human metabolic pathways are shown in Figure 21.

Figure 21: Sponsor's proposed metabolic pathway of OCA in human plasma



Gluc = glucuronic acid,

The mean %AUC<sub>0-t</sub> values were present in the figure.

#### 2.3.7.7.1.1 Metabolites

In addition to OCA, nine metabolites were detected with corresponding radioactive peaks in various matrices from humans after a single administration of [<sup>14</sup>C]OCA at 25 mg (34 MBq). Unchanged OCA was one of the major circulating entities, accounting for about 7.58% of AUC<sub>0-t</sub> by total radioactivity (TRA) in plasma, and was a major drug-related entity (35.5% of dose) in human feces. Glyco-OCA and tauro-OCA were the most abundant metabolites,

accounting for 47.4% and 22.7% of TRA AUC<sub>0-t</sub>, respectively. (b) (4) impurity (b) (4) and OCA 3 glucuronide were the less abundant metabolites, accounting for about (b) (4) % and 5.52% of TRA AUC<sub>0-t</sub>, respectively. OCA 24 glucuronide was detectable in human plasma only by LC/MS.

OCA was not detectable in the pooled human urine. No single metabolite in urine accounted for >1% of the dose. Five metabolites, (b) (4) Impurity (b) (4) M436/2, M436/3, M436/4, and M436/5, were tentatively identified in feces, each accounting for (b) (4) %, 4.30%, 0.96%, 7.89%, and 2.48% of the dose in the pooled human feces, respectively.

One radioactive peak accounting for 4.78% of the dose in the pooled sample was not identified since it was not detected in human plasma and urine samples.

Pharmacological activity of the metabolites: Both glyco- and tauro-OCA are active metabolites. OCA-3 glucuronide and OCA-24 glucuronide do not have pharmacological activity. See pharmacology/toxicology review for details.

#### **2.3.7.8 What are the characteristics of drug excretion?**

Mass balance study indicated that about 87% of the radioactive dose was recovered in feces and less than 3% in urine from healthy subjects indicating that OCA is primarily excreted in feces.

#### **2.3.7.9 Based on PK parameters, what is the degree of linearity or non-linearity based on the dose-concentration relationship?**

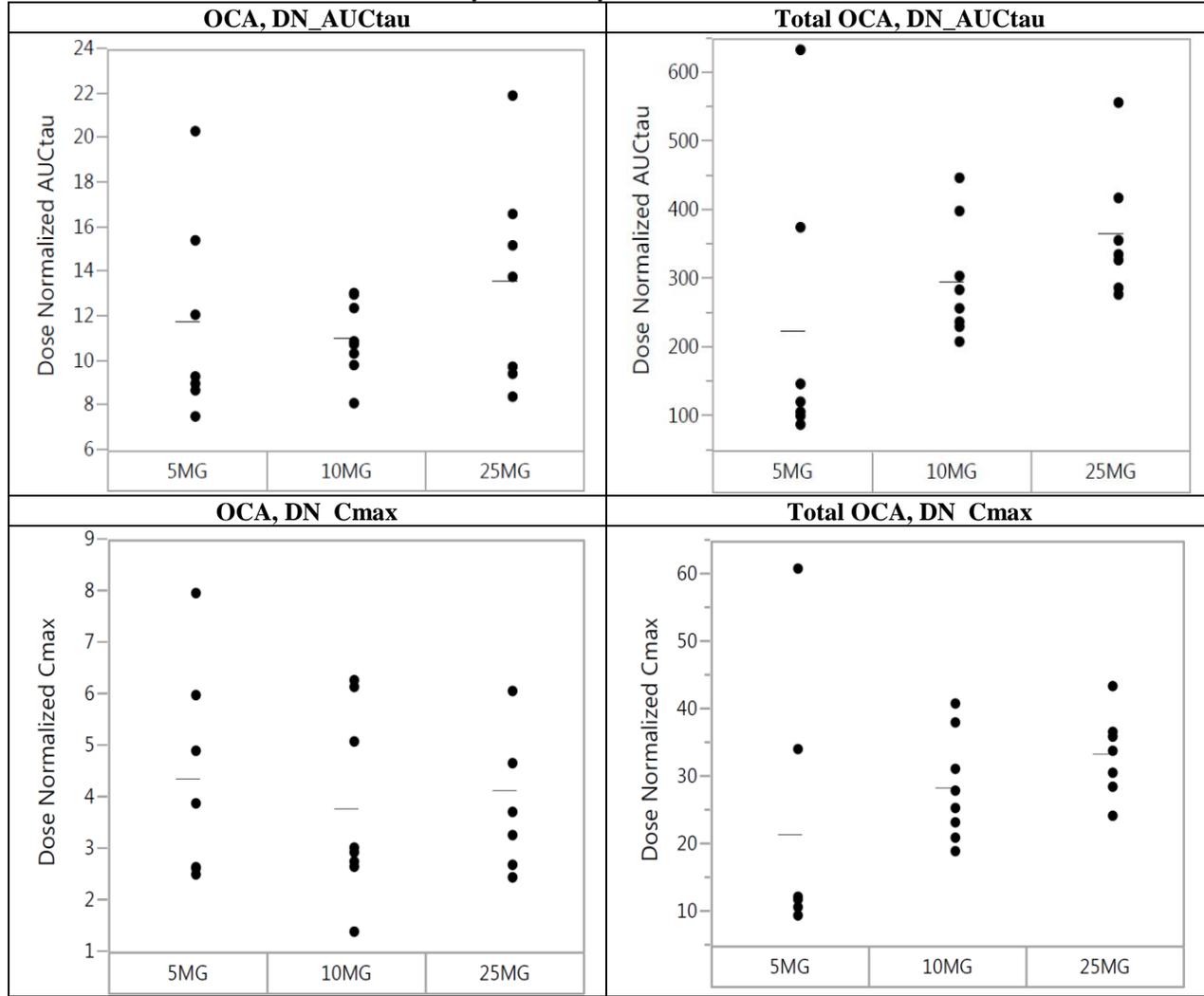
##### Single doses

Following single dose of 5 mg, 10 mg, and 25 mg OCA, dose-proportionality was concluded for C<sub>max</sub> and AUC<sub>0-t</sub> and all analytes (OCA, glyco-OCA and tauro-OCA) with the exception of AUC<sub>t</sub> for OCA which increased in a more than dose-proportional manner. Due to its extensive hepatic enterohepatic recirculation, AUC<sub>0-t</sub> determined by 60 hours PK sampling does not reflect the total systemic exposure following single doses.

##### Multiple doses

Following multiple-dose administration of 5, 10, and 25 mg QD for 14 days, dose-proportionality was concluded for the parent drug only. For the conjugates and total OCA, C<sub>max</sub> and AUC<sub>0-24h</sub> increased more than proportionally with dose.

Figure 22: Individual and mean of dose normalized (DN) systemic exposure (AUCtau and Cmax) to OCA and total OCA on Day 14 (Study 747-105)



Source Data: Reviewer's analysis

Following multiple-dose administration of 25, 50, and 100mg QD for 14 days, dose-proportionality was concluded for OCA and its conjugates. Following multiple-dose administration of 250 mg QD of OCA for 14 days, systemic exposure of OCA increases dose proportionally. However, glyco-OCA and tauro-OCA increased less than dose proportionally.

### 2.3.7.10 How do the PK parameters change with time following chronic dosing?

PK of OCA and its conjugates do not appear to change with time because as OCA is not a substrate of CYP enzymes. The metabolism of OCA is through conjugation. Thus, the PK of OCA should not change either by auto-induction or auto-inhibition. The changes of PK parameter with time was not well characterized in phase 1 single and multiple doses studies as the sampling time in single dose study was only up to 60 hours. Due to extensive hepatic recirculation and the sampling time limitation, the AUCinf was not estimable in the single dose studies.

Following multiple doses of 5, 10, and 25 mg OCA for 14 days, the systemic exposures (C<sub>max</sub> and AUC<sub>0-24h</sub>) are greater than that of single doses across all dose levels (Table 20).

Table 20: Ratios of AUC<sub>0-24h</sub> (RAUC) between Day 14 and Day 1 for various doses of OCA (Study 747-105)

| DOSE (mg)   | Analytes  | N | Mean | CV%  |
|---|-----------|---|------|------|
| 5   | OCA       | 5 | 1.9  | 15.4 |
|   | Glyco-OCA | 7 | 4.5  | 25.7 |
|   | Tauro-OCA | 7 | 4.3  | 40.2 |
| 10  | OCA       | 7 | 2.1  | 33.9 |
|   | Glyco-OCA | 8 | 6.4  | 67.7 |
|   | Tauro-OCA | 8 | 9.4  | 28.3 |
| 25  | OCA       | 7 | 2.0  | 13.0 |
|   | Glyco-OCA | 7 | 6.8  | 35.4 |
|   | Tauro-OCA | 7 | 13.6 | 30.6 |
| RAUC=AUC <sub>0-24,ss</sub> /AUC <sub>0-24,Day1</sub> |           |   |      |      |

Following multiple doses of 25, 50, 100, and 250 mg OCA for 14 days, the systemic exposures (C<sub>max</sub> and AUC<sub>0-24h</sub>) are greater than that of single doses across all dose levels (Table 21).

Table 21: Ratios of AUC0-24h (RAUC) between Day 14 and Day 1 for various doses of OCA (Study 747-102)

| DOSE (mg)                    | Analytes  | N  | Mean  | CV% |
|------------------------------|-----------|----|-------|-----|
| 25                           | OCA       | 8  | 2.17  | 29  |
|                              | Glyco-OCA | 8  | 5.01  | 21  |
|                              | Tauro-OCA | 8  | 11.24 | 48  |
| 50                           | OCA       | 8  | 2.11  | 32  |
|                              | Glyco-OCA | 8  | 4.22  | 34  |
|                              | Tauro-OCA | 8  | 13.83 | 44  |
| 100                          | OCA       | 16 | 2.09  | 30  |
|                              | Glyco-OCA | 16 | 4.23  | 31  |
|                              | Tauro-OCA | 16 | 11.24 | 58  |
| 250                          | OCA       | 8  | 1.33  | 64  |
|                              | Glyco-OCA | 7  | 3.29  | 17  |
|                              | Tauro-OCA | 7  | 7.06  | 40  |
| RAUC=AUC0-24,ss/AUC0-24,Day1 |           |    |       |     |

## 2.4 INTRINSIC FACTORS

### 2.4.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

**Age:** Using pop-PK analysis, age was not identified as a significant predictor of exposure/clearance for OCA and its conjugates. Age ranged from 18 to 71 years in the population PK analysis dataset.

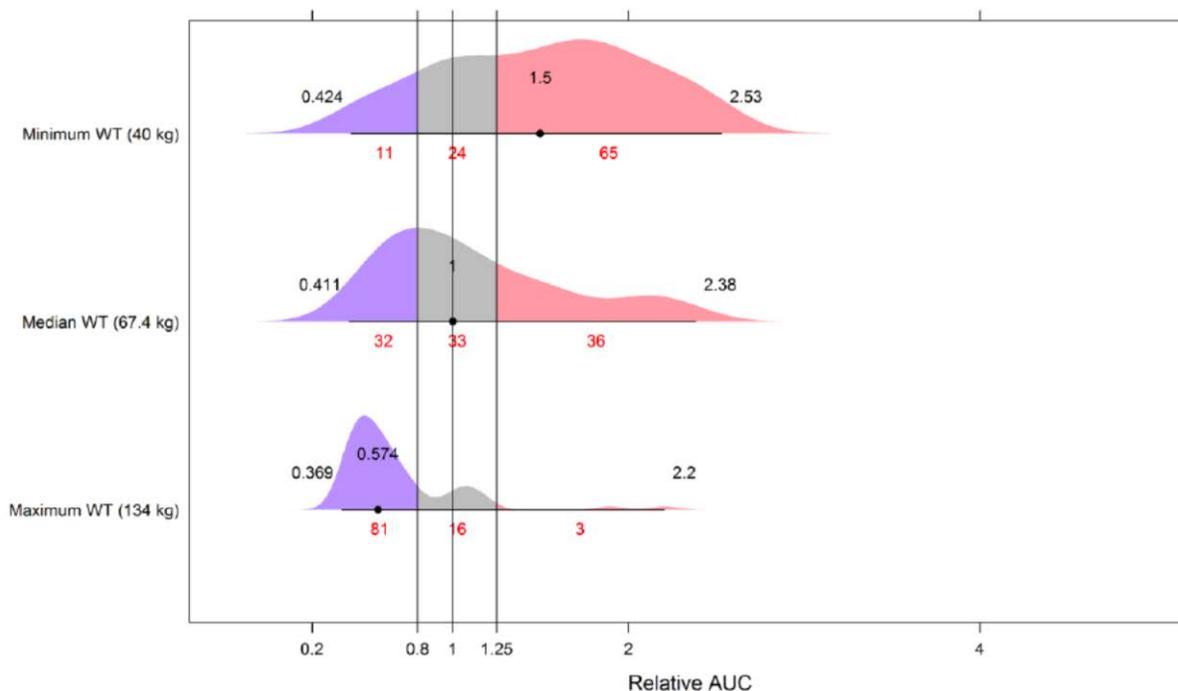
**Gender:** Using pop-PK analysis, gender was not identified as a significant predictor of exposure/clearance for OCA and its conjugates. The population PK analysis dataset had 301 female and 505 male subjects.

**Race:** Using pop-PK analysis, race was not identified as a significant predictor of exposure/clearance for OCA and its conjugates. The population PK analysis dataset had 10 Asian, 233 Black, 554 White and 9 Other subjects.

**Weight:** Body weight was identified as an important covariate on volume of distribution of OCA and its conjugates as well as on rate of gall bladder emptying for glyco- and tauro-OCA, during gallbladder contraction. Body weight ranged from 41 to 112 kg in the population PK analysis dataset. Based on the distribution of body weights in the Phase 3 study 747-301, a forest plot was generated to evaluate effect of body weight on total OCA (Figure 23). Based on this plot, the median AUC for a 40 kg subject is expected to be 50% higher and median AUC for a 134 kg subject is expected to be 43% lower compared to the AUC for a typical 67 kg subject. The body

weight effect is not expected to cause a meaningful impact on efficacy as concentrations of total OCA are predicted to be well above the estimated  $IC_{50}$  for efficacy after daily administration of OCA at 5 mg and 10 mg doses.

Figure 23: Forest plot of relationship between body weight and AUC of total OCA



AUC = area under the curve; n = number of subjects; OCA = obeticholic acid; WT = body weight

Note: the above figure assumed after daily dose of 10 mg of OCA at 8 AM and meals taken at 8 AM, 12 PM and 6 PM with a dosing at 8 AM; Black numbers represent the 5th, 50th and 95th percentiles of the relative AUC for each category, red numbers represent the proportion below 0.8, within 0.8 and 1.25 and above 1.25 of the reference AUC value in 4332 mg·h/mL.

Source Data: Sponsor's Population PK/PD and Simulation Report, Figure 8.5

We evaluated the impact of body weight on titrations with the hypothesis that if the efficacy is impacted by differences in concentration attributed to body weight, then we should see a differential titration rate with subjects with high body weight (associated with low concentration) being up-titrated more than the subjects with lower body weight based on response and tolerability criteria. In such a circumstance, a higher starting dose may be desirable in subjects with high body weight. The Table 22 shows that there was no trend of titration occurring preferably in higher body weight subjects over lower body weight subjects. This suggests that the impact of body weight is not clinically meaningful to suggest dose recommendation based on body weight.

Table 22: Fraction of patients up-titrated from 5 mg to 10 mg QD dose in the titration arm across quartiles of body weight

| Weight Group (kg) | Patients up-titrated from 5 mg to 10 mg at month 6, n/N (%) |
|-------------------|---|
| 41 – 60.1         | 11/19 (57.9 %)  |
| 60.1 – 68         | 9/18 (50.0 %)   |
| 68 – 78           | 6/14 (42.9 %)   |
| 78 – 134          | 6/14 (42.9 %)   |

We also evaluated the impact of BMI on primary efficacy (responder) criteria across low (<30 kg/m<sup>2</sup>) and high (≥30 kg/m<sup>2</sup>) BMI categories in order to assess whether a higher starting dose is desirable for subjects with high BMI. There was initially a lower response at week 2 in high BMI group with 5 mg QD starting dose vis-à-vis 10 mg QD starting dose, but this difference vanishes by 6 months (Table 23). Also the drug is to be taken for lifetime and there is no clinical urgency to get a more rapid response. Rather, dose discontinuation due to pruritus is a major concern with a potential higher starting dose. Thus, the OCP review team does not recommend a higher starting dose based on a higher body weight or high BMI criteria.

Table 23: Percentage of patients meeting primary efficacy endpoint (responder) criteria at different visits across low and high BMI categories

| BMI (kg/m <sup>2</sup> ) | OCA*    | Week 2      | Month 3     | Month 6     |
|--------------------------|---------|-------------|-------------|-------------|
| < 30                     | Placebo | 0%          | 0%          | 5% (3/58)   |
|                          | 5 mg    | 21% (12/58) | 38% (22/58) | 34% (20/58) |
|                          | 10 mg   | 23% (14/61) | 41% (25/61) | 54% (33/61) |
| ≥ 30                     | Placebo | 0%          | 13% (2/15)  | 13% (2/15)  |
|                          | 5 mg    | 8% (1/12)   | 25% (3/12)  | 33% (4/12)  |
|                          | 10 mg   | 33% (4/12)  | 33% (4/12)  | 33% (4/12)  |

Disease: Refer to Section 2.3.7.1.2 and Section 2.3.7.2 regarding patients with PBC.

**2.4.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.**

**2.4.2.1 Pediatric patients**

The PK of OCA has not been studied in pediatric subjects. PBC is usually diagnosed at 40 to 60

years of age. In addition, OCA was granted orphan drug designation on April 9, 2008. Therefore, pediatric assessment is not required for this NDA.

### 2.4.2.2 Renal impairment

A dedicated renal impairment study was not conducted. In study 747-113 using radiolabelled OCA, <3% of the dose was excreted in urine. Based on population PK analysis, renal function (eGFR) was not identified as a significant covariate for OCA clearance/exposure. The renal function data in the population PK analysis involved eGFR ranging from 52 to 433 mL/min/1.73 m<sup>2</sup> with 5 subjects with moderate renal impairment (30 to <60 mL/min/1.73 m<sup>2</sup>), and 210 subjects with mild renal impairment (60 to <90 mL/min/1.73 m<sup>2</sup>). The effect of severe renal impairment on the systemic exposures of OCA and its conjugates is unknown.

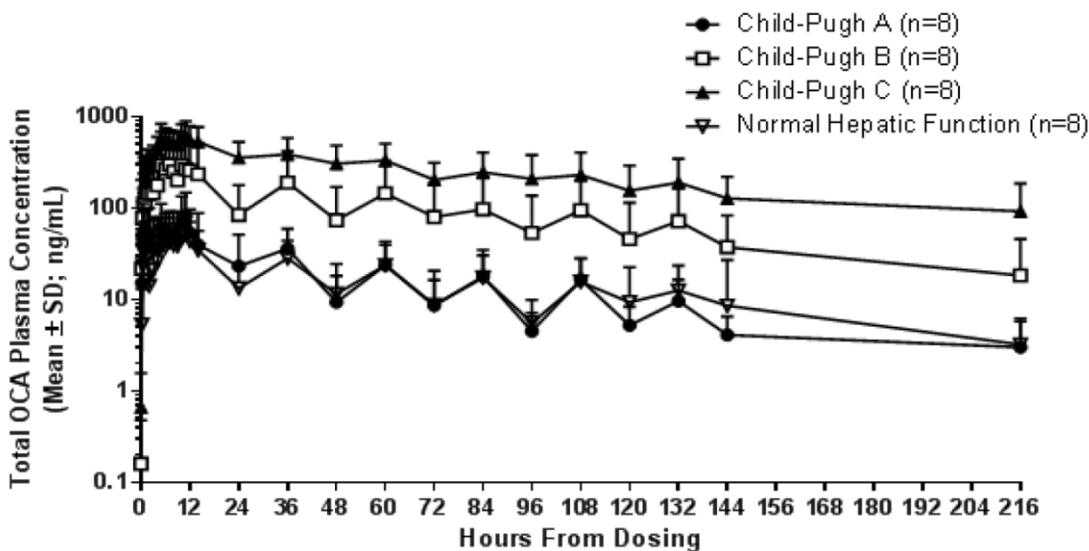
### 2.4.2.3 Hepatic impairment

A dedicated hepatic impairment study was conducted. Single dose of 10 mg OCA was administered to healthy subjects (control), and patients with mild, moderate, or severe hepatic impairment using Child-Pugh Classification system.

The AUC<sub>0-t</sub> of total OCA were 13%, 320%, and 1630% higher in patients with mild, moderate, or severe hepatic impairment, respectively (Table 26). Similarly, C<sub>max</sub> of total OCA were 49%, 276%, and 875% higher in patients with mild, moderate, or severe hepatic impairment, respectively.

The mean total OCA concentration-time profile is presented below.

Figure 24: Mean plasma concentration-time profile of total OCA following a single oral dose of 10 mg OCA (Semi-log)



Source Data: Section 2.7.2, Figure 8

Mean (SD) PK parameters of OCA, glyco-OCA and tauro-OCA following single dose of 10 mg OCA are shown in the table below.

Table 24: Mean (SD) parameter of plasma OCA, glyco-OCA and tauro-OCA

| Analyte | Parameters | Normal Hepatic | Mild | Moderate | Severe |
|---------|------------|----------------|------|----------|--------|
|---------|------------|----------------|------|----------|--------|

|  |                             | Function (N=8)      | (N=8)               | (N=8)               | (N=8)               |
|--|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| OCA  | Cmax (ng/mL)                | 54.0 (18.9)         | 80.0 (49.6)         | 141 (143)           | 254 (84.9)          |
|  | Median Tmax (hr) (min, max) | 1.000 (0.500, 4.00) | 1.125 (0.500, 1.50) | 1.125 (0.500, 3.00) | 1.250 (0.500, 3.00) |
|  | AUC0-t (hr*ng/mL)           | 175 (114)           | 252 (181)           | 563 (645)           | 1113 (406)          |
| Glyco-OCA  | Cmax (ng/mL)                | 49.5 (24.8)         | 79.8 (66.5)         | 223 (190)           | 408 (180)           |
|  | Median Tmax (hr) (min, max) | 11.0 (5.0, 14.0)    | 11.0 (6.0, 11.0)    | 8.5 (4.0, 12.0)     | 10.0 (5.0, 11.0)    |
|  | AUC0-t (hr*ng/mL)           | 1720 (962)          | 2400 (2090)         | 8570 (9320)         | 20300 (9830)        |
| Tauro-OCA  | Cmax (ng/mL)                | 21.9 (17.2)         | 16.9 (13.5)         | 176 (251)           | 385 (226)           |
|  | Median Tmax (hr) (min, max) | 8.5 (5.0, 108 †)    | 11.0 (10.0, 12.0)   | 8.5 (5.0, 10.0)     | 10.5 (5.0, 14.0)    |
|  | AUC0-t (hr*ng/mL)           | 1000 (1200)         | 533 (359)           | 9510 (13400)        | 27700 (19600)       |
| † The plasma concentration versus time profile for one showed multiple peaks of approximately the same height. The highest peak occurred at 108 hours post-dose. |                             |                     |                     |                     |                     |

Mean (SD) PK parameters of total OCA following single dose of 10 mg OCA are shown in the table below.

Table 25: Mean (SD) parameter of plasma total OCA

| Parameters        | Normal Hepatic Function (N=8) | Mild (N=8)  | Moderate (N=8) | Severe (N=8)  |
|-------------------|-------------------------------|-------------|----------------|---------------|
| Cmax (ng/mL)      | 68.3 (27.6)                   | 107 (65.1)  | 348 (377)      | 674 (281)     |
| AUC0-t (hr*ng/mL) | 2480 (1810)                   | 2770 (2060) | 15700 (19100)  | 41000 (21900) |

Distribution of individual Cmax and AUC0-t of OCA and its conjugates in patients with various degree of hepatic impairment is shown in Figure 25 and Figure 26.

Figure 25: Individual Cmax and AUC of OCA and its conjugates in patients with mild, moderate and severe hepatic impairment vs normal subjects.

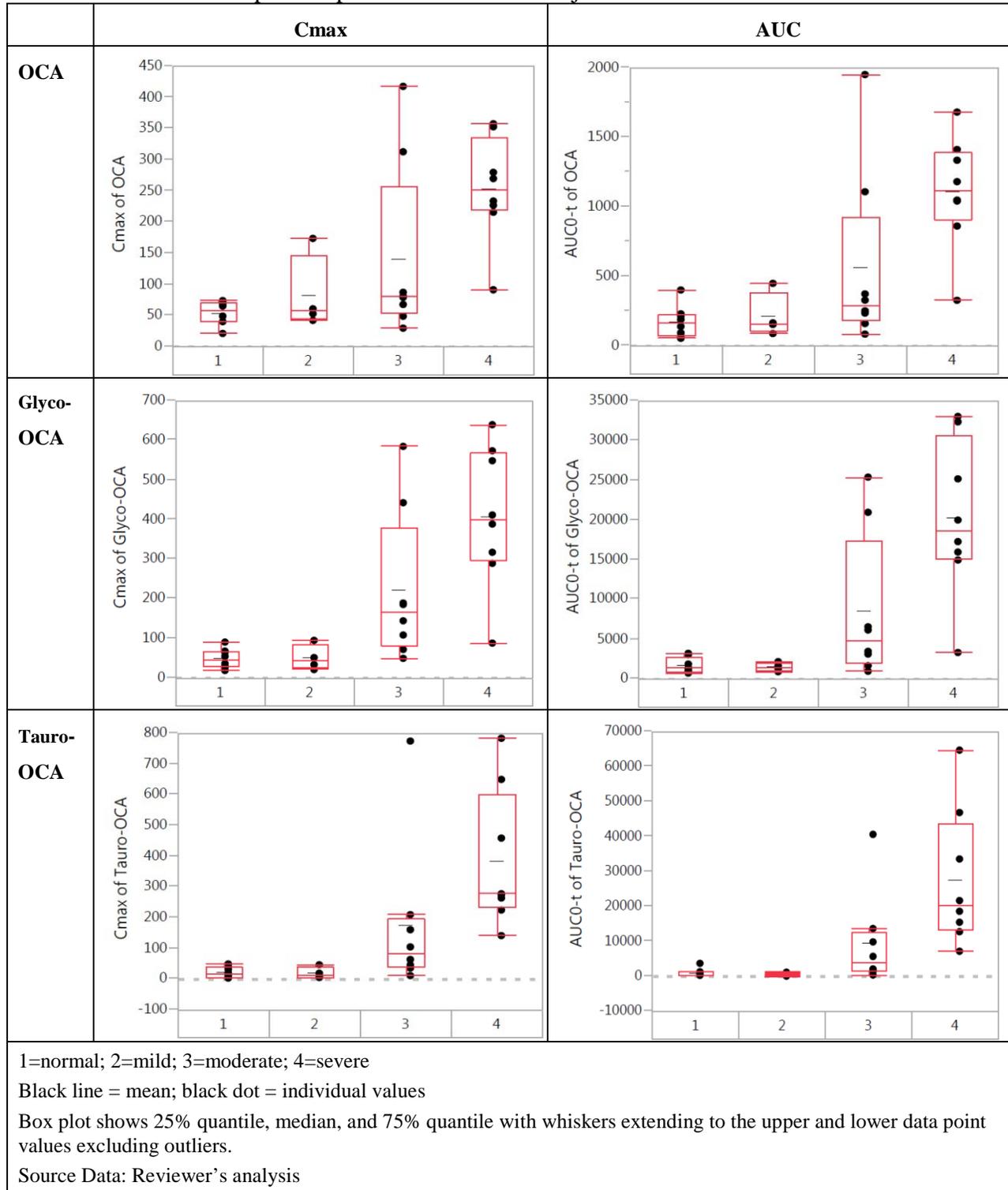
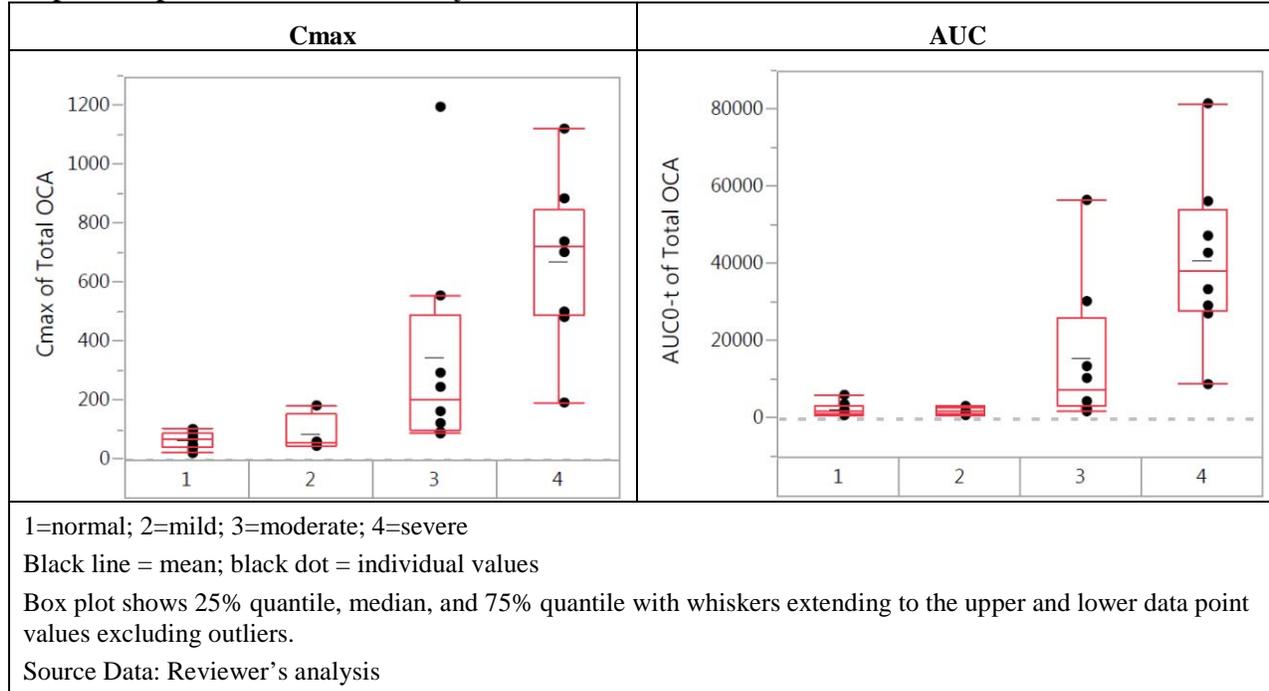


Figure 26: Individual Cmax and AUC of total OCA in patients with mild, moderate and severe hepatic impairment vs normal subjects.



The summary statistics of systemic exposure (Cmax and AUCt) to OCA and its conjugates are shown in Table 26.

Table 26: Statistical comparison of AUC0-t and Cmax (747-103)

| Comparison         | Parameters | OCA  |            | Glyco-OCA |            | Tauro-OCA |             | Total OCA |            |
|--------------------|------------|------|------------|-----------|------------|-----------|-------------|-----------|------------|
|                    |            | GMR  | 90% CI     | GMR       | 90% CI     | GMR       | 90% CI      | GMR       | 90% CI     |
| Mild vs Normal     | AUC        | 1.38 | 72.8 - 261 | 1.27      | 64.7 - 250 | 7.09      | 29.6 - 170  | 1.13      | 56.5 - 225 |
|                    | Cmax       | 1.35 | 79.8 - 228 | 1.43      | 79.5 - 256 | 8.72      | 40.4 - 188  | 1.49      | 86.3 - 256 |
| Moderate vs Normal | AUC        | 2.41 | 127 - 456  | 3.33      | 169 - 654  | 6.86      | 286 - 1640  | 4.20      | 211 - 838  |
|                    | Cmax       | 1.91 | 113 - 323  | 3.73      | 208 - 670  | 5.63      | 261 - 1220  | 3.76      | 218 - 647  |
| Severe vs Normal   | AUC        | 7.03 | 372 - 1330 | 11.40     | 579 - 2240 | 36.80     | 1540 - 8830 | 17.30     | 867 - 3440 |
|                    | Cmax       | 4.70 | 278 - 796  | 8.12      | 452 - 1460 | 21.40     | 991 - 4630  | 9.75      | 566 - 1680 |

### Changes in protein binding (%Fu)

Plasma protein binding was measured using equilibrium dialysis methods. OCA, glyco-OCA, and tauro-OCA were highly protein bound across all groups (mean %Fu values for each group and analyte were  $\leq 0.65\%$ ; the extent of protein binding ranged from 99.4% to 99.9%). There was no pattern in change of mean %Fu with increasing hepatic impairment for OCA and tauro-OCA; however, mean %Fu glyco-OCA increased with increasing hepatic impairment. See table below.

Table 27: Statistical comparisons of %Fu OCA, glyco-OCA, and tauro-OCA in plasma

| Comparison <sup>a</sup>                  | Analyte <sup>b</sup> | LS Means |           | Difference Test - Reference |                   |         |
|--|----------------------|----------|-----------|-----------------------------|-------------------|---------|
|  |                      | Test     | Reference | LS Mean                     | 90% CI            | p-value |
| Mild (A; test) vs Normal (reference)     | OCA                  | 0.2131   | 0.1218    | 0.0913                      | -0.0226 to 0.2053 | 0.18    |
|  | Glyco-OCA            | 0.1652   | 0.1355    | 0.0297                      | -0.1175 to 0.1770 | 0.73    |
|  | Tauro-OCA            | 0.3042   | 0.5114    | -0.2072                     | -0.6238 to 0.2094 | 0.40    |
| Moderate (B; test) vs Normal (reference) | OCA                  | 0.0893   | 0.1218    | -0.0325                     | -0.1464 to 0.0814 | 0.63    |
|  | Glyco-OCA            | 0.2320   | 0.1355    | 0.0965                      | -0.0560 to 0.2489 | 0.29    |
|  | Tauro-OCA            | 0.2512   | 0.5114    | -0.2603                     | -0.6915 to 0.1710 | 0.31    |
| Severe (C; test) vs Normal (reference)   | OCA                  | 0.1803   | 0.1218    | 0.0585                      | -0.0554 to 0.1724 | 0.39    |
|  | Glyco-OCA            | 0.6500   | 0.1355    | 0.5145                      | 0.3672 to 0.6618  | <0.001  |
|  | Tauro-OCA            | 0.6465   | 0.5114    | 0.1350                      | -0.2816 to 0.5516 | 0.59    |

ANOVA = analysis of variance; CI = confidence interval; glyco-OCA = glycine 6 $\alpha$ -ethyl-chenodeoxycholic acid; OCA = obeticholic acid; PK = pharmacokinetic; tauro-OCA = taurine 6 $\alpha$ -ethyl-chenodeoxycholic acid

<sup>a</sup> Mild hepatic impairment (Child-Pugh A); moderate hepatic impairment (Child-Pugh B); severe hepatic impairment (Child-Pugh C); normal hepatic function

<sup>b</sup> Protein binding was assessed at the collection time corresponding to the highest plasma OCA concentration (at 0.75, 1, or 1.5 hours postdose) for OCA and at 6 hours postdose for glyco-OCA and tauro-OCA.

Note: Least-squares means, mean differences, confidence intervals, and p-values are from one-way ANOVA.

Refer to section 2.3.4.4 for details of dosing recommendation for moderate and severe hepatic impairment based on total plasma exposure matching to normal to mild hepatic impairment subjects using exposures derived from PK modeling and taking into consideration the dose-response relationship for safety (pruritus).

#### 2.4.2.4 What pregnancy and lactation use information is there in the application?

The PK of OCA has not been studied in pregnant women. In addition, no clinical studies were performed to determine if OCA is excreted into human milk.

## 2.5 EXTRINSIC FACTORS

### 2.5.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Drugs for bile salt sequestration are likely to reduce the absorption of OCA. As such, it is recommended that bile acid sequestrants be administered at least 4 hours before or 4 hours after (or at as great an interval as feasible) OCA dosing.

As this drug is a bile acid derivative, it may enhance the solubilization and consequently the bioavailability of some drugs.

There were no specific studies or analyses designed to evaluate the effects of factors such as

herbal products, diet (other than high-fat meal), smoking or alcohol use on the PK or PD of OCA. The effect of a high fat meal is discussed in Section 2.6.4. Based on the information on the metabolism profile of OCA, smoking and herbal products are unlikely to alter the PK of this drug. Drug-drug interactions are discussed below.

## **2.5.2 Drug-drug interactions**

### **2.5.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?**

Yes.

*Effect of OCA on other drugs:* Based on the in vitro studies, obeticholic acid is a CYP3A4 inhibitor (with midazolam as a substrate) and potential in vivo drug interaction via inhibition of CYP3A4 at the intestine level cannot be ruled out. OCA, glyco-OCA, and tauro-OCA are OATP1B1/OATP1B3 inhibitors and an in-vivo drug interaction study with rosuvastatin, a substrate of OATP1B1/OATP1B3, was conducted.

*Effect of other drugs on OCA:* In vitro study results indicate that bile acid sequestrants (i.e., colestevlam and cholestyramine) bind to OCA, glyco-OCA, and tauro-OCA. As such, it is recommended that bile acid sequestrants be administered at least 4 hours before or 4 hours after (or at as great an interval as feasible) OCA dosing.

### **2.5.2.2 Is the drug a substrate of CYP enzymes?**

No. Obeticholic acid does not appear to be a substrate of CYP enzymes. In vitro study using pooled human liver microsomes suggest that obeticholic acid is not metabolized to any significant extent by CYP450 enzymes. This is in agreement with the in vivo finding that the major metabolites of obeticholic acid in human plasma are amino acid conjugates, i.e., glyco-OCA and tauro-OCA.

### **2.5.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?**

#### **2.5.2.3.1 In vitro studies**

##### **2.5.2.3.1.1 Inhibition potential**

Based on the *in vitro* studies using human microsomes, there was potential for OCA to inhibit CYP3A4 (only at the gut level) at the therapeutic dose. There was no potential for OCA and the glyco- and tauro-conjugates to inhibit other CYP enzymes either at the systemic level or in the gut. The details are given below.

*CYP inhibition at the systemic level:* In vitro studies using human liver microsomes suggest that OCA, glyco-OCA, and tauro-OCA (at concentrations up to 50  $\mu$ M) are likely not inhibitors of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4 at the anticipated systemic level (following OCA 10 mg QD dosing). The calculated R values (i.e.,  $1+[I]/K_i$ ) were less than the cut-off value of 1.1, when the IC<sub>50</sub> values were reported for CYPs 2B6, 2C8, 2C9, 2C19, and 3A4 (Table 28 and Table 29). Inhibition of CYP1A2 and CYP2D6 enzymes was weak with an IC<sub>50</sub> value >50  $\mu$ M or no inhibition was observed at concentrations up to 50  $\mu$ M. It should be noted that the calculated R values for CYP2B6 and CYP2C9 inhibition were greater than the cut-off value of 1.1 at OCA 25 mg dose level (Table 30), although that dosage was not proposed for the current

application.

*CYP inhibition in the gut:* The alternate R value (i.e.,  $1 + [I]_{\text{gut}}/K_i$ ) for CYP3A4 inhibition (with midazolam as the probe substrate) was equal to the cut-off value of 11, suggesting a potential in vivo drug interaction via inhibition of CYP3A4 at the intestine level cannot be ruled out. An in vivo drug interaction study with midazolam, a CYP3A substrate, has been conducted.

Table 28: In vitro inhibition of CYP enzymes by OCA for 10 mg QD dosing.

| Inhibition            | IC50 (µM) | R (or alternate R) | In vivo CYP inhibition potential (based on in vitro R value) | In vivo study conducted (yes or no) |
|-----------------------|-----------|--------------------|--|-------------------------------------|
| CYP1A2                | >50       | <1.01              | No   | Yes (caffeine)                      |
| CYP2B6                | 15        | 1.034              | No   | No                                  |
| CYP2C8                | 40        | 1.013              | No   | No                                  |
| CYP2C9                | 12        | 1.042              | No   | Yes (warfarin)                      |
| CYP2C19               | >50       | <1.01              | No   | Yes (omeprazole)                    |
| CYP2D6                | >50       | <1.01              | No   | Yes (dextromethorphan)              |
| CYP3A4 (Midazolam)    | 19        | 1.027 (11.01)      | Yes, alternate R >11   | Yes (midazolam)                     |
| CYP3A4 (Testosterone) | >50       | <1.01              | No   | No                                  |

OCA = obeticholic acid;  $R = 1 + [I]/K_i$  (or alternate  $R = 1 + [I]_{\text{gut}}/K_i$ ), whereas  $K_i$  was calculated as  $IC_{50}/2$ . Mean OCA  $C_{\text{max}}$  = 107 ng/ml (~0.254 µM) in patients with PBC following 10 mg OCA QD.

Table 29: In vitro inhibition of CYP enzymes by glyco-OCA and tauro-OCA for 10 mg QD dosing.

| Inhibition            | Glyco-OCA |        | Tauro-OCA |        | In vivo CYP inhibition potential (based on in vitro R value) |
|-----------------------|-----------|--------|-----------|--------|--|
|                       | IC50 (µM) | R      | IC50 (µM) | R      |  |
| CYP1A2                | NI        | -      | NI        | -      | No   |
| CYP2B6                | 13        | 1.068  | 13        | 1.064  | No   |
| CYP2C8                | >50       | <1.018 | >50       | <1.017 | No   |
| CYP2C9                | 9.2       | 1.097  | 11        | 1.075  | No   |
| CYP2C19               | >50       | <1.018 | 50        | 1.017  | No   |
| CYP2D6                | NI        | -      | >50       | <1.017 | No   |
| CYP3A4 (Midazolam)    | 35        | 1.025  | 44        | 1.019  | No   |
| CYP3A4 (Testosterone) | >50       | <1.018 | >50       | <1.017 | No   |

NI = no inhibition observed; OCA = obeticholic acid;  $R = 1 + [I]/K_i$ , whereas  $K_i$  was calculated as  $IC_{50}/2$ . Mean glyco-OCA  $C_{\text{max}}$  = 212 ng/ml (~0.444 µM) and mean tauro-OCA  $C_{\text{max}}$  = 219 ng/ml (~0.415 µM) in patients with PBC following 10 mg OCA QD.

**Reviewer's comment:** Mean  $C_{\text{max}}$  values in patients with PBC appeared higher than those in healthy volunteers at 10 mg dose level, and thus were used in the calculation of the R values as a

conservative approach to avoid false negative estimations.

Table 30: In vitro inhibition of CYP enzymes by OCA, glyco-OCA, and tauro-OCA for 25 mg QD dosing.

| Inhibition            | OCA       |                         | Glyco-OCA |              | Tauro-OCA |              | In vivo CYP inhibition potential (based on in vitro R value) |
|-----------------------|-----------|-------------------------|-----------|--------------|-----------|--------------|--|
|                       | IC50 (µM) | R (or alternate R)      | IC50 (µM) | R            | IC50 (µM) | R            |  |
| CYP1A2                | >50       | <1.010                  | NI        | -            | NI        | -            | No   |
| CYP2B6                | 15        | 1.033                   | 13        | <b>1.163</b> | 13        | <b>1.141</b> | Yes  |
| CYP2C8                | 40        | 1.012                   | >50       | <1.042       | >50       | <1.037       | No   |
| CYP2C9                | 12        | 1.041                   | 9.2       | <b>1.230</b> | 11        | <b>1.167</b> | Yes  |
| CYP2C19               | >50       | <1.010                  | >50       | <1.042       | 50        | 1.037        | No   |
| CYP2D6                | >50       | <1.010                  | NI        | -            | >50       | <1.037       | No   |
| CYP3A4 (Midazolam)    | 19        | 1.026<br><b>(26.02)</b> | 35        | 1.061        | 44        | 1.042        | Yes  |
| CYP3A4 (Testosterone) | >50       | <1.010                  | >50       | <1.042       | >50       | <1.037       | No   |

NI = no inhibition observed; OCA = obeticholic acid;  $R = 1 + [I]/K_i$  (or alternate  $R = 1 + [I]_{gut}/K_i$ ), whereas  $K_i$  was calculated as  $IC_{50}/2$ .

Mean OCA C<sub>max</sub> = 104 ng/ml, mean glyco-OCA C<sub>max</sub> = 506 ng/ml, and mean tauro-OCA C<sub>max</sub> = 484 ng/ml in healthy subjects following 25 mg OCA QD.

In vitro data also suggest that OCA, glyco-OCA, and tauro-OCA are not either a time- or metabolism-dependent inhibitor of the tested CYP enzymes (CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4). There was no shift in the IC<sub>50</sub> values when OCA, glyco-OCA, or tauro-OCA was pre-incubated with human liver microsomes in the absence and presence of NADPH for 30 minutes prior to adding the corresponding probe substrates.

#### 2.5.2.3.1.2 Potential for modulating mRNA expression or activity of CYP enzymes

In vitro studies using human sandwich-cultured hepatocyte system suggest that OCA and its glyco- and tauro-conjugates do not induce CYP enzymes at the therapeutic concentrations. Rather, down regulation of CYP1A2 and CYP3A4 after a 3-day culture was observed. Therefore, co-administration of OCA with drugs that are substrates of CYP1A2 cannot be ruled out.

*Induction:* In vitro study with human sandwich-cultured hepatocytes suggests OCA, glyco-OCA, and tauro-OCA do not induce the CYP mRNA levels (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) to any significant extent at concentrations of 0.003 - 3 µM for OCA, glyco-OCA, or tauro-OCA. For CYP1A2, CYP2B6, and CYP3A4, enzyme activity assays also suggest no induction by OCA, glyco-OCA, and tauro-OCA.

*Down-regulation:* However, the mRNA down-regulation was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by OCA, glyco-OCA, and tauro-OCA. CYP1A2 mRNA levels decreased more than 50% (i.e., a two-fold suppression) in two of the three donors as compared to the vehicle control, with the largest fold reduction of 7.9-fold. CYP3A4 mRNA

levels decreased more than 50% in all three donors, with the largest fold reduction of 21.9-fold. The activities for CYP1A2 and CYP3A4 also tended to decrease in a concentration-dependent fashion by all three analytes.

**Reviewer’s comments:** Cytotoxicity was observed at OCA concentrations  $\geq 1 \mu\text{M}$  in a study using fresh human hepatocytes by measuring lactate dehydrogenase (LDH) (Report 8261773). However, no cytotoxicity was observed in human sandwich-cultured hepatocytes for OCA, glyco-OCA, and tauro-OCA at concentrations up to 100  $\mu\text{M}$  (Report #ICPT-1002-3). Literature review suggests that human sandwich-cultured hepatocyte system is more physiologically appropriate in vitro hepatocyte preparation that maintains hepatic cytomorphology and function, thus more representative of what should be expected in the *in vivo* setting (Swift B, et al. Drug Metab Rev. 2010 August ; 42(3): 446–471). Additionally, reviewers’ literature search did not find any data to support the effect of FXR activation on CYP1A2 mRNA down regulation.

### 2.5.2.3.2 ***In vivo* studies: OCA as a perpetrator drug**

#### 2.5.2.3.2.1 **Effect of OCA on midazolam, a sensitive CYP3A substrate**

Effect of multiple doses of OCA 10 and 25 mg on CYP3A substrate midazolam was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-109). Single oral dose of 2 mg midazolam was given on Day 1 and Day 19. OCA 10 or 25 mg QD alone was given for 13 days before the second dose of midazolam.

Following multiple doses of OCA 10 mg QD, no change in systemic exposures (AUC<sub>inf</sub> and C<sub>max</sub>) to midazolam was found (Table 31 and Table 32). Minimal change in systemic exposures in alpha-hydroxymidazolam was found.

However, following multiple doses of OCA 25 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of midazolam increased by 26% and 17%, respectively (Table 31 and Table 32). AUC<sub>inf</sub> and C<sub>max</sub> of alpha-hydroxymidazolam increased by 6% only.

No dose adjustment is needed when 10 mg OCA is co-administered with a CYP3A substrate.

Table 31: Statistical analysis of C<sub>max</sub> and AUC<sub>inf</sub> of midazolam

| Treatment Arm | Parameter          | N  | GMR   | 90% CI        |
|---------------|--------------------|----|-------|---------------|
| 10 mg QD      | AUC <sub>inf</sub> | 23 | 1.02  | 0.930 – 1.119 |
|               | C <sub>max</sub>   | 24 | 1.017 | 0.919 – 1.126 |
| 25 mg QD      | AUC <sub>inf</sub> | 23 | 1.259 | 1.135 – 1.397 |
|               | C <sub>max</sub>   | 23 | 1.173 | 1.052 – 1.309 |

Table 32: Statistical analysis of C<sub>max</sub> and AUC<sub>inf</sub> of alpha-hydroxymidazolam

| Treatment Arm | Parameter          | N  | GMR   | 90% CI        |
|---------------|--------------------|----|-------|---------------|
| 10 mg QD      | AUC <sub>inf</sub> | 18 | 1.074 | 0.933 – 1.236 |
|               | C <sub>max</sub>   | 24 | 1.038 | 0.905 – 1.191 |
| 25 mg QD      | AUC <sub>inf</sub> | 20 | 1.052 | 0.949 – 1.166 |
|               | C <sub>max</sub>   | 23 | 1.059 | 0.940 – 1.192 |

### 2.5.2.3.2.2

#### Effect of OCA on caffeine, a sensitive substrate of CYP1A2

Effect of multiple doses of OCA 10 and 25 mg on CYP1A2 substrate caffeine was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-109). Single oral dose of 200 mg caffeine was given on Day 1 and Day 19. OCA 10 or 25 mg QD alone was given for 14 days before the second dose of caffeine.

Following multiple doses of OCA 10 mg QD, AUCinf and Cmax of caffeine increased by 42% and 6%, respectively (Table 33 and Table 34). AUCinf and Cmax of paraxanthine decreased by about 6% and 23%, respectively.

Following multiple doses of OCA 25 mg QD, AUCinf and Cmax of caffeine increased by 65% and 10%, respectively (Table 33 and Table 34). AUCinf and Cmax of paraxanthine decreased by 2% and 28%, respectively.

Table 33: Statistical analysis of AUCinf and Cmax of caffeine

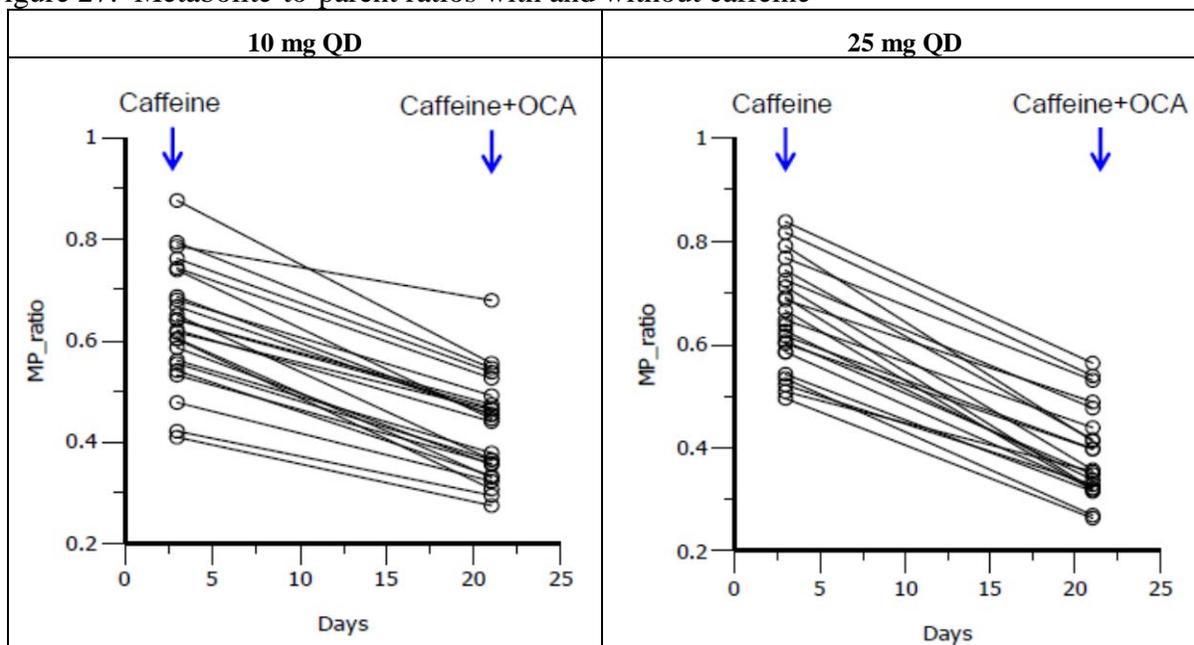
| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 24 | 1.417 | 1.350 - 1.488 |
|               | Cmax      | 24 | 1.061 | 1.014 - 1.111 |
| 25 mg QD      | AUCinf    | 21 | 1.654 | 1.557 - 1.747 |
|               | Cmax      | 21 | 1.099 | 1.043 - 1.159 |

Table 34: Statistical analysis of AUCinf and Cmax of paraxanthine

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 24 | 0.944 | 0.910 - 0.979 |
|               | Cmax      | 24 | 0.768 | 0.738 - 0.800 |
| 25 mg QD      | AUCinf    | 21 | 0.977 | 0.928 - 1.028 |
|               | Cmax      | 21 | 0.720 | 0.679 - 0.763 |

The changes of metabolite-to-parent ratio of AUCinf are shown in the figure below. The CYP1A2 activity appeared to be inhibited in every subject with co-administration of OCA. The inhibition was dose dependent.

Figure 27: Metabolite-to-parent ratios with and without caffeine



Source data: Reviewer's analysis

It is noteworthy that paraxanthine is also metabolized by CYP1A2 which may complicate the interpretation of this study. No published literature indicates that activation of FXR will lead to down regulation of CYP1A2. In vitro results did not show inhibitory effect of OCA on CYP1A2. The only evidence of CYP1A2 mRNA down regulation was found in an induction study.

An in vivo study with another sensitive CYP1A2 substrate (e.g. theophylline) would complement the interpretation of OCA effect on CYP1A2. Meanwhile, therapeutic monitoring should be implemented when OCA is co-administered with a CYP1A2 sensitive substrate which has narrow therapeutic index.

### 2.5.2.3.2.3 Effect of OCA on warfarin, a sensitive substrate of CYP2C9

Effect of multiple doses of OCA 10 and 25 mg on CYP2C9 substrate warfarin was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-110). Single oral dose of 25 mg warfarin was given on Day 1 and Day 21. OCA 10 or 25 mg QD alone was given for 13 days before the second dose of warfarin.

Following multiple doses of OCA 10 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of S-warfarin increased by 13% and 12%, respectively (Table 35). The maximum INR (E<sub>max</sub>) decreased by 11.1% while the accumulative INR (AUEC<sub>0-168h</sub>) in 24 hours decreased by 3.3% (Table 36).

Following multiple doses of OCA 25 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of S-warfarin increased by 18% and 6%, respectively (Table 35). The maximum INR (E<sub>max</sub>) decreased by 7.2% while the accumulative INR (AUEC<sub>0-168h</sub>) in 24 hours decreased by 1.8% (Table 36).

Table 35: Statistical analysis of AUCinf and Cmax of S-warfarin

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 21 | 1.126 | 1.097 - 1.155 |
|               | Cmax      | 21 | 1.120 | 1.052 - 1.193 |
| 25 mg QD      | AUCinf    | 22 | 1.181 | 1.142 - 1.220 |
|               | Cmax      | 22 | 1.058 | 0.990 - 1.131 |

Table 36: Statistical analysis of AUEC0-168h and Emax of INR

| Treatment Arm | Parameter  | N  | GMR   | 90% CI        |
|---------------|------------|----|-------|---------------|
| 10 mg QD      | AUEC0-168h | 21 | 0.967 | 0.947 - 0.988 |
|               | Emax       | 21 | 0.889 | 0.852 - 0.927 |
| 25 mg QD      | AUEC0-168h | 22 | 0.982 | 0.963 - 1.002 |
|               | Emax       | 22 | 0.928 | 0.896 - 0.962 |

Although the systemic exposure of S-warfarin was increased following multiple doses of OCA 10 or 25 mg QD, the INR changes were <10% except the Emax change, which was only 1.1% more than 10%, following 10 mg dose. Considering warfarin has a narrow therapeutic index and that this drug interaction study conducted in healthy subjects, monitor INR when OCA is co-administered with warfarin is recommended.

Following 10 mg OCA, AUCinf and Cmax of R-warfarin increased by about 21% and 11%, respectively. Following 25 mg OCA, AUCinf and Cmax of R-warfarin increased by about 32% and 5%, respectively. Increase in systemic exposure to R-warfarin is potentially due to inhibitory effect of OCA on CYP1A2 and CYP3A. However, the anticoagulation effect of warfarin is due to of S-warfarin and not R-warfarin. Thus, changes in R-warfarin have no clinical relevance.

#### 2.5.2.3.2.4 Effect of OCA on omeprazole, a sensitive substrate of CYP2C19 and moderate CYP2C19 inhibitor

Effect of multiple doses of OCA 10 and 25 mg on CYP2C19 substrate omeprazole was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-112). Single oral dose of 20 mg omeprazole was given on Day 1 and Day 18. OCA 10 or 25 mg QD was given for 17 days before the second dose of omeprazole.

Following multiple doses of OCA 10 mg QD, AUCinf and Cmax of omeprazole increased by 32% and 33%, respectively (Table 37). AUCinf and Cmax of 5-hydroxy-omeprazole increased by about 19% and 17%, respectively (Table 38).

Table 37: Statistical analysis of AUCinf and Cmax of omeprazole

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 21 | 1.321 | 1.217 – 1.434 |
|               | Cmax      | 23 | 1.327 | 1.167 – 1.508 |
| 25 mg QD      | AUCinf    | 19 | 1.366 | 1.242 – 1.502 |
|               | Cmax      | 24 | 1.148 | 0.965 – 1.366 |

Table 38: Statistical analysis of AUCinf and Cmax of 5-hydroxy-omeprazole

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 23 | 1.193 | 1.108 – 1.285 |
|               | Cmax      | 23 | 1.167 | 1.047 – 1.299 |
| 25 mg QD      | AUCinf    | 24 | 1.182 | 1.117 – 1.251 |
|               | Cmax      | 24 | 1.034 | 0.908 – 1.177 |

The increase in systemic exposure of omeprazole does not have clinical effect as omeprazole can be dosed up to 60 mg QD.

Following multiple doses of OCA 25 mg QD, AUCinf and Cmax of omeprazole increased by 36% and 15%, respectively (Table 37). AUCinf and Cmax of 5-hydroxy-omeprazole increased by about 18% and 3.4%, respectively (Table 38).

#### 2.5.2.3.2.5 Effect of OCA on dextromethorphan, a sensitive substrate of CYP2D6

Effect of multiple doses of OCA 10 and 25 mg on CYP2D6 substrate dextromethorphan (DXM) was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-112). Single oral dose of 30 mg DXM was given on Day 1 and Day 18. OCA 10 or 25 mg QD was given for 17 days before the second dose of DXM.

Following multiple doses of OCA 10 mg QD, AUCinf and Cmax of DXM decreased by 11% and 12%, respectively (Table 39). AUCinf and Cmax of dextrophan increased by about 6.7% and 7.1%, respectively (Table 40).

Following multiple doses of OCA 25 mg QD, AUCinf and Cmax of DXM decreased by 11% and 17.4%, respectively (Table 39). AUCinf and Cmax of dextrophan increased by about 5.9% and 9%, respectively (Table 40).

Table 39: Statistical analysis of AUCinf and Cmax of DXM

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 19 | 0.891 | 0.747 - 1.063 |
|               | Cmax      | 23 | 0.879 | 0.725 - 1.065 |
| 25 mg QD      | AUCinf    | 19 | 0.895 | 0.785 - 1.021 |
|               | Cmax      | 24 | 0.826 | 0.728 - 0.937 |

Table 40: Statistical analysis of AUCinf and Cmax of dextrophan

| Treatment Arm | Parameter | N  | GMR   | 90% CI      |
|---------------|-----------|----|-------|-------------|
| 10 mg QD      | AUCinf    | 22 | 1.067 | 0.917-1.241 |
|               | Cmax      | 23 | 1.071 | 0.907-1.265 |
| 25 mg QD      | AUCinf    | 23 | 1.059 | 0.973-1.153 |
|               | Cmax      | 24 | 1.090 | 0.970-1.226 |

The changes in systemic exposures to DXM and dextrophan are small. Thus, no dose adjustment is needed when co-administering a CYP2D6 substrate with OCA.

## 2.5.2.4 Is the drug a substrate and/or an inhibitor of transport processes?

### 2.5.2.4.1 *In vitro* studies

#### Substrate

Based on the *in vitro* study results, OCA, glyco-OCA, and tauro-OCA are not substrates for BCRP, MRP2, MRP3, or MRP4, and are weak substrates for P-gp.

OCA is not a substrate for bile salt export pump (BSEP), apical sodium dependent bile acid transporter (ASBT), sodium/taurocholate cotransporting polypeptide (NTCP), MATE1, MATE2-K, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, or OCT2.

Glyco-OCA and tauro-OCA are substrates for ASBT, NTCP, OAT3, OATP1B1, and OATP1B3, but not for MATE1, MATE2-K, OAT1, OCT1, or OCT2 transporters. Additionally, tauro-OCA is a substrate for BSEP.

**Reviewer's comment:** In the *in vitro* bi-directional transporter assay (Report XBL13694), OCA and its conjugates (glyco-OCA and tauro-OCA) appeared not to be substrates for P-gp in the MDR1-expressing membrane vesicles; however, they were found to be substrates for P-gp in the MDR1-transfected MDCKII cell line. In a separate bi-directional transporter assay with human Caco-2 cells (Report XBL14661), the results indicate that OCA and its two conjugates are not a substrate of P-gp as the net flux ratios were <2 at concentrations of 1-25  $\mu\text{M}$ ). Considering the totality of the data, OCA, glyco-OCA and tauro-OCA are considered weak P-gp substrates.

#### Inhibition

*In vitro* studies indicated that there is potential for OCA and its conjugates to inhibit OATP1B1 and OATP1B3, but not other transporters. The details are given below.

Inhibition of p-gp, breast cancer resistance protein transporter (BCRP), organic acid transporter proteins (OATP), organic cation transporters (OCT), organic anion transporters (OAT), bile-salt export pump (BSEP), sodium/taurocholate co-transporting peptide (NTCP), multidrug resistance-associated proteins (MRP), apical sodium dependent bile acid transporter (ASBT), and multidrug and toxin extrusion (MATE) transporters by OCA, glyco-OCA, and tauro-OCA was studied *in vitro*.

*In vitro* studies suggest that OCA and glyco-OCA inhibit p-gp and BCRP in a concentration-dependent manner. Tauro-OCA does not show obvious inhibition of p-gp up to 300  $\mu\text{M}$  concentration and slightly inhibits BCRP with  $\text{IC}_{50} > 300 \mu\text{M}$ . In addition, OCA, glyco-OCA, and tauro-OCA inhibit OAT3, OATP1B1, OATP1B3, NTCP1, BSEP, MRP2, MRP3, MRP4, ASBT, and OCT1 in a concentration-dependent manner. OCA and tauro-OCA also inhibit OAT1 in a concentration-dependent manner.

Following 10 mg QD dosing (i.e., the proposed highest dosage), the calculated  $[\text{I}]/\text{IC}_{50}$  values for most transporters were less than the cut-off value of 0.1, except for OATP1B1 and OATP1B3, and the calculated  $[\text{I}]_{\text{gut}}/\text{IC}_{50}$  value for BCRP was less than the cut-off value of 10 (Table 41). Thus, significant drug interaction via inhibition of transporters appears unlikely based on the calculated  $[\text{I}]/\text{IC}_{50}$  (or  $[\text{I}]_{\text{gut}}/\text{IC}_{50}$ ) values, except for OATP1B1/OATP1B3,

whereas an in-vivo drug interaction via inhibition of OATP1B1/OATP1B3 cannot be ruled out. An in vivo drug interaction study with a substrate of OATP1B1/OATP1B3 has been conducted.

At 25 mg QD dose level, the calculated [I]/IC50 values for OATP1B1, OATP1B3, NTCP, and BSEP were greater than the cut-off value of 0.1 (Table 42). It should be noted that BSEP induction was also observed in a separate assay by OCA and its conjugates. In additional, the calculated [I]<sub>gut</sub>/IC50 value for BCRP was greater than the cut-off value of 10.

Table 41: In vitro inhibition of transporters by OCA, glyco-OCA, and tauro-OCA for 10 mg QD dosing.

| Inhibition | OCA       |  | Glyco-OCA |              | Tauro-OCA |              | In vivo DDI study needed based on in vitro data (yes or no) |
|------------|-----------|--|-----------|--------------|-----------|--------------|---|
|            | IC50 (μM) | [I]/IC50 (or [I] <sub>gut</sub> /IC50) | IC50 (μM) | [I]/IC50     | IC50 (μM) | [I]/IC50     |   |
| MDR1       | >100      | <0.003                                 | >100      | <0.004       | >100      | <0.004       | No  |
| BCRP       | 21.1      | 0.012 (4.5)                            | >300      | <0.002       | 146       | <0.002       | No  |
| OAT1[a]    | 9.86      | 0.0003                                 | 35        | 0.0001       | >30       | <0.004       | No  |
| OAT3[a]    | 4.4       | 0.0006                                 | 10.6      | 0.0004       | 4.46      | 0.001        | No  |
| OATP1B1    | 2.57      | 0.099                                  | 4.05      | <b>0.110</b> | 3.01      | <b>0.138</b> | Yes ([I]/IC50 >0.1)   |
| OATP1B3    | 2.15      | <b>0.118</b>                           | 2.93      | <b>0.152</b> | 2.95      | <b>0.141</b> | Yes ([I]/IC50 >0.1)   |
| OCT2       | >30       | <0.0001                                | >30       | <0.0001      | >30       | <0.0001      | No  |
| NTCP1      | 7.04      | 0.036                                  | 6.83      | 0.065        | 4.99      | 0.083        | No  |
| BSEP       | 13.7      | 0.019                                  | 6.9       | 0.064        | 10.5      | 0.040        | No  |
| MRP2       | 69.4      | 0.004                                  | 126       | 0.004        | 205       | 0.002        | No  |
| MRP3       | 5.64      | 0.045                                  | 14.6      | 0.030        | 51        | 0.008        | No  |
| MRP4       | 45.6      | 0.006                                  | 68.5      | 0.006        | 131       | 0.003        | No  |
| ASBT       | 43.1      | 0.006                                  | 27.2      | 0.016        | 21.5      | 0.019        | No  |
| OCT1       | 30        | 0.008                                  | 93.3      | 0.005        | 138       | 0.003        | No  |
| MATE1      | NA        | -                                      | NA        | -            | NA        | -            | No  |
| MATE2      | NA        | -                                      | NA        | -            | NA        | -            | No  |

[a] Unbound C<sub>max</sub> was used in the calculation of for OAT1 and OAT3.

NA – not applicable, no >50% inhibition was observed under experimental conditions; OCA = obeticholic acid. Mean OCA C<sub>max</sub> = 107 ng/ml (~0.254 μM), mean glyco-OCA C<sub>max</sub> = 212 ng/ml (~0.444 μM), and mean tauro-OCA C<sub>max</sub> = 219 ng/ml (~0.415 μM) in patients with PBC following 10 mg OCA QD.

Table 42: In vitro inhibition of transporters by OCA, glyco-OCA, and tauro-OCA for 25 mg QD dosing.

| Inhibition | OCA       |                           | Glyco-OCA |              | Tauro-OCA |              | In vivo DDI study needed based on in vitro data (yes or no) |
|------------|-----------|---------------------------|-----------|--------------|-----------|--------------|---|
|            | IC50 (µM) | [I]/IC50 (or [I]gut/IC50) | IC50 (µM) | [I]/IC50     | IC50 (µM) | [I]/IC50     |   |
| MDR1       | >100      | <0.002                    | >100      | <0.011       | >100      | <0.009       | No  |
| BCRP       | 21.1      | 0.012 (11.27)             | >300      | <0.004       | 146       | 0.006        | Yes   |
| OAT1[a]    | 9.86      | 0.0003                    | 35        | 0.0003       | >30       | <0.0003      | No  |
| OAT3[a]    | 4.4       | 0.0006                    | 10.6      | 0.0010       | 4.46      | 0.0021       | No  |
| OATP1B1    | 2.57      | 0.096                     | 4.05      | <b>0.262</b> | 3.01      | <b>0.305</b> | Yes   |
| OATP1B3    | 2.15      | <b>0.115</b>              | 2.93      | <b>0.362</b> | 2.95      | <b>0.311</b> | Yes   |
| OCT2       | >30       | <0.0001                   | >30       | <0.0004      | >30       | <0.0003      | No  |
| NTCP       | 7.04      | 0.035                     | 6.83      | <b>0.155</b> | 4.99      | <b>0.184</b> | Yes   |
| BSEP       | 13.7      | 0.018                     | 6.9       | <b>0.154</b> | 10.5      | 0.087        | Yes   |
| MRP2       | 69.4      | 0.004                     | 126       | 0.008        | 205       | 0.004        | No  |
| MRP3       | 5.64      | 0.044                     | 14.6      | 0.073        | 51        | 0.018        | No  |
| MRP4       | 45.6      | 0.005                     | 68.5      | 0.015        | 131       | 0.007        | No  |
| ASBT       | 43.1      | 0.006                     | 27.2      | 0.039        | 21.5      | 0.043        | No  |
| OCT1       | 30        | 0.008                     | 93.3      | 0.011        | 138       | 0.007        | No  |
| MATE1      | NA        | -                         | NA        | -            | NA        | -            | No  |
| MATE2      | NA        | -                         | NA        | -            | NA        | -            | No  |

[a] Unbound Cmax was used in the calculation of for OAT1 and OAT3.

NA – not applicable, no >50% inhibition was observed under experimental conditions; OCA = obeticholic acid.

Mean OCA Cmax = 104 ng/ml, mean glyco-OCA Cmax = 506 ng/ml, and mean tauro-OCA Cmax = 484 ng/ml in healthy subjects following 25 mg OCA QD.

#### 2.5.2.4.2 In vivo study – Effect of OCA on digoxin, a P-gp substrate

Effect of multiple doses of OCA 10 and 25 mg on P-gp substrate digoxin was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-114). Single oral dose of 0.25 mg digoxin was given on Day 1 and Day 19. OCA 10 or 25 mg QD was given alone for 13 days before the second dose of digoxin.

Following multiple doses of OCA 10 mg QD, AUCinf of digoxin increased by 1.2% while Cmax decreased by 3.3% (Table 43). Renal clearance of digoxin remained the same (Table 44).

Following multiple doses of OCA 25 mg QD, AUCinf and Cmax of digoxin are increased by 7.3% and 23.6%, respectively (Table 43). Renal clearance of digoxin is reduced by 2.1% (Table 44).

Table 43: Statistical analysis of AUCinf and Cmax of digoxin

| Treatment Arm | Parameter | N  | GMR   | 90% CI        |
|---------------|-----------|----|-------|---------------|
| 10 mg QD      | AUCinf    | 24 | 1.012 | 0.954 – 1.073 |
|               | Cmax      | 24 | 0.967 | 0.869 – 1.076 |
| 25 mg QD      | AUCinf    | 24 | 1.073 | 0.994 – 1.157 |
|               | Cmax      | 24 | 1.236 | 1.083 – 1.411 |

Table 44: Statistical analysis of renal clearance (CL<sub>r</sub>) of digoxin

| Treatment Arm | N  | GMR   | 90% CI        |
|---------------|----|-------|---------------|
| 10 mg QD      | 24 | 0.990 | 0.927 – 1.057 |
| 25 mg QD      | 24 | 0.979 | 0.902 – 1.061 |

No dose adjustment is needed when 10 mg OCA is co-administered with digoxin.

### 2.5.2.4.3 In vivo study – Effect of OCA on rosuvastatin, a substrate of OATP1B1, OATP1B3, and BCRP

Effect of multiple doses of OCA 10 and 25 mg on rosuvastatin (RSV), a substrate of OATP1B1, OATP1B3, and BCRP was evaluated in a fixed-sequence and 2-period study in healthy subjects (Study 747-111). Single oral dose of 20 mg RSV was given on Day 1 and Day 19. OCA 10 or 25 mg QD was given for 13 days before the second dose of RSV.

Following multiple doses of OCA 10 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of RSV increased by 22% and 27%, respectively (Table 45). AUC<sub>inf</sub> of N-desmethyl-RSV increased by 1.1% while C<sub>max</sub> of N-desmethyl-RSV decreased by 1.3% (Table 46).

Following multiple doses of OCA 25 mg QD, AUC<sub>inf</sub> and C<sub>max</sub> of RSV increased by 30% and 26%, respectively (Table 45). AUC<sub>inf</sub> and C<sub>max</sub> of N-desmethyl-RSV decreased by 15% and 17%, respectively (Table 46).

Table 45: Statistical analysis of AUC<sub>inf</sub> and C<sub>max</sub> of RSV

| Treatment Arm | Parameter          | N  | GMR   | 90% CI      |
|---------------|--------------------|----|-------|-------------|
| 10 mg QD      | AUC <sub>inf</sub> | 24 | 1.219 | 1.125-1.321 |
|               | C <sub>max</sub>   | 24 | 1.272 | 1.150-1.408 |
| 25 mg QD      | AUC <sub>inf</sub> | 24 | 1.296 | 1.158-1.450 |
|               | C <sub>max</sub>   | 24 | 1.258 | 1.092-1.451 |

Table 46: Statistical analysis of AUC<sub>inf</sub> and C<sub>max</sub> of N-desmethyl-RSV

| Treatment Arm | Parameter          | N  | GMR   | 90% CI      |
|---------------|--------------------|----|-------|-------------|
| 10 mg QD      | AUC <sub>inf</sub> | 24 | 1.011 | 0.920-1.110 |
|               | C <sub>max</sub>   | 24 | 0.987 | 0.886-1.100 |
| 25 mg QD      | AUC <sub>inf</sub> | 19 | 0.848 | 0.728-0.986 |
|               | C <sub>max</sub>   | 24 | 0.832 | 0.714-0.970 |

The changes in systemic exposures to RSV are small. Thus, no dose adjustment is needed when co-administering a substrate of OATP1B1, OATP1B3, and BCRP with OCA.

### 2.5.2.5 Reviewer’s discussion of drug-drug interaction

Summary of in vitro and in vivo drug interaction results are presented in the table below (Table 47).

Table 47: Change of systemic exposure to the victim drugs following co-administration with multiple doses of OCA.

| In vitro finding | Victim Drug(s)   | Multiple Doses of OCA | GMR C <sub>max</sub> | GMR AUC | Conclusions        |
|------------------|--|-----------------------|----------------------|---------|--------------------|
| +                | Midazolam<br>CYP3A substrate                                 | 10 mg                 | 1.017                | 1.02    | Dose dependent     |
|                  |  | 25 mg                 | ↑1.173               | ↑1.259  |                    |
| +                | Caffeine<br>CYP1A2 substrate                                 | 10 mg                 | 1.061                | ↑1.417  | Dose dependent     |
|                  |  | 25 mg                 | 1.099                | ↑1.654  |                    |
| +                | Warfarin<br>CYP2C9 substrate                                 | 10 mg                 | 1.120                | 1.126   |                    |
|                  |  | 25 mg                 | 1.058                | 1.184   |                    |
| -                | Omeprazole<br>CYP2C19 substrate                              | 10 mg                 | ↑1.327               | ↑1.321  | Not dose-dependent |
|                  |  | 25 mg                 | ↑1.148               | ↑1.366  |                    |
| -                | Dextromethorphan<br>CYP2D6 substrate                         | 10 mg                 | ↓0.897               | ↓0.891  | Not dose-dependent |
|                  |  | 25 mg                 | ↓0.826               | ↓0.895  |                    |
| -                | Digoxin<br>P-gp substrate                                    | 10 mg                 | 0.967                | 1.012   |                    |
|                  |  | 25 mg                 | ↑1.236               | 1.073   |                    |
| +                | Rosuvastatin<br>a substrate of OATP1B1,<br>OATP1B3, and BCRP | 10 mg                 | ↑1.272               | ↑1.219  | Not dose-dependent |
|                  |  | 25 mg                 | ↑1.258               | ↑1.296  |                    |

↑: 90%CI exceed 125% upper bound; ↓: 90%CI is less than 80% lower bound

Source data: Reviewer's summary

Among these interactions, the mechanism of inhibition of OCA upon CYP1A2 is not well understood. No inhibition was found in the in vitro inhibition study. However, the mRNA of CYP1A2 was down regulated in the in vitro induction study. Literature search did not suggest that activation of FXR would have resulted in down regulation of CYP1A2 expression. In addition, the metabolism pathway of caffeine indicated that metabolite paraxanthine is further metabolized by CYP1A2. Thus, it is unclear the apparent changes in exposure to caffeine is a result of CYP1A2 down regulation or some other unknown mechanism. Another in vivo DDI study using a sensitive substrate probe (e.g. theophylline) would be necessary to confirm/rule out the involvement of CYP1A2.

#### 2.5.2.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

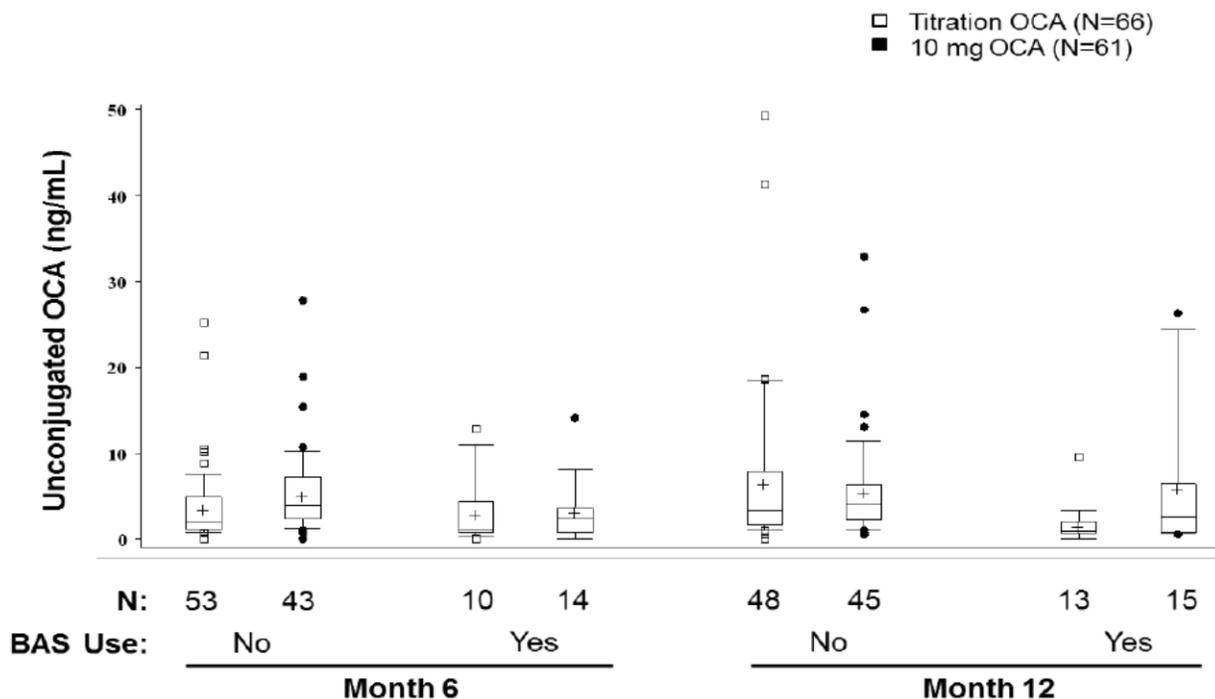
The Sponsor conducted an in vitro equilibrium binding study using bile acid sequestrants,

cholestyramine and colestevlam. Briefly, bile acid sequestrant (0.003 g) was suspended in BES (N,N-Bis(2-hydroxyethyl)-2-aminoethanesulfonic acid) buffer (3 mL, pH=7.2) with OCA, glyco-OCA, or tauro-OCA at an initial concentration of 0.3 to 1.5 mM. The mixture was rigorously stirred for 24 hours at 37°C and then bile acid concentration was determined by using an HPLC-ES-MS/MS method. The study results indicate that bile acid sequestrants (i.e., colestevlam and cholestyramine) bind to OCA, glyco-OCA, and tauro-OCA at the studied in vitro conditions.

No designated drug interaction study with bile acid sequestrants has been conducted for OCA. However, drugs with a known interaction with colestevlam or those have not been tested for interaction with colestevlam should be administered at least 4 hours prior to colestevlam dosing. It is also recommended that other drugs should be taken at least 1 hour before or 4 to 6 hours after cholestyramine to avoid impeding their absorption. As such, it is recommended that bile acid sequestrant be administered at least 4 hours before or 4 hours after (or at as great an interval as feasible) OCA dosing.

The label specifies the co-administration of bile acid binding resins or sequestrants (BAS) for some of the subjects. BAS binds bile acids and prevent their update into entero-hepatic circulation, thus decreasing the bioavailability. The effect of BAS on the PK of OCA and its efficacy was examined in Phase 3 study 747-301. The Phase 3 study protocol specified that subjects taking a BAS should stagger their dosing of OCA (and UDCA) and BAS by at least 4 hours. With these dosing instructions, modestly lower trough concentrations of OCA were observed at Month 6 and Month 12 in subjects taking BAS (Figure 28).

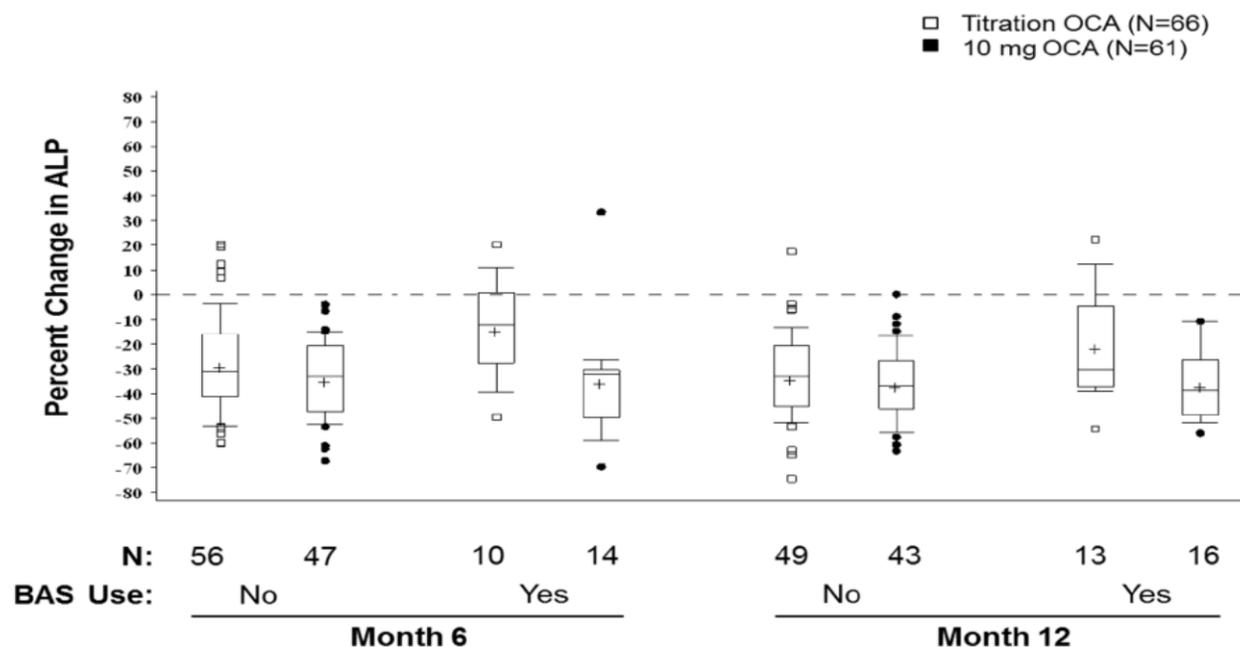
Figure 28: Trough PK concentration of OCA at month 6 and month 12 stratified by BAS use (No/Yes) and dose (5 mg [Titration] OCA and 10 mg OCA) for subjects with PBC in Phase 3 Study 747-301



BSA = bile acid sequestrants; OCA = obeticholic acid; PBC = primary biliary cirrhosis; PK = pharmacokinetic  
Source Data: CSR 747-301, Figure 29

This difference in PK was associated with a modest attenuation of efficacy for the 5 mg dose group but no meaningful effect for the 10 mg dose group (Figure 29). Thus, the same approach of staggered dosing of BAS as followed in Phase 3 protocol is acceptable to us.

Figure 29: Box plots of percent change from Baseline in ALP by BAS exposure (No/Yes) at 6 months and at 12 months in PK population (N = 127) for subjects with PBC in Phase 3 Study 747-301



Source Data: CSR 747-301, Figure 29

## 2.6 GENERAL BIOPHARMACEUTICS

### 2.6.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The drug substance used in OCA drug product appears to be BCS Class II. It is based on its aqueous solubility and CaCo-2 permeability results. The solubility of OCA increases as a function of increasing pH, with a plateau observed at about pH 7 (greater than 500  $\mu\text{M}$ ). The BCS committee review of the data was not requested as this is a Class II substance.

**In vitro permeability:** The bidirectional permeability of OCA, glyco-OCA, and tauro-OCA in Caco-2 cell system was assessed at 1, 10, and 100  $\mu\text{M}$ . Atenolol, labetalol, and antipyrine were included at 10  $\mu\text{M}$  test concentrations in all experiments as the internal low, medium, and high permeability standards, respectively. In the Caco-2 permeability assay, OCA at concentrations of 1-100  $\mu\text{M}$  displayed high absorptive permeability; glyco-OCA and tauro-OCA displayed high absorptive permeability at concentrations of 1 and 10  $\mu\text{M}$  and a saturated absorptive permeability at 100  $\mu\text{M}$ .

Summary of Caco-2 permeability of OCA, glyco-OCA, and tauro-OCA is presented below:

Table 48: In vitro permeability

| Compound                | Concentration<br>( $\mu\text{M}$ ) | $P_{\text{app}}^{\text{a}}$ ( $10^{-6}$ cm/s) |   |
|-------------------------|------------------------------------|---|---|
|                         |                                    | $P_{\text{app}}^{\text{(absorptive) b}}$      | $P_{\text{app}}^{\text{(secretory) c}}$ |
| OCA                     | 1                                  | 27.6  | 10.1                                    |
|                         | 10                                 | 36.2  | 8.62                                    |
|                         | 100                                | 46.1  | 8.79                                    |
| Glyco-OCA               | 1                                  | 22.2  | 11.6                                    |
|                         | 10                                 | 21.3  | 8.48                                    |
|                         | 100                                | 4.67  | 12.4                                    |
| Tauro-OCA               | 1                                  | 28.8  | 9.66                                    |
|                         | 10                                 | 26.7  | 7.65                                    |
|                         | 100                                | 6.64  | 10.3                                    |
| Atenolol <sup>e</sup>   | 10                                 | 0.08  | NA                                      |
| Labetalol <sup>e</sup>  | 10                                 | 7.01  | NA                                      |
| Antipyrine <sup>e</sup> | 10                                 | 70.7  | NA                                      |

### 2.6.2 What is the composition of the to-be-marketed formulation?

The to-be-marketed formulation of OCA drug product is a commercial image tablet. OCA tablets are formulated as an immediate release solid dosage form available in 2 strengths, 5 mg and 10 mg of OCA drug substance per tablet. The components of the drug product, as well as the quantity, function and quality standard of each component, are summarized in Table 49.

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Table 49: Composition of OCA tablet formulations

| Component                                      | Amount Per Tablet (mg) | Function          | Reference to Quality Standard |
|--|------------------------|-------------------|-------------------------------|
| <b>5 mg tablet</b>                             |                        |                   |                               |
| Obeticholic acid <sup>a</sup>                  | 5.0 <sup>a</sup>       | Active ingredient | (b) (4)                       |
| Microcrystalline cellulose                     | (b) (4)                |                   | NF/Ph. Eur.                   |
| Sodium starch glycolate                        |                        |                   | NF/Ph. Eur.                   |
| Magnesium stearate                             |                        |                   | NF/Ph. Eur.                   |
| Opadry II Yellow coating material <sup>b</sup> | (b) (4)                | Coating material  | (b) (4)                       |
|  |                        |                   | (b) (4) USP/Ph. Eur.          |
| Total weight                                   | 208.0                  |                   |                               |
| <b>10 mg tablet</b>                            |                        |                   |                               |
| Obeticholic acid <sup>a</sup>                  | 10.0 <sup>a</sup>      | Active ingredient | (b) (4)                       |
| Microcrystalline cellulose                     | (b) (4)                |                   | NF/Ph. Eur.                   |
| Sodium starch glycolate                        |                        |                   | NF/ Ph. Eur.                  |
| Magnesium stearate                             |                        |                   | NF/ Ph. Eur.                  |
| <b>10 mg tablet</b>                            |                        |                   |                               |
| Opadry II Yellow coating material <sup>b</sup> | (b) (4)                | Coating material  | (b) (4)                       |
|  |                        |                   | (b) (4) USP/Ph. Eur.          |
| Total weight                                   | 208.0                  |                   |                               |

NF = National Formulary; Ph. Eur. = European Pharmacopeia

<sup>a</sup> OCA drug substance amount added assumes the drug substance content is 100%; actual amount added is adjusted based on the potency of the drug substance lot used; the amount of microcrystalline cellulose is correspondingly decreased.

<sup>b</sup> Refer to Module 3.2.P.4, Control of Excipients, for a summary of the components and composition of Opadry II Yellow (b) (4) Opadry II coating material is manufactured from NF compendial excipients or from colorant meeting compliance with Directive 2008/12/EC (formerly 95/45/EC) and Federal Food, Drug, and Cosmetic Act standards.

(b) (4)

Source data: Section 3.2.P.1, Table 1

### 2.6.3 How is the proposed to-be-marketed formulation linked to other formulations used in the clinical studies?

Four formulations were used in the clinical development program of OCA. Formulations used in the clinical studies are shown in Table 50 and Table 51.

Table 50: Drug product formulations used in clinical studies listed by individual study

| Clinical Study Number | Study Title   | (b) (4) |
|-----------------------|---|---------|
| 747-101               | A Single-Center, Single-Dose, Double-Blind, Dose-Escalation Study to Determine the Initial Safety and Tolerability of INT-747 (6-ECDCA)   |         |
| 747-102               | A Single-Center, Multi-Dose, Double-Blind, Dose-Escalation Study to Determine the Safety and Tolerability of INT-747 (6-ECDCA)  |         |
| D8601002              | A Double-Blind, Placebo-Controlled, Randomized, Ascending Single-Dose and Multiple-Dose Study to Investigate the Safety and Pharmacokinetics of DSP-1747 and Open-Label, Single-Dose, Two-Period, Crossover Study to Determine the Effect of Food on the Pharmacokinetics of DSP-1747 in Healthy Japanese Male Subjects |         |
| 747-103               | An Open-Label, Single-Dose Trial to Assess the Effects of Hepatic Impairment on the Pharmacokinetics of Obeticholic Acid (OCA)  |         |
| 747-104               | An Open-Label Trial to Assess the Effects of Food on the Pharmacokinetic Parameters of Obeticholic Acid (OCA)   |         |
| 747-105               | An Open-Label, Randomized, Single-Dose and Multiple-Dose Trial to Assess the Pharmacokinetics of Obeticholic Acid (OCA)   |         |
| 747-107               | An Open-Label Pilot Trial to Identify an Appropriate Dosing Regimen of Obeticholic Acid (OCA) for the Study of QT Intervals in Healthy Subjects   |         |
| 747-108               | A Randomized, Double-blind, Double-Dummy, Placebo- and Positive-controlled, Parallel-group Trial to Assess the Electrophysiological Effects of Obeticholic Acid at Therapeutic and Supratherapeutic Concentrations on the 12-Lead Electrocardiogram QT Interval in Healthy Subjects                                     |         |
| 747-109               | Drug Interaction Trial to Assess the Effect of Obeticholic Acid on the Single Dose Plasma Pharmacokinetics of Midazolam and Caffeine in Healthy Adult Subjects.   |         |
| 747-110               | Drug Interaction Trial to Assess the Effect of Obeticholic Acid on the Single-Dose Plasma Pharmacokinetics and Pharmacodynamics of Warfarin in Healthy Adult Subjects   |         |
| 747-111               | Drug Interaction Trial to Assess the Effect of Obeticholic Acid on the Single-Dose Plasma Pharmacokinetics of Rosuvastatin in Healthy Adult Subjects  |         |
| 747-112               | Drug Interaction Trial to Assess the Effect of Obeticholic Acid on the Single Dose Plasma Pharmacokinetics of Dextromethorphan and Omeprazole and the Effect of Omeprazole on Obeticholic Acid Pharmacokinetics in Healthy Adult Subjects   |         |
| 747-113               | A Phase 1, Open-Label Trial of the Absorption, Metabolism, Excretion, and Absolute Bioavailability of Obeticholic Acid in Healthy Male Subjects   |         |

| Clinical Study Number                                 | Study Title   | (b) (4)            |
|---|---|--------------------|
| 747-114   | Drug Interaction Trial to Assess the Effect of Obeticholic Acid on the Single-Dose Plasma Pharmacokinetics of Digoxin in Healthy Adult Subjects   |                    |
| 747-115   | 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                                |                    |
| 747-116   | An Open-Label, Two-Way Crossover Trial to Assess the Biocomparability of a Capsule Formulation Compared to a Tablet Formulation of Obeticholic Acid After a Single Dose in Healthy Adult Subjects |                    |
| 747-201<br>(Double-blind phase plus safety extension) | A Study of INT-747 (6-ECDCA) Monotherapy in Patients with Primary Biliary Cirrhosis   |                    |
| 747-202<br>(Double-blind phase plus safety extension) | A Study of INT-747 (6-ECDCA) in Combination with Ursodeoxycholic Acid (URSO®, UDCA) in Subjects with Primary Biliary Cirrhosis  |                    |
| 747-203   | An Exploratory Study of OCA in Patients with Type 2 Diabetes Mellitus and Presumed Nonalcoholic Fatty Liver Disease   |                    |
| 747-204   | A Pilot Study to Evaluate the Safety, Tolerability and Efficacy of Obeticholic Acid (INT-747) for the Treatment of Portal Hypertension (PESTO)  |                    |
| 747-205   | A Phase 2 Clinical Trial Investigating the Effects of Obeticholic Acid on Lipoprotein Metabolism in Subjects with Primary Biliary Cirrhosis   |                    |
| 747-301<br>(Double-blind phase plus safety extension) | A Phase 3, Double-Blind, Placebo-Controlled Trial and Long-Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis   |                    |
| LTSE = long-term, safety extension:                   |   | (b) (4)<br>(b) (4) |

Source Data: Section 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

Table 51: Drug product formulations used in clinical studies listed by individual formulation

|   | Drug Product Formulation      | Strength (mg)       | Development Phase  |
|---|-------------------------------|---------------------|--|
| A | Capsules                      | 10, 25 ,<br>50, 100 | 747-101, 747-102<br>Phase 2 supportive studies (747-201 and 747-202), 747-202 LTSE<br>Ongoing 747-201 LTSE   |
| B | Clinical tablets<br>(b) (4)   | 5, 10, 25           | Phase 3 pivotal study (747-301)<br>Phase 1 clinical pharmacology study DSP 8601002<br>Ongoing 747-201 LTSE   |
| C | Commercial tablets<br>(b) (4) | 5, 10, 25           | Phase 1 clinical pharmacology studies (747-103, 747-104, 747-105, and 747-107)<br>Phase 1 clinical pharmacology studies (747-109 and 747-110)<br>Ongoing 747-201 LTSE and 747-301 LTSE Phase 2 study (747-205)<br>Phase 1 clinical pharmacology studies (747-108, 747-111, 747-112, 747-113, 747-114, and 747-115) |
| D | Commercial Image tablets      | 5, 10               | To-be-marketed formulation   |

Source Data: Table 1 of SDN123, IND submission

Formulation bridging studies were conducted between Formulations A and D as well as between Formulations B and D as Formulation B was used in the pivotal Phase 3 study. Since Formulations C and D (b) (4)

The design of the two formulation bridging studies is identical. A single dose two-way crossover design examining the bioequivalence (BE) of the two 10 mg formulations is employed. The results from the two BE studies are provided in Table 52 and Table 53.

### 2.6.3.1 Bridging of clinical capsules and clinical tablets to the to-be-marketed formulation

The capsule formulation is bioequivalent to the to-be-marketed formulation. However, the C<sub>max</sub> of OCA from the to-be-marketed formulation is (b) (4) than the clinical tablet. The upper bound of the 90% CI of geometric mean ratio exceeded 125%, indicating that C<sub>max</sub> of the two formulations are different. However, (b) (4)% difference in C<sub>max</sub> of OCA is not considered clinically meaningful as the conjugates of the OCAs (b) (4). The systemic exposures to the conjugates are several folds of the parent drug with similar pharmacological activity.

Table 52: Statistical analysis of BE of OCA between formulation (b) (4) (A) and commercial image tablet (D) (Study 747-116)

| Analyte   | Parameter                 | Geometric Mean<br>(b) (4) (Test)<br>(N=152) | Geometric Mean<br>Commercial Image<br>Tablet (Reference)<br>(N=152) | Geometric Mean Ratio<br>(Test/Reference) ×<br>100% | 90%<br>Confidence<br>Interval |
|-----------|---------------------------|---|---|--|-------------------------------|
| OCA       | Cmax (ng/mL)              | 32.9  | 35.6  | 92.3   | 84.8, 100                     |
|           | AUC (0-168)<br>(hr•ng/mL) | 126   | 124   | 101  | 95.5, 108                     |
| Glyco-OCA | Cmax (ng/mL)              | 38.3  | 38.3  | 100  | 95.7, 105                     |
|           | AUC (0-168)<br>(hr•ng/mL) | 1170  | 1140  | 103  | 99.9, 106                     |
| Tauro-OCA | Cmax (ng/mL)              | 11.8  | 11.7  | 100  | 95.1, 106                     |
|           | AUC (0-168)<br>(hr•ng/mL) | 471   | 451   | 104  | 99.9, 109                     |

Table 53: Statistical analysis of BE of OCA between formulation clinical tablet (B) and commercial image tablet (D) (Study 747-115)

| Analyte   | Parameter                 | Geometric Mean<br>Commercial Image<br>Tablet (Test)<br>(N=157) | Geometric Mean<br>Clinical Tablet<br>(Reference)<br>(N=157) | Geometric Mean Ratio<br>(Test/Reference) ×<br>100% | 90%<br>Confidence<br>Interval |
|-----------|---------------------------|--|---|--|-------------------------------|
| OCA       | Cmax (ng/mL)              | 36.4   | 30.9  | 118  | 108, 129                      |
|           | AUC (0-168)<br>(hr•ng/mL) | 137  | 131   | 104  | 99.7, 109                     |
| Glyco-OCA | Cmax (ng/mL)              | 40.3   | 39.4  | 102  | 98.1, 107                     |
|           | AUC (0-168)<br>(hr•ng/mL) | 1220   | 1190  | 103  | 99.6, 106                     |
| Tauro-OCA | Cmax (ng/mL)              | 12.4   | 12.9  | 96.2   | 91.1, 102                     |
|           | AUC (0-168)<br>(hr•ng/mL) | 506  | 512   | 98.8   | 94.3, 103                     |

**2.6.4 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?**

The effect of high-fat meal on PK of OCA was evaluated in the single dose, two-period, crossover study in 32 healthy adult subjects. 10 and 25 mg strength clinical tablets were studied. The high fat breakfast meal served during the fed state consisted of 2 whole chicken eggs fried in real butter, 2 strips of fried bacon, 2 slices of white toast with 2 teaspoons of butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk. The amount of calories from fat was approximately 50 percent of total caloric content of the meal.

Administration of 10 mg OCA with a high fat breakfast resulted in an 11% increase in AUC and 4% increase in C<sub>max</sub> of OCA (Table 54). The C<sub>max</sub> and AUC changes in glyco-OCA and tauro-OCA are considered minimal as the 90% CIs of geometric mean ratios are contained within BE boundary of 80% to 125%. The median T<sub>max</sub> was increased by no more than 0.5 hours under fed condition. However, an 11% increase in AUC of OCA under fed condition is unlikely to affect clinical efficacy of OCA. Therefore, 10 mg OCA can be taken without regard to meals.

Table 54: Statistical comparison of C<sub>max</sub> and AUC of 10 mg OCA between fed and fasted states

| Pharmacokinetic Parameter | Geometric LS Means |                          | 10 mg OCA Tablet Fed (Test) Versus Fasted (Reference) |                         |
|---------------------------|--------------------|--------------------------|---|-------------------------|
|                           | 10 mg Fed (Test)   | 10 mg Fasted (Reference) | Geometric LS Mean Ratio (%)                           | 90% Confidence Interval |
| <b>OCA (N=15)</b>         |                    |                          |   |                         |
| AUC <sub>t</sub>          | 158.6              | 142.8                    | 111.1   | 88.0 – 140.2            |
| C <sub>max</sub>          | 40.0               | 38.5                     | 104.0   | 74.2 – 145.9            |
| <b>Glyco-OCA (N=14)</b>   |                    |                          |   |                         |
| AUC <sub>t</sub>          | 1741.5             | 1720.6                   | 101.2   | 88.2 – 116.2            |
| C <sub>max</sub>          | 61.7               | 57.6                     | 107.1   | 91.4 – 125.5            |
| <b>Tauro-OCA (N=14)</b>   |                    |                          |   |                         |
| AUC <sub>t</sub>          | 496.8              | 504.7                    | 98.4  | 84.2 – 115.1            |
| C <sub>max</sub>          | 15.0               | 16.1                     | 93.6  | 81.3 – 107.7            |

Parameters were ln-transformed prior to analysis.

Geometric least-squares (LS) means, mean ratios, and confidence intervals are calculated by exponentiating the LS means from the ANOVA.

Geometric LS Mean Ratio (%) = 100\*(Test/Reference)

Subject 19 was not included in the Evaluable PK Population for glyco-OCA or tauro-OCA, because the predose glyco-OCA and tauro-OCA concentrations in Period 2 were >5% of C<sub>max</sub>.

Per protocol, a snack was scheduled after the PK sample collection at Hour 132. The snack was given prior to the PK sample collection at Hour 132; therefore, the concentration-time data at Hour 132 were excluded from the calculation of the PK parameters for all subjects in both periods for all analytes.

Source: [Table 14.2.1.1.5](#), [Table 14.2.1.2.5](#), and [Table 14.2.1.3.5](#)

As 25 mg is not going to be an approved dose for PBC, the food effect of 25 mg OCA is not summarized here.

### 2.6.5 What is the effect of gastric acid reducing agents on the bioavailability of OCA from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product?

The effect of gastric pH-altering agents (20 mg omeprazole, a proton pump inhibitor) on the absorption of OCA was evaluated in the single dose (10 mg), fixed sequence study fourth period in 48 healthy adult subjects.

Administration of 10 mg OCA with omeprazole 20 mg QD for 4 days resulted in 19% increase in steady-state C<sub>max</sub> and AUC of OCA. C<sub>max</sub> and AUC of glyco-OCA are increased by 20% and 16%, respectively. C<sub>max</sub> and AUC of tauro-OCA are increased by 15% and 13%, respectively. The magnitude of increase in systemic exposure to OCA and its conjugates do not

have a significantly clinical impact.

Administration of 25 mg OCA with omeprazole 20 mg QD for 4 days resulted in 20% and 16% increase in steady-state C<sub>max</sub> and AUC of OCA, respectively. C<sub>max</sub> and AUC of glyco-OCA are increased by 22% and 25%, respectively. C<sub>max</sub> and AUC of tauro-OCA are increased by 28% and 33%, respectively. The proposed maximum clinical dose is 10 mg for PBC.

Table 55: Statistical comparison of C<sub>max</sub> and AUC of 10 mg and 25 mg OCA with or without the presence of omeprazole 20 mg.

| <b>OCA</b>                                 |    |                |           |                          |                     |
|--|----|----------------|-----------|--------------------------|---------------------|
| Treatment Arm<br>OCA PK<br>Parameter       | n  | Geometric LSMs |           | OME+OCA Versus OCA Alone |                     |
|  |    | OME+OCA        | OCA Alone | Geometric LSM<br>Ratio   | 90% CI of the Ratio |
| <b>OCA 10 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 23 | 135.69         | 114.00    | 1.190                    | 1.091 - 1.298       |
| C <sub>max</sub> (ng/mL)                   | 23 | 34.05          | 28.52     | 1.194                    | 0.922 - 1.547       |
| <b>OCA 25 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 24 | 307.67         | 275.72    | 1.116                    | 1.032 - 1.207       |
| C <sub>max</sub> (ng/mL)                   | 24 | 79.84          | 66.57     | 1.199                    | 0.994 - 1.448       |
| <b>Glyco-OCA</b>                           |    |                |           |                          |                     |
| Treatment Arm<br>Glyco-OCA PK<br>Parameter | n  | Geometric LSMs |           | OME+OCA Versus OCA Alone |                     |
|  |    | OME+OCA        | OCA Alone | Geometric LSM<br>Ratio   | 90% CI of the Ratio |
| <b>OCA 10 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 23 | 2250.04        | 1932.10   | 1.165                    | 1.075 - 1.262       |
| C <sub>max</sub> (ng/mL)                   | 23 | 211.95         | 176.14    | 1.203                    | 1.096 - 1.321       |
| <b>OCA 25 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 24 | 6116.98        | 4914.84   | 1.245                    | 1.139 - 1.359       |
| C <sub>max</sub> (ng/mL)                   | 24 | 603.22         | 494.06    | 1.221                    | 1.091 - 1.366       |
| <b>Tauro-OCA</b>                           |    |                |           |                          |                     |
| Treatment Arm<br>Tauro-OCA PK<br>Parameter | n  | Geometric LSMs |           | OME+OCA Versus OCA Alone |                     |
|  |    | OME+OCA        | OCA Alone | Geometric LSM<br>Ratio   | 90% CI of the Ratio |
| <b>OCA 10 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 23 | 1286.95        | 1137.13   | 1.132                    | 1.006 - 1.274       |
| C <sub>max</sub> (ng/mL)                   | 23 | 129.56         | 112.77    | 1.149                    | 1.024 - 1.289       |
| <b>OCA 25 mg Arm</b>                       |    |                |           |                          |                     |
| AUC <sub>tau</sub> (h-ng/mL)               | 24 | 4639.60        | 3480.54   | 1.333                    | 1.240 - 1.433       |
| C <sub>max</sub> (ng/mL)                   | 24 | 482.45         | 376.18    | 1.282                    | 1.160 - 1.418       |

## 2.7 ANALYTICAL SECTION

### 2.7.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. Active metabolites glyco-OCA and tauro-OCA are measured.

### 2.7.2 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

Yes.

The concentrations of OCA, glyco-OCA, and tauro-OCA were determined in plasma and urine using a validated high performance liquid chromatography tandem mass spectrometry (LC/MS/MS) method. Four validated plasma and three validated urine LC/MS/MS methods were developed to characterize the pharmacokinetic properties of OCA and its conjugates. The list of seven validation reports is shown in the two tables below.

Table 56: Plasma Bioanalytical Method Validation Reports

| Report      | Title  |
|-------------|--|
| VAL-RPT-633 | 6-ECDCA, 6-EGCDCA and 6-ETCDCA in Human Plasma via HPLC-MS/MS Assay Validation   |
| RPT01947    | Method Validation of an LC-MS/MS Assay for the Determination of 6-ECDCA (INT-747), 6-EGCDCA and 6-ETCDCA in Human Plasma   |
| RPT02968    | Method Validation of an LC-MS/MS Assay for the Determination of 6-ECDCA (OCA, INT-747) and its Metabolites 6-EGCDCA (G-OCA) and 6-ETCDCA (T-OCA) in Human Plasma |
| PRD11-209   | Validation of Analytical Method of DSP-1747 and its Two Conjugate Metabolites in Human Plasma  |

6-ECDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid; 6-EGCDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid glyco conjugated or glyco-OCA; 6-ETCDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid tauro conjugated or tauro-OCA; HPLC-MS/MS = high performance liquid chromatography with mass spectrometry/mass spectrometry detection; LC-MS/MS = liquid chromatography with mass spectrometry/mass spectrometry detection; OCA = obeticholic acid

Table 57: Urine Bioanalytical Method Validation Reports

| Report      | Title  |
|-------------|--|
| VAL-RPT-560 | 6-ECDCA, 6-EGCDCA and 6-ETCDCA in Human Urine via HPLC-MS/MS Assay Validation  |
| RPT03237    | Method Validation of an LC-MS/MS Assay for the Determination of 6-ECDCA (OCA, INT-747), and its Metabolites 6-EGCDCA (G-OCA) and 6-ETCDCA (T-OCA) in Human Urine |
| PRD11-210   | Validation of Analytical Method of DSP-1747 and its Two Conjugate Metabolites in Human Urine   |

6-ECDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid; 6-EGCDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid glyco conjugated or glyco-OCA; 6-ETCDCA = 6 $\alpha$ -ethyl-chenodeoxycholic acid tauro conjugated or tauro-OCA; HPLC-MS/MS = high performance liquid chromatography with mass spectrometry/mass spectrometry detection; LC-MS/MS = liquid chromatography with mass spectrometry/mass spectrometry detection; OCA = obeticholic acid

A summary of the bioanalytical method validation data (including linearity range, sensitivity, accuracy, and precision) for all analytes in plasma and urine matrices are provided in Table 58 and Table 59 below.

The original LC/MS/MS method used at (b) (4) (VAL-RPT-633) to characterize the plasma PK of OCA, glyco-OCA, and tauro-OCA for Study 747-101 (CSR 747-101) was not sensitive enough to characterize the PK properties after a 50-mg or 100-mg dose with the lower limit of quantitation (LLOQ) being 100 ng/mL. The plasma assay was then validated at (b) (4) (RPT01947) to increase the sensitivity for OCA (LLOQ = 1.00 ng/mL), glyco-OCA (LLOQ = 5.00 ng/mL), and tauro-OCA (LLOQ = 1.00 ng/mL) for Study 747-102 (CSR 747-102). The assay was then further refined at (b) (4) (RPT02968) to increase the sensitivity of OCA, glyco-OCA and tauro-OCA (LLOQ = 0.500 ng/mL for all analytes) and was used for all subsequent analysis of OCA and its conjugates in plasma. The plasma exposures of OCA, glyco-OCA, and tauro-OCA were determined in Japanese subjects from Study D8601002 (CSR D8601002) using a validated method (PRD11-209).

It is noteworthy that, although trough concentrations of OCA and its conjugates were measured in two Phase 2 studies (Study 747-201 and Study 744-202) and reported in the individual clinical study reports (CSR), the Sponsor has stated that these samples were not measured by a validated analytical method.

The elimination of OCA, glyco-OCA, and tauro-OCA in urine was characterized using a validated LC/MS/MS method (VAL-RPT-560) which had a LLOQ of 20.0 ng/mL (CSR 747-101 and CSR 747-102). A more sensitive urine assay was then developed at (b) (4) (RPT03237) with a LLOQ of 1.00 ng/mL and was used in to characterize the elimination of OCA and its conjugates in urine for Study 747-103 (CSR 747-103) and Study 747-105 (CSR 747-105). The urine elimination of OCA, glyco-OCA, and tauro-OCA were determined in Japanese subjects from Study D8601002 (CSR D8601002) using a validated method (PRD11-210).

Table 58: Plasma Bioanalytical Method Validation Summary

| Attribute  | VAL-RPT-633 <sup>a,b</sup>                    |   |   | RPT01947 <sup>b</sup>                        |   |  | RPT02968 <sup>b</sup>                               |   |   | PRD11-209 <sup>b</sup>                       |  |  |
|--|---|---|---|--|---|--|---|---|---|--|--|--|
|  | Analyte                                       |   |   | Analyte                                      |   |  | Analyte   |   |   | Analyte                                      |  |  |
|  | OCA (ng/mL)                                   | Glyco-OCA (ng/mL)                             | Tauro-OCA (ng/mL)                             | OCA (ng/mL)                                  | Glyco-OCA (ng/mL)                           | Tauro-OCA (ng/mL)                            | OCA (ng/mL)   | Glyco-OCA (ng/mL)                                   | Tauro-OCA (ng/mL)                                   | OCA (ng/mL)                                  | Glyco-OCA (ng/mL)                            | Tauro-OCA (ng/mL)                            |
| Standard Concentrations  | 100, 200, 500, 1000, 2500, 5000, 10000, 25000 | 100, 200, 500, 1000, 2500, 5000, 10000, 25000 | 100, 200, 500, 1000, 2500, 5000, 10000, 25000 | 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 250 | 5.00, 10.0, 25.0, 50.0, 100, 250, 500, 1250 | 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 250 | 0.500, 1.00, 2.50, 5.00, 12.5, 25.0, 50.0, 100, 250 | 0.500, 1.00, 2.50, 5.00, 12.5, 25.0, 50.0, 100, 250 | 0.500, 1.00, 2.50, 5.00, 12.5, 25.0, 50.0, 100, 250 | 0.500, 1.00, 3.00, 10.0, 30.0, 100, 300, 500 | 0.500, 1.00, 3.00, 10.0, 30.0, 100, 300, 500 | 0.500, 1.00, 3.00, 10.0, 30.0, 100, 300, 500 |
| Linear Range   | 100 – 25000                                   | 100 – 25000                                   | 100 – 25000                                   | 1.00 – 250                                   | 5.00 – 1250                                 | 1.00 – 250                                   | 0.500 – 250   | 0.500 – 250   | 0.500 – 250   | 0.500 – 500                                  | 0.500 – 500                                  | 0.500 – 500                                  |
| Correlation Coefficient (r) / Correlation Coefficient Determination (r <sup>2</sup> ): <i>4g</i> | r <sup>2</sup> > 0.9952                       | r <sup>2</sup> > 0.9950                       | r <sup>2</sup> > 0.9892                       | r <sup>2</sup> = 0.9913                      | r <sup>2</sup> = 0.9888                     | r <sup>2</sup> = 0.9938                      | r <sup>2</sup> = 0.9955                             | r <sup>2</sup> = 0.9981                             | r <sup>2</sup> = 0.9968                             | r <sup>2</sup> > 0.9976                      | r <sup>2</sup> > 0.9947                      | r <sup>2</sup> > 0.9935                      |
| Accuracy Across Standard Curve Concentrations (% Difference from nominal concentration)          | -0.80 – 6.0                                   | -8.0 – 2.8                                    | -9.0 – 9.0                                    | -5.40 – 6.20                                 | -2.40 – 4.60                                | -7.20 – 5.20                                 | -4.00 – 4.00  | -1.40 – 3.00  | -4.00 – 5.00  | -10.4 – 9                                    | -12.6 – 8.7                                  | -16.0 – 14.0                                 |
| Recovery (%)   | 104.0   | 173.0   | 124.0   | 104.9  | 99.5  | 98.3   | 88.1  | 82.5  | 86.0  | 99.3   | 97.6   | 98.2   |
| Analyte Low  | NA  | NA  | NA  | 100.1  | 98.9  | 99.2   | NA  | NA  | NA  | 99.0   | 100.0  | 96.3   |
| Medium   | 98.0  | 102.0   | 99.0  | 99.1   | 98.4  | 100.6  | 77.6  | 85.2  | 85.5  | 105.8  | 100.7  | 100.0  |
| Analyte High   | 92.0  | 92.0  | 92.0  | 97.1 – 98.1                                  | 95.8 – 98.0                                 | 95.8 – 98.0                                  | 76.3 – 83.1   | 84.3 – 85.7   | 80.9 – 81.6   | 74.6   | 84.6   | 78.8   |
| Internal Standard  |   |   |   |  |   |  |   |   |   |  |  |  |
| LLOQ   | 100   | 100   | 100   | 1.00   | 5.00  | 1.00   | 0.500   | 0.500   | 0.500   | 0.500  | 0.500  | 0.500  |
| ULOQ   | 25000   | 25000   | 25000   | 250  | 1250  | 250  | 250   | 250   | 250   | 500  | 500  | 500  |
| Selectivity *  | 100-120                                       | 100-110                                       | 90.0-120                                      | No interference in the region of interest    | No interference in the region of interest   | No interference in the region of interest    | No interference in the region of interest           | No interference in the region of interest           | No interference in the region of interest           | No interfering peak                          | No interfering peak                          | No interfering peak                          |

| Attribute  | VAL-RPT-633 <sup>a,b</sup>                |   |  | RPT01947 <sup>b</sup>  |  |  | RPT02968 <sup>b</sup>  |   |   | PRD11-209 <sup>b</sup>                 |  |   |
|--|---|---|--|--|--|--|--|---|---|--|--|---|
|  | Analyte                                   |   |  | Analyte  |  |  | Analyte  |   |   | Analyte                                |  |   |
|  | OCA (ng/mL)                               | Glyco-OCA (ng/mL)                       | Tauro-OCA (ng/mL)                        | OCA (ng/mL)  | Glyco-OCA (ng/mL)  | Tauro-OCA (ng/mL)  | OCA (ng/mL)  | Glyco-OCA (ng/mL)   | Tauro-OCA (ng/mL)   | OCA (ng/mL)                            | Glyco-OCA (ng/mL)                      | Tauro-OCA (ng/mL)                       |
| QC Conc.:  |   |   |  |  |  |  |  |   |   |  |  |   |
| QC LLOQ  |   |   |  | 1.00   | 5.00   | 1.00   | 0.500  | 0.500   | 0.500   | NA                                     | NA                                     | NA                                      |
| QCL  | 300                                       | 300                                     | 300                                      | 3.00   | 15.0   | 3.00   | 1.50   | 1.50  | 1.50  | 1.5                                    | 1.5                                    | 1.5                                     |
| QCM  | 2000                                      | 2000                                    | 2000                                     | 100  | 500  | 100  | 100  | 100   | 100   | 20.0                                   | 20.0                                   | 20.0                                    |
| QCH  | 20000                                     | 20000                                   | 20000                                    | 200  | 1000   | 200  | 200  | 200   | 200   | 400                                    | 400                                    | 400                                     |
| Intra-Run Precision (%CV) of Quality Control Samples         | 300 = 6.5<br>2000 = 5.9<br>20000 = 4.3    | 300 = 6.5<br>2000 = 4.5<br>20000 = 4.0  | 300 = 6.5<br>2000 = 7.7<br>20000 = 10.3  | 1.00 = 8.3 – 16.0<br>3.00 = 5.1 – 10.8<br>100 = 1.3 – 5.3<br>200 = 3.8 – 6.6   | 5.00 = 8.2 – 11.9<br>15.0 = 2.0 – 4.1<br>500 = 2.8 – 4.6<br>1000 = 2.2 – 6.5   | 1.00 = 9.0 – 16.6<br>3.00 = 4.5 – 10.6<br>100 = 4.7 – 6.4<br>200 = 4.8 – 7.0       | 0.500 = 3.7 – 6.7<br>1.50 = 3.1 – 5.6<br>100 = 1.9 – 4.8<br>200 = 3.7 – 5.6      | 0.500 = 3.0 – 12.8<br>1.50 = 3.1 – 8.4<br>100 = 3.0 – 4.8<br>200 = 3.9 – 6.0  | 0.500 = 5.0 – 9.9<br>1.50 = 5.0 – 8.6<br>100 = 1.9 – 6.2<br>200 = 1.5 – 3.9   | 1.50 = 3.4<br>20.0 = 1.9<br>400 = 4.6  | 1.50 = 5.8<br>20.0 = 2.4<br>400 = 4.5  | 1.50 = 1.4<br>20.0 = 2.4<br>400 = 4.3   |
| Inter-Run Precision (%CV) of Quality Control Samples         | 300 = 10.3<br>2000 = 6.9<br>20000 = 9.0   | 300 = 3.3<br>2000 = 4.7<br>20000 = 4.8  | 300 = 10.0<br>2000 = 7.2<br>20000 = 10.3 | 1.00 = 13.5<br>3.00 = 7.7<br>100 = 5.1<br>200 = 5.6                            | 5.00 = 9.3<br>15.0 = 4.5<br>500 = 5.5<br>1000 = 6.9                            | 1.00 = 14.1<br>3.00 = 9.8<br>100 = 6.7<br>200 = 6.8                                | 0.500 = 11.9<br>1.50 = 5.1<br>100 = 3.0<br>200 = 4.6                             | 0.500 = 8.9<br>1.50 = 7.5<br>100 = 4.3<br>200 = 5.0                           | 0.500 = 8.7<br>1.50 = 6.2<br>100 = 3.8<br>200 = 2.8                           | 1.50 = 9.3<br>20.0 = 4.8<br>400 = 6.3  | 1.50 = 7.3<br>20.0 = 5.4<br>400 = 6.2  | 1.50 = 4.1<br>20.0 = 5.0<br>400 = 7.2   |
| Intra-Run Accuracy (% Difference) of Quality Control Samples | 300 = 3.3<br>2000 = 1.0<br>20000 = 6.4    | 300 = 3.3<br>2000 = 0.0<br>20000 = 0.3  | 300 = 3.3<br>2000 = 4.0<br>20000 = 8.4   | 1.00 = -3.7 – 8.0<br>3.00 = -3.7 – 1.7<br>100 = -3.4 – 5.0<br>200 = -4.0 – 3.5 | 5.00 = 4.2 – 8.6<br>15.0 = -2.7 – 4.7<br>500 = -3.0 – 6.8<br>1000 = -4.5 – 8.0 | 1.00 = -8.40 – 11.0<br>3.00 = -3.3 – 8.7<br>100 = 1.0 – 10.0<br>200 = -8.50 – -1.5 | 0.500 = -10.2 – 13.4<br>1.50 = 3.3 – 12.0<br>100 = 2.0 – 2.0<br>200 = -1.5 – 2.5 | 0.500 = -4.6 – 1.2<br>1.50 = -3.3 – 8.7<br>100 = 1.0 – 6.0<br>200 = 1.0 – 3.0 | 0.500 = -4.6 – 6.8<br>1.50 = 6.7 – 10.7<br>100 = 6.0 – 8.0<br>200 = 3.5 – 4.0 | 1.50 = -0.7<br>20.0 = 7.0<br>400 = 3.0 | 1.50 = 3.3<br>20.0 = 4.0<br>400 = 1.0  | 1.50 = -1.3<br>20.0 = 4.5<br>400 = 0.0  |
| Inter-Run Accuracy (% Difference) of Quality Control Samples | 300 = -3.3<br>2000 = -6.0<br>20000 = -1.5 | 300 = 0.0<br>2000 = -4.5<br>20000 = 2.9 | 300 = 0.0<br>2000 = -3.0<br>20000 = 0.5  | 1.00 = 1.0<br>3.00 = -1.7<br>100 = 1.0<br>200 = -0.5                           | 5.00 = 5.8<br>15.0 = 1.3<br>500 = 3.2<br>1000 = 1.0                            | 1.00 = 1.0<br>3.00 = 1.3<br>100 = 4.0<br>200 = -6.0                                | 0.500 = 4.8<br>1.50 = 7.3<br>100 = 2.0<br>200 = 0.5                              | 0.500 = -2.2<br>1.50 = 2.7<br>100 = 4.0<br>200 = 2.5                          | 0.500 = 2.4<br>1.50 = 8.0<br>100 = 7.0<br>200 = 3.5                           | 1.50 = 0.0<br>20.0 = 4.5<br>400 = 0.0  | 1.50 = 0.7<br>20.0 = 1.5<br>400 = -3.0 | 1.50 = -2.7<br>20.0 = 0.5<br>400 = -6.0 |

| Attribute                                       | VAL-RPT-633 <sup>a,b</sup>            |                                       |                                       | RPT01947 <sup>b</sup>        |                              |                              | RPT02968 <sup>b</sup>   |   |   | PRD11-209 <sup>b</sup>                  |   |   |
|---|---------------------------------------|---------------------------------------|---------------------------------------|------------------------------|------------------------------|------------------------------|---|---|---|---|---|---|
|   | Analyte                               |                                       |                                       | Analyte                      |                              |                              | Analyte   |   |   | Analyte                                 |   |   |
|   | OCA (ng/mL)                           | Glyco-OCA (ng/mL)                     | Tauro-OCA (ng/mL)                     | OCA (ng/mL)                  | Glyco-OCA (ng/mL)            | Tauro-OCA (ng/mL)            | OCA (ng/mL)   | Glyco-OCA (ng/mL)   | Tauro-OCA (ng/mL)   | OCA (ng/mL)                             | Glyco-OCA (ng/mL)                       | Tauro-OCA (ng/mL)                       |
| Stability                                       |                                       |                                       |                                       |                              |                              |                              |   |   |   |   |   |   |
| Substock Standard Solution Stability in Solvent | At least 3 months at 4°C in methanol. | At least 3 months at 4°C in methanol. | At least 3 months at 4°C in methanol. | NA                           | NA                           | NA                           | ~6 hours at room temperature in methanol<br>363 days at -20°C in methanol | ~6 hours at room temperature in methanol<br>363 days at -20°C in methanol | ~6 hours at room temperature in methanol<br>363 days at -20°C in methanol | At least 3 months at 4°C in methanol    | At least 3 months at 4°C in methanol    | At least 3 months at 4°C in methanol    |
| Freeze and Thaw Stability                       | Three freeze/thaw cycles              | Three freeze/thaw cycles              | Three freeze/thaw cycles              | Three freeze/thaw cycles     | Three freeze/thaw cycles     | Three freeze/thaw cycles     | Five freeze/thaw cycles   | Five freeze/thaw cycles   | Five freeze/thaw cycles   | Five freeze/thaw cycles                 | Five freeze/thaw cycles                 | Five freeze/thaw cycles                 |
| Dilution Integrity                              | 20000 ng/mL diluted 10-folds          | 20000 ng/mL diluted 10-folds          | 20000 ng/mL diluted 10-folds          | 200 ng/mL diluted 10-folds   | 1000 ng/mL diluted 10-folds  | 200 ng/mL diluted 10-folds   | 1000 ng/mL diluted 5-folds  | 1000 ng/mL diluted 5-folds  | 1000 ng/mL diluted 5-folds  | 2000 ng/mL diluted 10-fold and 100-fold | 2000 ng/mL diluted 10-fold and 100-fold | 2000 ng/mL diluted 10-fold and 100-fold |
| Storage Stability at room temperature           | At least 24 hours                     | At least 24 hours                     | At least 24 hours                     | At least 18 hours            | At least 26 hours            | At least 28 hours            | At least 24 hours   | At least 24 hours   | At least 24 hours   | At least 24 hours                       | At least 24 hours                       | At least 24 hours                       |
| Storage Stability refrigerated (2-6°C)          | at least 24 hours                     | at least 24 hours                     | at least 24 hours                     | NA                           | NA                           | NA                           | NA  | NA  | NA  | 15 days                                 | 15 days                                 | 15 days                                 |
| Long-Term Stability -20°C ≤ -70 °C <sup>f</sup> | Under investigation at <-60°C         | Under investigation at <-60°C         | Under investigation at <-60°C         | 803 days                     | 760 days                     | 762 days                     | 94 days   | 94 days   | 47 days   | 99 days                                 | 100 days                                | 100 days                                |
| Stability of Processed Samples                  | At least 24 hours at room temperature | At least 24 hours at room temperature | At least 24 hours at room temperature | ~11 days at room temperature | ~11 days at room temperature | ~11 days at room temperature | ~115 hours at 4°C<br>~118 hours at room temperature                       | ~115 hours at 4°C<br>~118 hours at room temperature                       | ~115 hours at 4°C<br>~118 hours at room temperature                       | At least 72 hours at 4°C                | At least 72 hours at 4°C                | At least 72 hours at 4°C                |

CV = coefficient of variation; glyco-OCA = glyco-obeticholic acid; LLOQ = lower limit of quantification; NA = not available; OCA = obeticholic acid; QCH = QC high; QCL = QC low; QC LLOQ = quality control lower limit of quantitation; QCM = QC medium; r<sup>2</sup> = coefficient of determination; tauro-OCA = tauro-obeticholic acid; ULOQ = upper limit of quantification

<sup>a</sup> For the method validation VAL-RPT-633, the concentration units were µg/mL but for comparison purposes the units were converted to ng/mL.

<sup>b</sup> Sodium heparin was used as anti-coagulant in VAL-RPT-633, RPT01947 and PRD11-209, and K<sub>2</sub>EDTA was used as anti-coagulant in RPT02968.

<sup>c</sup> For the method validation VAL-RPT-633, the coefficient of determination (r<sup>2</sup>) was determined by a weighted (1/concentration<sup>2</sup>) 2nd order quadratic regression for OCA and glyco-OCA. The coefficient of determination was determined by a weighted (1/ peak area ratio<sup>2</sup>) 2nd order quadratic regression for tauro-OCA. The peak area ratio = drug peak area/internal standard peak area.

<sup>d</sup> For the method validation RPT01947, RPT02968, and PRD11-209, the coefficient of determination was determined by a weighted (1/concentration<sup>2</sup>) 2nd order quadratic regression for OCA, glyco-OCA and tauro-OCA.

<sup>e</sup> The spiking concentration was 100 ng/ml and the value acceptable range was 90.0 – 120.

<sup>f</sup> For the method validation PRD11-209 ≤ -80 °C.

<sup>g</sup> For the method validation RPT01947 and RPT02968, the mean was reported.

Table 59: Urine Bioanalytical Method Validation Summary

| Attribute  | VAL-RPT-560*                 |                              |                               | RPT03237                                   |  |  | PRD11-210                    |                                |                               |
|--|------------------------------|------------------------------|-------------------------------|--|--|--|------------------------------|--------------------------------|-------------------------------|
|  | Analyte                      |                              |                               | Analyte                                    |  |  | Analyte                      |                                |                               |
|  | OCA (ng/mL)                  | Glyco-OCA (ng/mL)            | Tauro-OCA (ng/mL)             | OCA (ng/mL)                                | Glyco-OCA (ng/mL)                          | Tauro-OCA (ng/mL)                          | OCA (ng/mL)                  | Glyco-OCA (ng/mL)              | Tauro-OCA (ng/mL)             |
| Standard Concentrations  | 20,                          | 20,                          | 20,                           | 1.00,                                      | 1.00,                                      | 1.00,                                      | 20.0,                        | 20.0,                          | 20.0,                         |
|  | 50,                          | 50,                          | 50,                           | 2.00,                                      | 2.00,                                      | 2.00,                                      | 40.0,                        | 40.0,                          | 40.0,                         |
|  | 200,                         | 200,                         | 200,                          | 5.00,                                      | 5.00,                                      | 5.00,                                      | 120,                         | 120,                           | 120,                          |
|  | 500,                         | 500,                         | 500,                          | 25.0,                                      | 25.0,                                      | 25.0,                                      | 400,                         | 400,                           | 400,                          |
|  | 1000,                        | 1000,                        | 1000,                         | 50.0,                                      | 50.0,                                      | 50.0,                                      | 1200,                        | 1200,                          | 1200,                         |
|  | 2500,                        | 2500,                        | 2500,                         | 250,                                       | 250,                                       | 250,                                       | 4000,                        | 4000,                          | 4000,                         |
|  | 5000,                        | 5000,                        | 5000,                         | 450,                                       | 450,                                       | 450,                                       | 12000,                       | 12000,                         | 12000,                        |
| 10000  | 10000                        | 10000                        | 500                           | 500  | 500  | 20000                                      | 20000                        | 20000                          |                               |
| Linear Range   | 20 – 10000                   | 20 – 10000                   | 20 – 10000                    | 1.00 - 500                                 | 1.00 - 500                                 | 1.00 - 500                                 | 20.0 - 20000                 | 20.0 - 20000                   | 20.0 - 20000                  |
| Correlation Coefficient (r) / Correlation Coefficient Determination (r <sup>2</sup> ) <sup>b</sup> | r <sup>2</sup> > 0.9885      | r <sup>2</sup> > 0.9924      | r <sup>2</sup> > 0.9861       | r <sup>2</sup> > 0.9942                    | r <sup>2</sup> > 0.9924                    | r <sup>2</sup> > 0.9929                    | r <sup>2</sup> >0.9974       | r <sup>2</sup> > 0.9986        | r <sup>2</sup> > 0.9988       |
| Accuracy Across Standard Curve Concentrations (% Difference from nominal concentration)            | -9.5 – 11.8                  | -6.0 – 8.0                   | -8.6 – 20.0                   | -4.20 – 4.40                               | -4.80 – 6.00                               | -5.00 – 7.60                               | -8.5 – 7.0                   | -5.8 – 7.8                     | -8.0 – 10.0                   |
| Recovery (%)<br>Analyte Low<br>Analyte Medium<br>Analyte High<br>Internal Standard                 | 72.5<br>63.0<br>80.7<br>86.9 | 83.8<br>72.1<br>81.6<br>86.9 | 106.3<br>80.7<br>86.7<br>86.9 | 109.8<br>NA<br>99.58<br>95.40 – 105.47     | 108.36<br>NA<br>103.24<br>96.71 – 103.54   | 106.27<br>NA<br>102.84<br>98.39 – 102.28   | 85.7<br>91.1<br>97.4<br>98.8 | 95.3<br>96.3<br>101.3<br>100.0 | 93.9<br>96.1<br>102.9<br>98.6 |
| LLOQ   | 20                           | 20                           | 20                            | 1.00                                       | 1.00                                       | 1.00                                       | 20.0                         | 20.0                           | 20.0                          |
| ULOQ   | 10000                        | 10000                        | 10000                         | 500  | 500  | 500  | 20000                        | 20000                          | 20000                         |
| Selectivity <sup>c</sup>   | 18 – 24                      | 19 – 22                      | 17 – 22                       | No interference in the region of interest. | No interference in the region of interest. | No interference in the region of interest. | No interfering peak          | No interfering peak            | No interfering peak           |

| Attribute  | VAL-RPT-560*                            |  |  | RPT03237   |  |  | PRD11-210                                   |   |   |
|--|---|--|--|--|--|--|---|---|---|
|  | Analyte                                 |  |  | Analyte  |  |  | Analyte                                     |   |   |
|  | OCA (ng/mL)                             | Glyco-OCA (ng/mL)                        | Tauro-OCA (ng/mL)                          | OCA (ng/mL)  | Glyco-OCA (ng/mL)  | Tauro-OCA (ng/mL)  | OCA (ng/mL)                                 | Glyco-OCA (ng/mL)                           | Tauro-OCA (ng/mL)                           |
| QC Concentrations  | 60<br>1000<br>7000                      | 60<br>1000<br>7000                       | 60<br>1000<br>7000                         | 3.00<br>200<br>400   | 3.00<br>200<br>400   | 3.00<br>200<br>400   | 60.0<br>800<br>1600                         | 60.0<br>800<br>1600                         | 60.0<br>800<br>1600                         |
| Intra-Run Precision (%CV) of Quality Control Samples         | 60 = 3.6%<br>1000 = 2.2%<br>7000 = 4.9% | 60 = 15.0%<br>1000 = 2.0%<br>7000 = 3.6% | 60 = 3.0%<br>1000 = 3.0%<br>7000 = 6.6%    | 3.00 = 2.77 – 5.35<br>200 = 1.32 – 4.85<br>400 = 4.19 – 5.54   | 3.00 = 5.46 – 9.81<br>200 = 2.35 – 5.20<br>400 = 2.35 – 4.05   | 3.00 = 2.77 – 5.35<br>200 = 1.32 – 4.85<br>400 = 4.19 – 5.54   | 60.0 = 5.7%<br>800 = 1.3%<br>1600 = 1.9%    | 60.0 = 4.6%<br>800 = 1.7%<br>1600 = 2.0%    | 60.0 = 2.8%<br>800 = 3.6%<br>1600 = 1.3%    |
| Inter-Run Precision (%CV) of Quality Control Samples         | 60 = 5.4%<br>1000 = 8.2%<br>7000 = 5.4% | 60 = 8.2%<br>1000 = 6.0%<br>7000 = 4.5%  | 60 = 4.5%<br>1000 = 5.0%<br>7000 = 7.8%    | 3.00 = 4.64<br>200 = 3.57<br>400 = 5.79                        | 3.00 = 4.64<br>200 = 3.57<br>400 = 5.79                        | 3.00 = 7.65<br>200 = 3.72<br>400 = 8.09                        | 60.0 = 6.6%<br>800 = 4.1%<br>1600 = 2.0%    | 60.0 = 4.8%<br>800 = 3.0%<br>1600 = 4.6%    | 60.0 = 3.5%<br>800 = 3.6%<br>1600 = 2.6%    |
| Intra-Run Accuracy (% Difference) of Quality Control Samples | 60 = 6.7%<br>1000 = 6.6%<br>7000 = 1.5% | 60 = 0.0%<br>1000 = 10.2%<br>7000 = 0.2% | 60 = 11.7%<br>1000 = 10.9%<br>7000 = 10.5% | 3.00 = 3.33 – 9.33<br>200 = -2.00 – 0.50<br>400 = -6.25 – 2.00 | 3.00 = 5.67 – 13.0<br>200 = -2.00 – 0.50<br>400 = -6.25 – 2.00 | 3.00 = 3.33 – 9.33<br>200 = -0.50 – 2.00<br>400 = -12.0 – 5.00 | 60.0 = -0.3%<br>800 = -0.1<br>1600 = -3.1   | 60.0 = -1.5%<br>800 = -3.0<br>1600 = -8.1   | 60.0 = -4.7%<br>800 = 0<br>1600 = -5.0      |
| Inter-Run Accuracy (% Difference) of Quality Control Samples | 60 = 6.7%<br>1000 = 2.2%<br>7000 = 1.0% | 60 = 1.7%<br>1000 = 2.9%<br>7000 = 1.1%  | 60 = 10.0%<br>1000 = 7.8%<br>7000 = 3.7%   | 3.00 = 5.67<br>200 = -0.50<br>400 = -1.50                      | 3.00 = 5.67<br>200 = -0.50<br>400 = -1.50                      | 3.00 = 8.00<br>200 = 1.00<br>400 = -3.25                       | 60.0 = -3.8%<br>800 = -4.4%<br>1600 = -5.0% | 60.0 = -2.7%<br>800 = -4.9%<br>1600 = -5.0% | 60.0 = -3.8%<br>800 = -2.9%<br>1600 = -5.0% |

| Attribute                                       | VAL-RPT-560 <sup>a</sup>              |                                       |                                       | RPT03237   |  |  | PRD11-210                                |  |  |
|---|---------------------------------------|---------------------------------------|---------------------------------------|--|--|--|--|--|--|
|   | Analyte                               |                                       |                                       | Analyte  |  |  | Analyte                                  |  |  |
|   | OCA (ng/mL)                           | Glyco-OCA (ng/mL)                     | Tauro-OCA (ng/mL)                     | OCA (ng/mL)  | Glyco-OCA (ng/mL)                                  | Tauro-OCA (ng/mL)                                  | OCA (ng/mL)                              | Glyco-OCA (ng/mL)                        | Tauro-OCA (ng/mL)                        |
| <b>Stability</b>                                |                                       |                                       |                                       |  |  |  |  |  |  |
| Substock Standard Solution Stability in Solvent | At least 3 months at 4°C in methanol. | At least 3 months at 4°C in methanol. | At least 3 months at 4°C in methanol. | NA   | NA   | NA   | NA                                       | NA                                       | NA                                       |
| Freeze and Thaw Stability                       | At least 3 cycles                     | At least 3 cycles                     | At least 3 cycles                     | Three freeze/thaw cycles                           | Three freeze/thaw cycles                           | Three freeze/thaw cycles                           | Five freeze/thaw cycles                  | Five freeze/thaw cycles                  | Five freeze/thaw cycles                  |
| Dilution Integrity                              | Was not investigated                  | Was not investigated                  | Was not investigated                  | 2000 ng/mL diluted 5-folds                         | 2000 ng/mL diluted 5-folds                         | 2000 ng/mL diluted 5-folds                         | 80000 ng/mL diluted 10-fold and 100 fold | 80000 ng/mL diluted 10-fold and 100 fold | 80000 ng/mL diluted 10-fold and 100 fold |
| Storage Stability at room temperature           | At least 48 hours                     | At least 48 hours                     | At least 48 hours                     | At least 16 hours                                  | At least 16 hours                                  | At least 16 hours                                  | At least 30 hours                        | At least 30 hours                        | At least 30 hours                        |
| Storage Stability refrigerated (2-6°C)          | At least 48 hours                     | At least 48 hours                     | At least 48 hours                     | NA   | NA   | NA   | At least 30 hours                        | At least 30 hours                        | At least 30 hours                        |
| Long-Term Stability -20°C ≤ -70 °C              | Under investigation at <-60°C         | Under investigation at <-60°C         | Under investigation at <-60°C         | 350 days<br>350 days                               | 350 days<br>350 days                               | 350 days<br>350 days                               | 35 days<br>35 days                       | 98 days<br>98 days                       | 98 days<br>98 days                       |
| Stability of Processed Samples                  | At least 72 hours at room temperature | At least 72 hours at room temperature | At least 72 hours at room temperature | ~120 hours at 4°C<br>~95 hours at room temperature | ~120 hours at 4°C<br>~95 hours at room temperature | ~120 hours at 4°C<br>~95 hours at room temperature | At least 72 hours at 4°C                 | At least 72 hours at 4°C                 | At least 72 hours at 4°C                 |

CV = coefficient of variation; glyco-OCA = glyco-obeticholic acid; LLOQ = lower limit of quantification; NA = not available; OCA = obeticholic acid; QCH = QC high; QCL = QC low; QC LLOQ = quality control lower limit of quantification; QCM = QC medium; r2 = coefficient of determination; tauro-OCA = tauro-obeticholic acid; ULOQ = upper limit of quantification

<sup>a</sup> For the method validation VAL-RPT-560, the concentration units were µg/mL but for comparison purposes the units were converted to ng/mL.

<sup>b</sup> The coefficient of determination (r<sup>2</sup>) was determined by a weighted (1/concentration<sup>2</sup>) and 2nd order quadratic regression for OCA, glyco-OCA, and tauro-OCA, respectively.

<sup>c</sup> The spiking concentration was 20 ng/ml and the value acceptable range was 16-24.

### 2.7.3 Were the analytical procedures used to determine primary clinical surrogate endpoint in this NDA acceptable?

Alkaline phosphate (ALP) and Total Bilirubin are the primary clinical endpoints used in Phase 3 trial.

Principal Entry Criterion: ALP ≥ 1.67x ULN (mean values, if applicable) and/or total bilirubin > ULN but < 2x ULN (mean values, if applicable).

Primary Endpoint Analysis (evaluated as a responder analysis):

- ALP < 1.67x ULN **and** total bilirubin within normal limits (WNL), **and**
- ALP decrease of ≥ 15% (to exclude clinically insignificant ALP changes)

#### 2.7.3.1 Assay Labs

(b) (4) served as a central clinical lab for this study. All the labs associated with (b) (4) are third-party partner organizations, which are not part of one global company. Three labs were utilized to support patient samples from US/Canada, Europe, and Australia. See table below. All three labs are accredited by their respective national authorities. For US/Canada, JCMC is CLIA accredited.



Table 61: Details about assay method for ALP

(b) (4)



Source data: Response to IR submitted on 9/25/2015

- For Total Bilirubin,

(b) (4)



Table 62: Details about assay method for bilirubin

(b) (4)



Source data: Response to IR submitted on 9/25/2015

### 2.7.3.2.1 *Assay Performance Validation*

Each of the three labs performed validation of the commercial tests to verify acceptable performance with focus on within run precision and total precision. The within run precision and total precision are reported to be < 5%. According the Sponsor, internal standard checks were performed daily using two QC sample levels. Additionally internal standard checks were performed if a new lot of reagent or maintenance and trouble shootings were performed on the equipment.

*Reviewer's assessment and conclusion:*

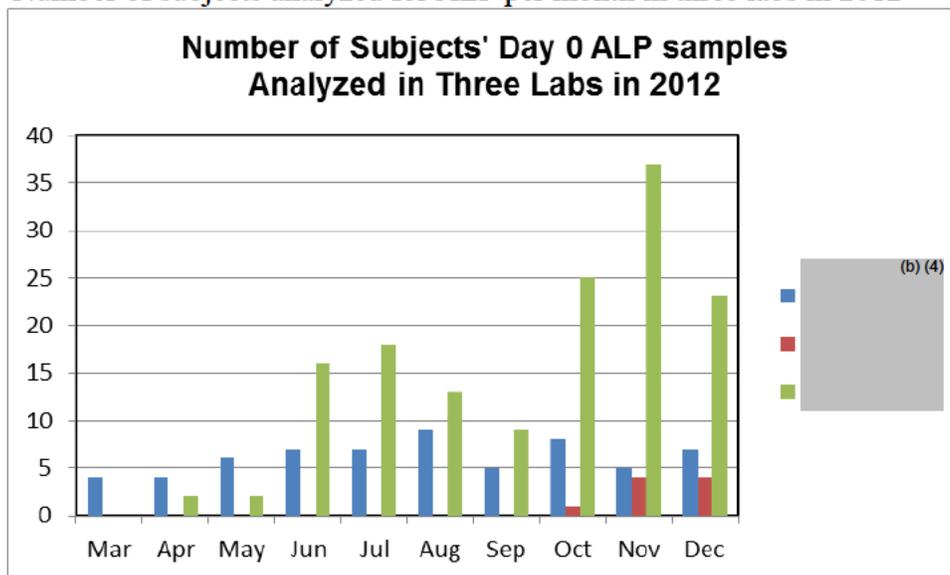
- At site (b) (4) accuracy was not evaluated. At (b) (4) experiment is used. This method, according to the document prepared by the manufacture for (b) (4)

In

addition, EP Evaluator offers an option to enter a precision goal (Allowable Random Error). When a goal is entered, the program will report that the test "passes" if the calculated SD does not exceed Allowable Random Error.

- At site (b) (4), accuracy was not reported.
- At site (b) (4) accuracy is defined by a slope of (b) (4) with an intercept of (b) (4) or less of the reference method's mean patient value. Alternatively, the acceptability criterion is a  $Y_m/X_m$  ratio of (b) (4). Accuracy met pre-defined criteria for both ALP and total bilirubin.
- The accuracy in each lab was not adequately evaluated according to the current recommendations on commercial diagnostic kits in Draft Guidance on Bioanalytical Method Validation published in September 2013, however, the pivotal trial started before the release of this Guidance. The interpretation of the clinical results are not impacted by the incomplete accuracy data because of the following:
  - The manufacturer reported that accuracy for the assay kits is within (b) (4)%. The kits are 510(k) approved and the labs are certified according to national standards. In US/Canada, (b) (4) is CLIA-certified.
  - For ALP, efficacy analysis in the pivotal Phase 3 study included the change of ALP from patients' own baseline, i.e.,  $\geq 15\%$  reduction, and an ALP  $< 1.67 \times \text{ULN}$ . Thus, a comparison within a subject whose ALP was measured using the same assay kit at the same lab is reasonably acceptable for the purpose of measuring changes from his/her own baseline. A within lab comparison between subjects' ALP and a lab's reference range is acceptable. This is also standard clinical practice.
  - For total bilirubin, the efficacy analysis specified that it needs to be  $\leq \text{ULN}$ . A within lab comparison between subjects' total bilirubin and the lab's reference range is acceptable. This is also standard clinical practice.
  -  (b) (4)
- Although the assay kits and reagents used for analysis of ALP and total bilirubin remained consistent at all three labs throughout the study, each lab analyzed a few enrolled subjects' samples every month from March to December 2012 as illustrated in the figure below.

Figure 30: Number of subjects analyzed for ALP per month in three labs in 2012



Source: Reviewer's plot

- *No stability data were reported from each lab. However, manufacturers have established storage and stability data.*
- *Although no formal accuracy data were provided from each lab, baseline assessment data shed some light into the accuracy for ALP and total bilirubin in each lab. Refer to Section 2.7.3.2.2.1 below.*

### 2.7.3.2.2 Harmonization

Instead of formal cross-validation, (b) (4) used their existing lab harmonization program to establish correction equations across labs.

#### 2.7.3.2.2.1 Reference lab selection

(b) (4) in Europe was selected as a reference lab because it showed better precision and total error when compared to (b) (4) when analyzing a common set of commutable human serum samples (b) (4), i.e. the reference values (RV), sent to both labs with concentrations of ALP and bilirubin covering the clinical range of interest.

The above (b) (4) samples were used for the establishment of inter lab harmonization. These samples provided an RV for each analyte. The RVs were assigned as the mean value obtained on the basis of three calibration runs, two replicates per run (n=6), and following one freeze-thaw cycle to control for any impact that freezing may have on the measurements. (b) (4) samples providing RV were provided by (b) (4)

The method and materials used for creating (b) (4) samples are credentialed and approved by the National Committee for Clinical Laboratory Standards

(<http://www.acronymfinder.com/National-Committee-for-Clinical-Laboratory-Standards-%28NCCLS%29.html>) (Document RS6-A).

To determine the precision and total error, the labs were asked to measure each of the analytes in each of the three <sup>(b) (4)</sup> samples (concentrations in low, medium and high) at three different times throughout the day (morning, mid-day, and late day) on three consecutive days. Therefore, for each sample, 9 test results were obtained over three days (see matrix illustration below in Table 63). These 9 tests for each of three samples formed a “baseline assessment” and were used for determining lab system performance.

Table 63: Method of determination of the baseline assessment

|   |  |  |  |
|---|--|--|--|
| <b>Day 1</b>  | Day 1                                  | Day 1                                  | Day 1                                  |
| Reference Samples   | Sample 1                               | Sample 2                               | Sample 3                               |
| Morning   | √                                      | √                                      | √                                      |
| Mid-day   | √                                      | √                                      | √                                      |
| Late day  | √                                      | √                                      | √                                      |
| Mean (M) of the measurement on each day                                     | M1,1                                   | M1,2                                   | M1,3                                   |
| <b>Day 2</b>  | Day 2                                  | Day 2                                  | Day 2                                  |
| Samples   | Sample 1                               | Sample 2                               | Sample 3                               |
| Morning   | √                                      | √                                      | √                                      |
| Mid-day   | √                                      | √                                      | √                                      |
| Late day  | √                                      | √                                      | √                                      |
| Mean of the measurement on each day   | M2,1                                   | M2,2                                   | M2,3                                   |
| <b>Day 3</b>  | Day 3                                  | Day 3                                  | Day 3                                  |
| Samples   | Sample 1                               | Sample 2                               | Sample 3                               |
| Morning   | √                                      | √                                      | √                                      |
| Mid-day   | √                                      | √                                      | √                                      |
| Late day  | √                                      | √                                      | √                                      |
| Mean of the measurement within each day                                     | M3,1                                   | M3,2                                   | M3,3                                   |
| <b>Total number of measurements on each sample within each day</b>          | <b>9</b>                               | <b>9</b>                               | <b>9</b>                               |
| <b>Within Sample Between Day Precision (CV%)*</b>                           | <b>from 9 measurements on Sample 1</b> | <b>from 9 measurements on Sample 2</b> | <b>from 9 measurements on Sample 3</b> |
| * Calculated as (SD of the 9 measurements)/(Mean of the 9 measurement)×100% |  |  |  |

Source data: Reviewer’s summary

Table 64: The Within Sample Between Day Precision (CV%) from each of the three labs' performance on 9 measurements for ALP and total bilirubin

| <b>ALP</b>                   |              |              |              |
|------------------------------|--------------|--------------|--------------|
| Reference value (RV) (U/L)   | <b>101.8</b> | <b>281.8</b> | <b>460.3</b> |
| (b) (4)                      | 2.979        | 3.156        | 2.445        |
| (b) (4)                      | 4.214        | 4.809        | 4.679        |
| (b) (4)                      | 2.067        | 1.126        | 1.475        |
| <b>Total Bilirubin</b>       |              |              |              |
| Reference value (RV) (mg/dL) | <b>0.905</b> | <b>2.426</b> | <b>4.038</b> |
| (b) (4)                      | 3.510        | 2.658        | 1.660        |
| (b) (4)                      | 1.989        | 0.494        | 0.670        |
| (b) (4)                      | 2.428        | 1.475        | 1.800        |

For ALP, (b) (4) had better precision than (b) (4) on all three reference samples. For total bilirubin, (b) (4) had only one precision data point worse than (b) (4) on the sample with highest concentration of 4.038 mg/dL, but the difference in the precision between the two labs was small, 0.14%. Over all, (b) (4) did have better precision than (b) (4). Note that initially there were only two labs: (b) (4). Comparison between (b) (4) was not made as (b) (4) was added as the third lab about four months later.

Table 65: The mean accuracy from each of the three labs' performance on 9 measurements for ALP and total bilirubin

| <b>ALP</b>   |              |              |              |
|--|--------------|--------------|--------------|
| Reference value (RV) (U/L)                         | <b>101.8</b> | <b>281.8</b> | <b>460.3</b> |
| (b) (4)  | -12.748      | -10.102      | -10.797      |
| (b) (4)  | -6.232       | -8.631       | -10.684      |
| (b) (4)  | -7.989       | -9.353       | -11.000      |
| <b>Total Bilirubin</b>                             |              |              |              |
| Reference value (RV) (mg/dL)                       | <b>0.905</b> | <b>2.426</b> | <b>4.038</b> |
| (b) (4)  | 38.064       | 11.040       | 7.617        |
| (b) (4)  | 1.409        | 1.958        | 2.583        |
| (b) (4)  | -1.453       | -2.748       | -2.014       |
| Accuracy = (mean of measured values – RV)/RV × 100 |              |              |              |

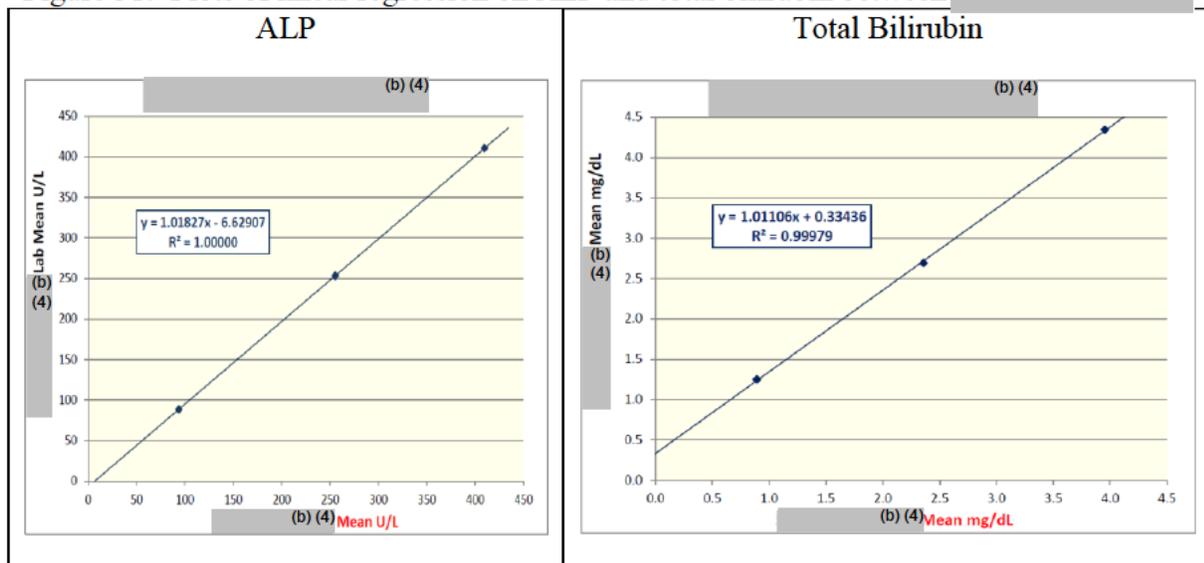
For ALP, (b) (4) had only one accuracy data point worse than (b) (4) on the sample with highest concentration of 460.3 U/L. The difference in the accuracy between the two labs was small, 0.203%. For total bilirubin, (b) (4) had better accuracy than (b) (4) on all three reference samples. Over all, (b) (4) did have better accuracy than (b) (4).

The Sponsor also looked at the total error, which was calculated as Total error (%) = 1.67 × %CV + Abs % bias to reference value (RV).<sup>1</sup> This parameter contained information of precision and accuracy. Precision and accuracy are discussed in Table 64 and Table 65.

### 2.7.3.2.2.2 Correction equations

The correction equations were generated from baseline assessment data (Table 63 and Table 64). The mean values of the measurements within each day for each sample, i.e., M1,1, M1,2, M1,3 etc., illustrated in the table above, from (b) (4) were plotted on the “y axis” and (b) (4) values on the “x axis”. See Figure 31 as an example. A linear regression equation for each analyte was derived and used for correcting measurements from patients’ samples assayed at (b) (4)

Figure 31: Plots of linear regression on ALP and total bilirubin between (b) (4)



Source data: Response to IR submitted on 12/15/2015

The Reviewer performed linear regression analysis using nine individual measurements on three reference samples instead of mean values between (b) (4). The reviewer found that Intercept and Coefficient are very close to those generated from using mean values. Thus, the correction equations generated using mean values and reported in Table 66 are acceptable.

Correction equations used to harmonize the ALP and total bilirubin values among the three labs are shown in Table 66.

<sup>1</sup> Callum G. Fraser: Changes in Serial Results in Biological Variation: from Principles to Practice, AACC Press, 2001.

Table 66: Correction equations applied to (b) (4)

| Lab     | Region        | Analytes        | Correction equations   | Number of patients |
|---------|---------------|-----------------|--|--------------------|
| (b) (4) | US and Canada | ALP             | $Y = 1.0183x - 6.6291$<br>$Y^{\ddagger} = 1.1063x + 12.6046$ | 62                 |
|         |               | Total Bilirubin | $Y = 1.0111x + 0.3344$<br>$Y^{\ddagger} = 1.0777x + 0.1289$  | 62                 |
|         | Australia     | ALP             | $Y = 0.9990x + 2.0208$                                       | 9                  |
|         |               | Total Bilirubin | $Y = 1.0520x - 0.0164$                                       | 9                  |
|         | Europe        | ALP             | n/a, reference lab   | 145                |
|         |               | Total Bilirubin | n/a, reference lab   | 145                |

Y is the original value, x is corrected value (Response to IR, SDN37) to be solved based on Y value.  
<sup>‡</sup> applied to samples analyzed on or after 11/28/2012 as (b) (4) implemented a new chemistry analyzer and subsequently a new baseline analysis was established (Response to IR on 12/15/2015, SDN37, Serial 0036)

Based upon dataset BASEEVAL.XPT submitted on 12/15/2015 (SDN37), the new baseline assessment for total bilirubin was analyzed between December 3 to 5, 2012 (data presented in Column ADT) when (b) (4) implemented a new chemistry analyzer. These new baseline values measured at (b) (4) were used against the original baseline values established in (b) (4) in February 2012. In other words, no new baseline analysis for total bilirubin was performed by (b) (4) in December 2012.

While the baseline assessment to establish a new correction equation for total bilirubin in (b) (4) was run from 12/3 to 12/5, 2012, eighteen patients' samples (each patient one sample) were analyzed from 11/26/2012 to 12/4/2012 at (b) (4) and corrected using the correction equation derived from the new baseline.

Based upon dataset BASEEVAL.XPT submitted on 12/15/2015 (SDN37), the new baseline assessment for ALP was analyzed on 11/14, 16, 19, 2012 (data presented in Column ADT) when (b) (4) implemented a new chemistry analyzer. These new baseline values measured at (b) (4) were used against the values established in (b) (4) on 11/15, 11/20, and 11/19, 2012. All the patients samples corrected with the second correction equation were run after 11/26/2012.

Because of the change in chemistry analyzer at (b) (4), eight patients' baseline values, defined as an average of all pre-treatment assessment per SAP, were corrected using two different equations as their Screening and Day 0 samples were analyzed by two different analyzers.

Total number of patients whose analytes were assayed at (b) (4) was 62. All the samples of ALP from patients assayed at (b) (4) were corrected. There are 49 samples of total bilirubin analyzed in (b) (4) were not corrected. For details as why 49 samples of total bilirubin were not corrected, see Section 2.7.3.3.1 below.

Among the three labs, (b) (4) received the most samples from patients, totaling 145.

(b) (4) analyzed the samples for patients studied in Australia. The total number of patients studied in Australia was small, nine.

### 2.7.3.3 Impact on primary clinical endpoints

#### 2.7.3.3.1 *Differences between corrected values and original (uncorrected values)*

The percentage difference, defined as (Corrected-Original)/Original×100, can be derived by the correction equation presented in Table 66 and shown below.

$$\text{Difference (\%)} = \left( \frac{y-b}{a} - 1 \right) \times 100$$

Note: y is original value, a is slope, b is intercept

The difference is dependent on the original value. The smaller the y is, the bigger the difference is.

For ALP, for example, the biggest difference of 19% was observed with the subject's ALP value of 59.8 U/L, the lowest value in the dataset. Overall, out of about 1296 samples, only 5 subjects or 11 samples in total showed a difference greater than 10% in ALP (Table 67). All of them were analyzed at (b) (4) using the second correction equation.

Table 67: Listing of subjects with differences greater than 10%

| Subject ID     | Treatment     | Visit    | Original (U/L) | Corrected (U/L) | Difference (%) |
|----------------|---------------|----------|----------------|-----------------|----------------|
| 747-301-111002 | 10 mg OCA     | MONTH 9  | 102.3          | 113.1           | 10.56          |
| 747-301-111002 | 10 mg OCA     | MONTH 12 | 84.1           | 95.2            | 13.20          |
| 747-301-112001 | Titration OCA | MONTH 12 | 105.2          | 115.9           | 10.17          |
| 747-301-119006 | 10 mg OCA     | MONTH 3  | 99.4           | 110.2           | 10.87          |
| 747-301-119006 | 10 mg OCA     | MONTH 6  | 91.3           | 102.2           | 11.94          |
| 747-301-119006 | 10 mg OCA     | MONTH 9  | 99.9           | 110.7           | 10.81          |
| 747-301-119006 | 10 mg OCA     | MONTH 12 | 96.4           | 107.3           | 11.31          |
| 747-301-146002 | 10 mg OCA     | MONTH 6  | 90.4           | 101.4           | 12.17          |
| 747-301-146002 | 10 mg OCA     | MONTH 9  | 81.6           | 92.7            | 13.60          |
| 747-301-146002 | 10 mg OCA     | MONTH 12 | 85.4           | 96.4            | 12.88          |
| 747-301-148003 | Titration OCA | MONTH 3  | 59.8           | 71.2            | 19.06          |

For total bilirubin, there were 49 samples were not corrected, i.e. “corrected value” = uncorrected value. All of them were found in (b) (4) with analysis dates between November 28, 2012 and January 15, 2013. The Sponsor stated that this was due to following reasons (Response to IR of January 2016, SDN46):

- There was a change in in analyzers at (b) (4) (b) (4) did plan to reanalyze the (b) (4) samples to establish a new harmonization formula. However, due to lack of (b) (4) samples the testing was not completed in a timely fashion until January 15, 2013. Therefore any samples processed between the two dates (28 November 2012 and 15 January 2013) did not have total bilirubin harmonization.

In those samples of total bilirubin being corrected, the difference between corrected and uncorrected values ranged from -68% to 2.6%. In other words, the corrected values were smaller than the uncorrected except one time point with a difference of 2.6%.

On February 25, 2015, the Sponsor submitted additional response to IR of January 4, 2016

indicating that the regression equation to harmonize lab values were not applied to a subset of total bilirubin samples and the sponsor opened an investigation and implemented a corrective action plan. The affected datasets will be updated as appropriate upon completion of the investigation.

The impact of correction for total bilirubin on primary endpoint analysis is discussed in Section 2.7.3.3.2.

### **Caveats based reviewer's assessments**

The caveat for using the correction equation for ALP analyzed in (b) (4) is that the first equation was established by using RVs with a concentration range of 101.8 to 460.3 U/L, while the second correction equation was established using a concentration range of 57.25 to 183.93 U/L. Of note, the concentration of ALP of patients' samples corrected with the first equation ranged from 108.3 to 829.5 U/L (Original values), i.e., some concentrations exceeding 460.3 U/L. Similarly, the concentration of ALP of patients' samples corrected with second equation ranged from 59.8 to 768.6 U/L, i.e., some concentrations exceeding 183.93 U/L.

Same caveat exists for using the correction equation for ALP analyzed in (b) (4) as the correction equation was established by using RV with a concentration range of 101.8 to 460.3 U/L, while the concentration of patients' ALP samples ranged from 169 to 642 U/L, i.e., some concentrations exceeding 460.3 U/L.

For total bilirubin, the RV concentration ranged from 0.905 mg/dL (15.476 µmol/L) to 4.038 mg/dL (69.050 µmol/L). No samples had concentration exceeding 4.038 mg/dL, however, there are patients' samples with concentrations less than 0.905 mg/dL.

Note that all the concentrations of patients' samples for ALP and total bilirubin were contained within the manufacturers' reportable range (Table 68).

Table 68: Manufacturer reportable range

|                         | (b) (4)  |              |              |
|-------------------------|----------|--------------|--------------|
| ALP (U/L)               | 5 - 1500 | 5 - 1200     | 1 - 1200     |
| Total bilirubin (mg/dL) | 0 - 30   | 0.146 - 28.0 | 0.146 - 28.0 |

Source data: Response to IR in September, 2015

### **2.7.3.3.2 Impact on primary efficacy analysis**

The Sponsor performed efficacy analysis on primary endpoints using uncorrected lab values and concluded that efficacy remained the same. Refer to Statistician's review.

#### **Total bilirubin**

Although the validation and harmonization methods for total bilirubin have pitfalls, the patients enrolled in this pivotal study had normal bilirubin to begin with, i.e., none of the patients had

total bilirubin > ULN but < 2X ULN, and the efficacy analysis on total bilirubin was total bilirubin < ULN. Therefore, these pitfalls do not have clinical impact on efficacy analysis.

Given the fact that some samples of total bilirubin were not corrected, the review team recommends to use uncorrected bilirubin values when analyzing phase 3 primary efficacy endpoint.

### ALP

Efficacy analysis in the pivotal Phase 3 study included the change of ALP from patients' own baseline, i.e.,  $\geq 15\%$  reduction, **and** an ALP  $< 1.67 \times \text{ULN}$ . Thus, a comparison within a subject whose ALP was measured using the same assay kit at the same lab is reasonably acceptable for the purpose of measuring changes from his/her own baseline. A within lab comparison between subjects' ALP and a lab's reference range is acceptable. This is also standard clinical practice. In addition, the difference between corrected and uncorrected ALP was small with majority of the samples being less than 10%, it is acceptable to use corrected ALP values in the final primary efficacy endpoint analysis.

Caution should be given to using corrected values due to the caveat found in establishing the correction equation. In addition, it should be noted that the lab assay validation did not test precision on ALP with concentrations higher than 300 U/L.

Because uncorrected values for total bilirubin are going to be used, it makes sense to also use uncorrected values for ALP when analyzing phase 3 primary efficacy endpoint as well.

### **3 LABELING RECOMMENDATIONS**

Labeling revisions are ongoing. Please refer to the final approved labeling when available. Detailed recommendations will be sent to the sponsor regarding the correct formatting and organization as well as the content related to Highlights, Dosage and Administration, Drug Interactions, Specific Populations as well as Clinical Pharmacology sections of the PLR labeling. The following dosing proposals or labeling language different from sponsor's original proposals are recommended by OCP:

- Dose recommendation in patients with hepatic impairment;
- Concomitant use of OCA with CYP1A2 substrates that have narrow therapeutic index;
- Concomitant use of OCA with resin binding agents;
- Concomitant use of OCA with warfarin;
- Format of drug-drug interaction in Section 12.3 according to Clinical Pharmacology Labeling Guidance;
- Addition of results from Thorough QT study to Electrocardiographic Evaluation in Section 12.2.

#### 4 APPENDIX A: PHARMACOMETRIC REVIEW

|  |                          |
|--|--------------------------|
| <b>Application Number</b>                | NDA207999                |
| <b>Drug Name</b>                         | Obeticholic Acid         |
| <b>Primary Pharmacometric Reviewer</b>   | Dhananjay Marathe, Ph.D. |
| <b>Secondary Pharmacometric Reviewer</b> | Nitin Mehrotra, Ph.D.    |

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## 1 Key Questions

The key pharmacometric review questions are discussed as part of the Clinical Pharmacology Question-Based-Review (QBR). See Section 1, Section 1.3.1, Section 1.3.2, Section 2.3.4.1, Section 2.3.4.3, Section 2.3.4.4, Section 2.3.5, Section 2.3.6, Section 2.3.7.2, Section 2.4.1 and Section 2.5.2.6 for details.

## 2 Results of Sponsor’s Analysis and reviewer’s comments

### 2.1 DOSE SELECTION

The Phase 2 Study 747-201 evaluated 10 mg and 50 mg QD dosing and another Phase 2 Study 747-202 evaluated 10 mg, 25 mg, and 50 mg QD dosing in PBC patients. In these studies, OCA significantly reduced ALP levels in subjects with PBC and no dose-relationship was observed (i.e., efficacy of OCA 10 mg was similar to OCA 50 mg). However, a dose-dependent increase in the incidence and severity of pruritus was observed across the studied dose range. Thus, it was hypothesized that it is feasible that a lower dose of OCA would be associated with a lower incidence of pruritus without compromising effectiveness. Accordingly, the Phase 3 Study 747-301 included assessment of a lower dose of 5 mg QD in addition to 10 mg QD for efficacy, safety, and tolerability.

### 2.2 POPULATION PHARMACOKINETIC (POP-PK) AND EXPOSURE-RESPONSE (E-R) ANALYSES

The Sponsor performed population pharmacokinetic (pop-PK) analyses in patients to:

1. Characterize the plasma PK of OCA, glyco-OCA and tauro-OCA in healthy volunteers, patients with PBC, and in special populations
2. Quantify the effects of relevant covariates on the plasma exposure of OCA and its conjugates.
3. Evaluate PK/PD relationships between biomarkers of efficacy (FGF-19, C4, and total bile acids) and exposure of OCA and its conjugates.
4. Evaluate exposure-response (E-R) relationships between efficacy endpoint and exposure of OCA and its conjugates.

### 2.2.1 Data

The dataset included concentration-time data for OCA, glyco-OCA, and tauro-OCA from 16 clinical studies with healthy volunteers, patients with PBC, as well as special populations (hepatic impairment) receiving oral administration of OCA. PK/PD relationship of a biomarker (C4) with PK exposures was assessed with data from 2 clinical studies (747-105 and 747-204). The Sponsor stated that Phase 3 Study 747-301 was not included in the pop-PK analysis due to the limited information of PK sampling and dosing times. However, the data from Study 747-301 was used to evaluate E-R relationship of response of change in alkaline phosphatase (ALP) and total bilirubin with observed trough PK concentrations at month 6. Also the data from Phase 3 Study 747-301 was used to graphically evaluate the relationship of changes in LDL and HDL with observed trough PK concentrations.

The overall pop-PK dataset consisted of a total of 25286, 31141 and 28976 measurable (non-BLQ) concentrations of OCA, glyco-OCA and tauro-OCA from the 16 studies which generally had rich PK sampling. Some non-BLQ concentrations (15, 38 and 42 for OCA, glyco-OCA and tauro-OCA respectively) were excluded due to measurable values prior to first OCA dosing.

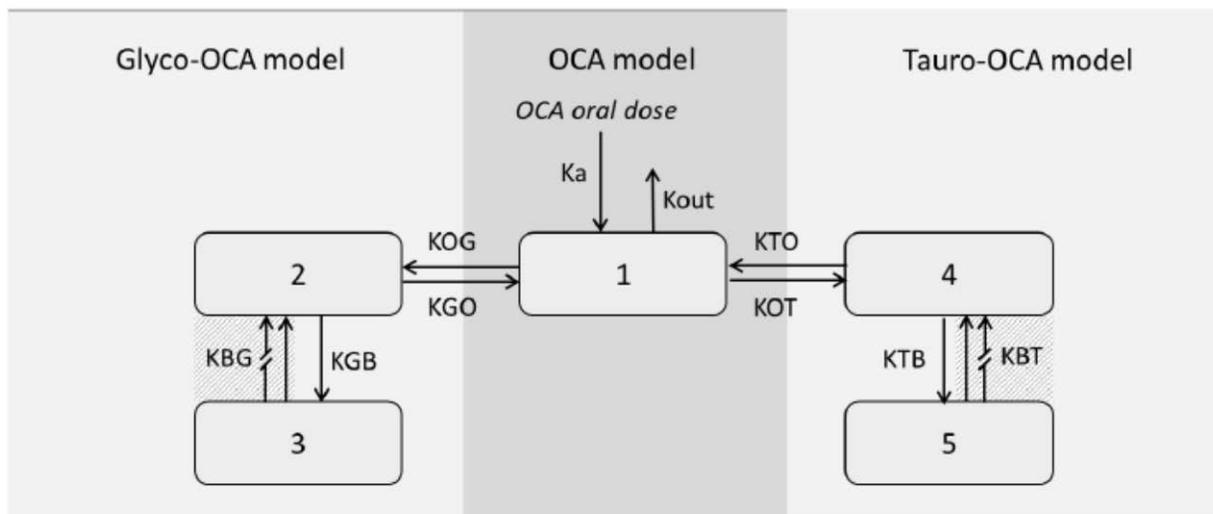
The PK/PD analysis dataset for biomarker C4 included a total of 378 samples of C4 from Studies 747-105 (332 rich samples) and 747-204 (46 sparse samples).

### 2.2.2 Results

The final pop-PK model consists of three central compartments (one for each analyte) and a gallbladder compartment for glyco-OCA and tauro-OCA. The model feature included description of enterohepatic recirculation of OCA and its conjugates. OCA absorption was modeled using a first order process. Glyco-OCA and tauro-OCA were assumed to accumulate in a gallbladder compartment following a first-order rate constant and gallbladder emptying was assumed to be directly into the central compartment. OCA model does not include a gallbladder compartment because the conjugation of OCA to its conjugates was assumed to be complete. The gallbladder compartment refers to the compartment where glyco-OCA and tauro-OCA accumulate and are released at meal times. Glyco- and tauro-OCA are assumed to accumulate in and be released from the gallbladder compartment following first-order rate constants (KGB and KTB). Although gallbladder emptying may occur between meals, in the model the onset of gallbladder emptying was assumed to occur only during 90 minutes starting at meal times.

Between-subject variability (BSV) was modeled on following parameters: rate of absorption ( $K_a$ ), rates of gallbladder emptying into the central compartment for glyco- and tauro-OCA (KGB and KBT), rates of conjugation of OCA to glyco- and tauro-OCA (KOG and KOT), rates of biotransformation of glyco- and tauro-OCA into OCA (KGO and KTO), rate of fecal elimination of OCA ( $K_{out}$ ), and volumes of distribution of OCA, glyco-OCA and tauro-OCA ( $V_{OCA}$ ,  $V_{glyco}$  and  $V_{tauro}$ ).

The structure of the pop-PK model is shown in **Figure 1**.



Compartments #1, 2, 4 represent the central compartment of OCA, glyco-OCA and tauro-OCA concentrations (ie, observed) in the plasma, respectively and compartments #3 and 5 represent the gallbladder compartments for glyco- and tauro-OCA, respectively; arrows with breaks correspond to intermittent gallbladder emptying

$K_a$  = first-order rate of absorption;  $K_{BG}$  = rate of gallbladder emptying into the central compartment for glyco-OCA during gallbladder contraction;  $K_{BT}$  = rate of gallbladder emptying into the central compartment for tauro-OCA during gallbladder contraction;  $K_{GB}$  = first-order rate for glyco-OCA accumulation in gallbladder;  $K_{GO}$  = biotransformation rate of glyco-OCA into OCA;  $K_{OG}$  = biotransformation rate of OCA into glyco-OCA;  $K_{OT}$  = biotransformation rate of OCA into tauro-OCA;  $K_{out}$  = rate of fecal elimination of OCA;  $K_{TB}$  = first-order rate for tauro-OCA accumulation in gallbladder;  $K_{TO}$  = biotransformation rate of tauro-OCA into OCA; OCA = obeticholic acid

**Figure 32:** Schematic Representation of the Structural Pop-PK Model of OCA and its Conjugates (Source: Sponsor’s Population PK/PD and Simulation Report, Figure 6.1)

### Covariate effects:

Hepatic impairment and body weight were the two key covariates identified to be important in the model:

- Hepatic impairment on  $VOCA$ ,  $V_{glyco}$ ,  $V_{tauro}$ ,  $K_{BG}$ ,  $K_{BT}$ ,  $K_{OG}$ ,  $K_{OT}$ ,  $K_{GO}$  and  $K_{TO}$
- Body weight on  $VOCA$ ,  $V_{glyco}$ ,  $V_{tauro}$ ,  $K_{BG}$  and  $K_{BT}$  of OCA, glyco-OCA and tauro-OCA.

The impact of these covariates on the exposures of OCA and its conjugates is as follows:

- For a typical subject with severe, moderate, and mild hepatic impairment the predicted AUC is expected to be 218%, 204% and 39% higher than those observed in a typical subject with normal liver function, respectively.
- The median AUC in a typical 40-kg subject is expected to be 50% higher and in a typical 134-kg is expected to be 42.6% lower than that in a typical 67.4-kg subject.

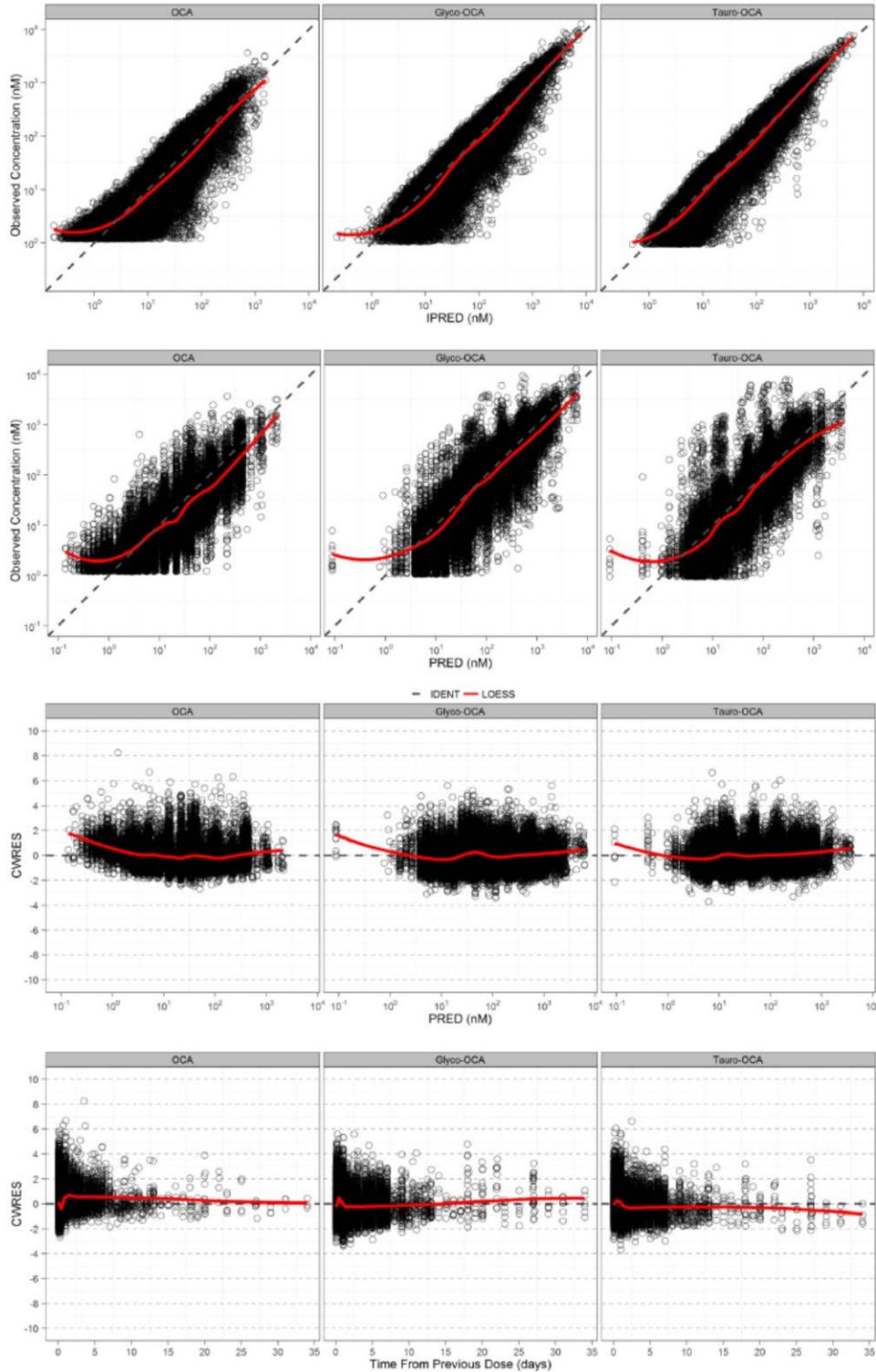
Final parameter estimates for the pop-PK model are summarized in **Table 1**. The goodness-of-fit (observed vs individual predicted concentrations etc.) plots for the model are provided in **Figure 2**.

Table 69: Pharmacokinetic parameter estimates of the final pop-PK model

| Parameter                       | Estimate | Parameter                                  | Estimate | Shrinkage (%) |
|---------------------------------|----------|--|----------|---------------|
| VOCA (L)                        | 176      | BSV Ka (%)                                 | 70.9     | 5.6           |
| Vglyco (L)                      | 195      | BSV VOCA (%)                               | 53.9     | 10.7          |
| Vtauro (L)                      | 175      | Variance between BSV Vglyco and BDV VOCA   | 0.318    |               |
| Ka (h <sup>-1</sup> )           | 0.817    | BSV Vglyco (%)                             | 67.7     | 7.4           |
| Kout (h <sup>-1</sup> )         | 0.365    | Variance between BSV Vtauro and BDV VOCA   | 0.400    |               |
| KOG (h <sup>-1</sup> )          | 0.585    | Variance between BSV Vtauro and BDV Vglyco | 0.547    |               |
| KOT (h <sup>-1</sup> )          | 0.140    | BSV Vtauro (%)                             | 89.3     | 9.4           |
| KGO (h <sup>-1</sup> )          | 0.0475   | BSV Kout (%)                               | 60.0     | 15.6          |
| KTO (h <sup>-1</sup> )          | 0.0201   | BSV KGO (%)                                | 24.2     | 14.9          |
| KGB (h <sup>-1</sup> )          | 0.112    | BSV KTO (%)                                | 53.1     | 13.5          |
| KBG (h <sup>-1</sup> )          | 5.48     | BSV KOG (%)                                | 17.2     | 34.7          |
| KTB (h <sup>-1</sup> )          | 0.142    | Variance between BSV KOG and BDV KOT       | -0.00139 |               |
| KBT (h <sup>-1</sup> )          | 6.38     | BSV KOT (%)                                | 23.3     | 45.9          |
| gbbl (fraction of tvKBG)        | 0.00896  | BSV KBG (%)                                | 129.5    | 8.5           |
| Prop Error OCA (%)              | 74.4     | Variance between BSV KBG and BDV KBT       | 1.66     |               |
| Prop Error Glyco-OCA (%)        | 50.9     | BSV KBT (%)                                | 129.5    | 8.3           |
| Prop Error Tauro-OCA (%)        | 52.4     |  |          |               |
| Additional Error OCA (nM)       | 0.44777  |  |          |               |
| Additional Error Glyco-OCA (nM) | 0.337664 |  |          |               |
| Additional Error Tauro-OCA (nM) | 0.050235 |  |          |               |

BSV = between subject variability; cpt = compartment; gbbl = constant rate of release from gall bladder emptying into the central compartment; Ka = first-order rate of absorption; KBG = rate of gall bladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gall bladder emptying into the central compartment for tauro-OCA during gallbladder contraction; KGB= first-order rate for glyco-OCA accumulation in gallbladder; KGO = biotransformation rate of glyco-OCA into OCA; KOG = biotransformation rate of OCA into glyco-OCA; KOT = biotransformation rate of OCA into tauro-OCA; Kout = rate of fecal elimination of OCA; KTB= first-order rate for tauro-OCA accumulation in gallbladder; KTO = biotransformation rate of tauro-OCA into OCA; MOF = minimum objective function; OCA = obeticholic acid; Prop. = proportional; Vglyco = volume if distribution for glyco-OCA; VOCA = volume if distribution for OCA; Vtauro = volume if distribution for tauro-OCA

Source: Sponsor's Population PK/PD and Simulation Report, Section 2.2.2



**Figure 33:** Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model (Source: Sponsor's Population PK/PD and Simulation Report, Section 2.2.3)

*Reviewer's comments:*

1. *The Sponsor's Pop-PK model provides reasonable description of OCA, glycol-OCA and tauro-OCA concentrations for individual predictions (observed vs. individual predicted concentrations in **Figure 2**). Visual inspection shows that the model reasonably predicts individual data over a range of concentrations from the included studies, with some under-prediction at low concentration values.*
2. *Residual trends were observed between hepatic impairment and eta values, in subjects with moderate or severe hepatic impairment. Based on VPC, the predicted concentrations were underestimated for the subjects with severe hepatic impairment. For this purpose, the Sponsor conducted simulations with their Physiologic PK model for generating exposure results for scenarios of alternative dosing regimens in hepatic impairment in response to Clinical Pharmacology review team's information requests. Refer to Appendix B for the details of Physiologic PK (PBPK) modeling. Based on the evidence of higher exposures with moderate and severe hepatic impairment and dose-response relationship for pruritus, the review team has proposed alternative dosing regimen with less frequent dosing for these subpopulations. Refer to the Executive Summary of Clinical Pharmacology Question-Based-Review (QBR) for the proposed dosing.*
3. *The Sponsor's graphical analyses of relationship of changes in HDL and LDL with trough concentrations of total OCA are described in section 2.3.4.3 of the QBR.*
4. *The Sponsor's graphical analysis of relationship of changes in C4 with total OCA  $C_{avg}$  is described in section 2.3.4.1 of the QBR.*
5. *The Sponsor's E-R relationships for change in ALP, change in bilirubin and probability of predicted responders (as per the primary efficacy endpoint criteria) with trough concentrations of total OCA are described in section 2.3.4.1 of the QBR. Typical  $I_{max}$  models are fit to the changes in ALP and bilirubin and an  $E_{max}$  model was used to describe the probability of predicted responders.*

### 3 Listing of analyses datasets, codes and output files

**Table 70: Analysis Data Sets**

| Study Number  | Name  | Link to EDR  |
|---|---|--|
| Pop-PK Dataset  | poppkdat.xpt  | \\cdsesub1\evsprod\nda207999\0001\m5\datasets\pk-empirical\analysis\adam\datasets\   |
| Physiologic PK Simulation Input/ Output Files                                     | ocasimin.xpt<br>cttotoca.xpt<br>ctoca xpt<br>pkparl xpt<br><br>a1out xpt<br>a2out xpt<br>b3out.xpt<br>b5out.xpt<br>simexp xpt | <a href="\\cdsesub1\evsprod\NDA207999\0019\m5\datasets\pk-physiological\analysis\legacy\datasets\">\\cdsesub1\evsprod\NDA207999\0019\m5\datasets\pk-physiological\analysis\legacy\datasets\</a><br><br><a href="\\CDSESUB1\evsprod\NDA207999\0039\m5\datasets\pk-physiological\analysis\legacy\datasets\">\\CDSESUB1\evsprod\NDA207999\0039\m5\datasets\pk-physiological\analysis\legacy\datasets\</a> |
| Efficacy/Safety:<br>Demographic<br>Efficacy<br><br>Responders<br><br>Vital Status | Adsl xpt<br>Adeff xpt<br>Adeff2.xpt<br>Adresp xpt<br>Adresp2.xpt<br>AdvS xpt  | <a href="\\cdsesub1\evsprod\nda207999\0001\m5\datasets\747-301\analysis\adam\datasets\">\\cdsesub1\evsprod\nda207999\0001\m5\datasets\747-301\analysis\adam\datasets\</a>  |

**Table 71: Codes and Output Files**

| File Name              | Description   | Location in<br>\\cdsnas\pharmacometrics\Reviews\<br>Ongoing PM Reviews\<br>Obeticholic_Acid_NDA207999_DDM\ |
|------------------------|---|--|
| OCA_HV_Patients.sas    | PK analysis   | ER_Analyses\codes  |
| OCA_WT_eff.sas         | Analysis for body weight/BMI                            | ER_Analyses\codes  |
| Longi_alp_response.sas | Analysis of longitudinal response of ALP and responders | ER_Analyses\codes  |
| OCA_HepImp.sas         | Analysis of hepatic impairment scenarios                | ER_Analyses\codes  |

**5 APPENDIX B: PHYSIOLOGICAL-BASED PHARMACOKINETIC (PBPK)  
MODELING REVIEW**

|                                |   |
|--------------------------------|---|
| <b>Application Number</b>      | NDA207999   |
| <b>Drug Name</b>               | Obeticholic Acid  |
| <b>Primary PBPK Reviewer</b>   | Ping Zhao, Ph.D., Yuching Yang, Ph.D. and<br>Dhananjay Marathe, Ph.D. |
| <b>Secondary PBPK Reviewer</b> | Nitin Mehrotra, Ph.D.   |

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## 1. OBJECTIVES

The main objective of this review is to evaluate the submitted physiologically-based pharmacokinetic (PBPK) modeling information that predicted the exposure of obeticholic acid (OCA) in the systemic circulation and the liver in healthy subjects and patients with hepatic impairment and to determine the adequacy of the model to support dosing recommendations of OCA in subjects with hepatic impairment.

To support its conclusion that no dose adjustment is required in patients with hepatic impairment, the applicant provided the following PBPK modeling and simulation information:

- Intercept: Response to Clinical Pharmacology Information request dated 09 September 2015 [1]
- Intercept: NDA207999 2.7.2. Summary of Clinical Pharmacology Studies [2]

## 2. PERTINENT BACKGROUND

Obeticholic Acid (OCA) is a farnesoid X receptor (FXR) agonist and a modified form of an endogenous bile acid chenodeoxycholic acid (CDCA) in humans. OCA is for the treatment of primary biliary cirrhosis (PBC) and other chronic liver diseases [3]. Consistent with endogenous bile acids such as CDCA, OCA undergoes extensive conjugation to glycine and taurine. The glyco- and tauro-conjugates (glyco-OCA and tauro-OCA) are secreted into the bile and further undergo enterohepatic recirculation. Conjugates are known to have pharmacological activities similar to OCA.

In a phase I study, subjects with varying degrees of hepatic impairment (severity based on Child-Pugh scores, CP scores) were given a single oral dose of 10 mg OCA [4]. Plasma exposure of OCA, glyco-OCA, tauro-OCA and total OCA are higher in subjects with hepatic impairment than in subjects with normal hepatic functions (**Table 1 and Supplementary Table 1**). For example, mean AUC<sub>t</sub> (AUC from time zero to the time of the last measurable concentration) of total OCA in plasma were approximately 1.1-fold, 4.2-fold, and 17-fold higher in subjects with mild, moderate, and severe hepatic impairment, respectively, compared with subjects with normal hepatic function. The magnitudes of exposure change appear to differ among OCA, glyco-OCA and tauro-OCA. In subjects with severe hepatic impairment, the magnitudes of increase in AUC<sub>t</sub> were 7, 11, and 37-fold for OCA, glyco-OCA, and tauro-OCA, respectively. Higher plasma concentrations of total endogenous bile acids were also observed in patients with severe hepatic impairment (**Supplementary Table 2**).

The observed higher plasma concentrations of OCA and endogenous bile acids in subjects with severe hepatic impairment from Study 747-103 [4] appear to be consistent with plasma levels of OCA and endogenous bile acids found in other studies. In a phase 2 study (Study 747-204), 10 or 25 mg of OCA were administered to patients with portal hypertension for 6-12 days, a condition defined by the applicant as hepatic impairment. On the last day of the treatment, plasma maximal concentration (C<sub>max</sub>) of total OCA were about 5 to 6-fold higher than the central values observed in healthy subjects receiving the same doses [1]. Fisher et al also measured endogenous bile acid levels in explanted liver samples from cholestasis (end-stage

chronic cholestasis) and non-cholestasis (cirrhosis of alcoholic/chronic hepatitis) patients with end-stage liver dysfunction [5]. Compared with subjects with normal hepatic function, there was a substantial increase in serum endogenous total bile acid concentrations in patients with hepatic impairment (17 and 23-fold for noncholestatic and cholestatic patients, respectively, [5], **Supplementary Table 2**). The authors also reported a modest increase in liver concentrations of total bile acids (2 and 4-fold higher for noncholestatic and cholestatic patients, respectively) (**Supplementary Table 2**) [5].

To evaluate that liver exposure of OCA in subjects with hepatic impairment, the applicant conducted modeling and simulation using a physiologically-based pharmacokinetic (PBPK) model, and predicted approximately 2-fold increase in total OCA in subjects with severe hepatic impairment [1]. Based on model predictions, the applicant suggested that significant elevation of total OCA in plasma does not represent exposure changes of OCA at the site of action for efficacy or safety (i.e., liver) in subjects with hepatic impairment [1]. In its proposed prescription information [6], the applicant stated that “Limited data exist in patients with moderate or severe hepatic impairment therefore caution should be exercised. The systemic exposure of obeticholic acid is increased in patients with moderate and severe hepatic impairment when compared to healthy controls and patients with mild hepatic impairment. Based on limited data, TRADENAME was generally well tolerated in patients with hepatic impairment. No dose adjustment is required in patients with hepatic impairment.” (Section 8.7), and “Despite higher systemic plasma exposure levels of obeticholic acid in patients with hepatic impairment, liver exposure was predicted to be similar to healthy controls based on a physiologic pharmacokinetic model. No dose adjustment is required in patients with hepatic impairment” (Section 12.3).

**Table 1: Geometric least square mean ratio (%) of plasma exposure of OCA, glyco-OCA, tauro-OCA, or total OCA following a single oral 10-mg OCA dose in subjects with hepatic impairment to those in subjects with normal hepatic function (Source, Tables 11, 14, 18, 21, Tables 14.2.1.1-4 4, [4]).**

| Hepatic functions <sup>a</sup> | Parameters        | OCA                                   |                         | Glyco-OCA                             |                         | Tauro-OCA                             |                         | Total OCA                             |                         |
|--------------------------------|-------------------|---------------------------------------|-------------------------|---------------------------------------|-------------------------|---------------------------------------|-------------------------|---------------------------------------|-------------------------|
|                                |                   | Geometric least square mean ratio (%) | 90% Confidence Interval | Geometric least square mean ratio (%) | 90% Confidence Interval | Geometric least square mean ratio (%) | 90% Confidence Interval | Geometric least square mean ratio (%) | 90% Confidence Interval |
| Mild/Normal                    | AUCt <sup>b</sup> | 138                                   | 73-261                  | 127                                   | 65-250                  | 71                                    | 30-170                  | 113                                   | 57-225                  |
|                                | AUC 24            | 146                                   | 80-268                  | 132                                   | 68-254                  | 76                                    | 34-171                  | 123                                   | 65-34                   |
|                                | Cmax              | 135                                   | 80-28                   | 143                                   | 80-256                  | 87                                    | 40-188                  | 149                                   | 86-256                  |
| Moderate/Normal                | AUCt <sup>b</sup> | 241                                   | 127-456                 | 333                                   | 169-654                 | 686                                   | 286-1643                | 420                                   | 211-838                 |
|                                | AUC 24            | 315                                   | 172-578                 | 393                                   | 204-758                 | 663                                   | 296-1485                | 440                                   | 232-837                 |
|                                | Cmax              | 191                                   | 113-323                 | 373                                   | 208-670                 | 563                                   | 261-1217                | 376                                   | 218-647                 |
| Severe/Normal                  | AUCt <sup>b</sup> | 703                                   | 372-1330                | 1138                                  | 579-2236                | 3684                                  | 1537-8830               | 1728                                  | 867-3444                |
|                                | AUC 24            | 830                                   | 462-1490                | 1142                                  | 593-2200                | 3298                                  | 1473-7385               | 1527                                  | 804-2901                |
|                                | Cmax              | 470                                   | 278-796                 | 812                                   | 452-1458                | 2142                                  | 991-4627                | 975                                   | 566-1680                |

<sup>a</sup>Mild (Child-Pugh A); moderate (Child-Pugh B); severe (Child-Pugh C) and normal hepatic function. Absolute, geometric mean values of exposures can be found in **Supplementary Table 1**. <sup>b</sup>AUCt AUC from time zero to the time of the last measurable concentration.

On Sep 9, 2015, FDA issued information requests regarding applicant’s PBPK modeling report (see 6.2.1). On Sep 20, 2015, the applicants provided responses to these requests [2].

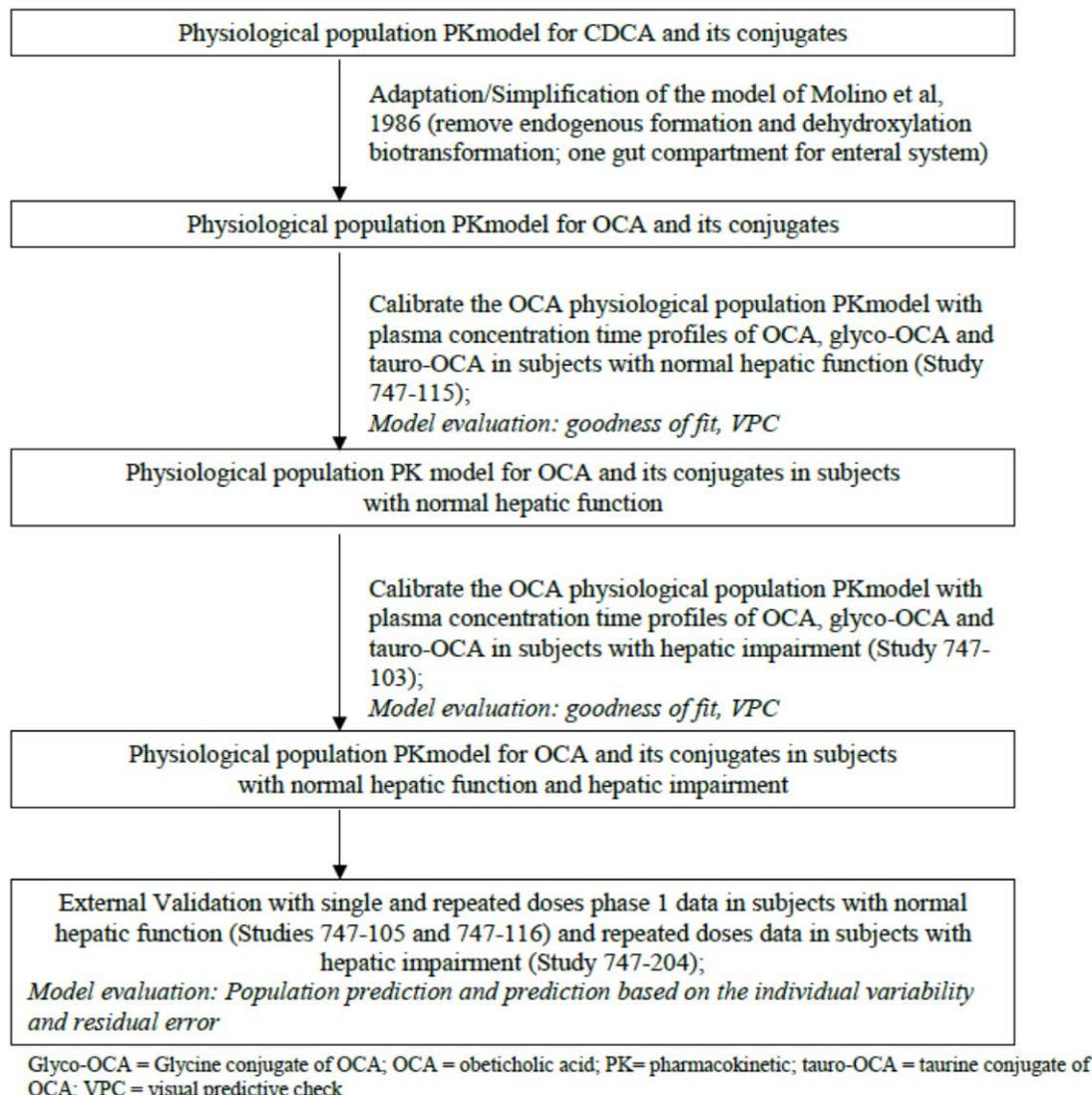
The primary objective of this review is to assess the adequacy of the applicant’s PBPK models

that were used to predict hepatic exposures of OCA and its metabolites and to support their labeling claims with regard to OCA dosing regimen in subjects with varying degrees of hepatic impairment.

### 3. METHODS

A previously developed multi-compartment PBPK model for chenodeoxycholic acid (CDCA), an endogenous bile acid [7], was adopted and modified by the applicant to construct PBPK models for OCA and its conjugates. The applicant used Phoenix® NLME™ 1.3 (Pharsight, A Certara Company, Cary, North Carolina, USA) to perform PBPK modeling and simulations. **Figure 1** represents a workflow of the development and application of integrated models for OCA and its conjugates.

**Figure 1: Workflow of the development of integrated OCA and its conjugates (Source: Figure 3.1, [1])**



### 3.1. Model fitting

The model [1] includes description of the relationships between plasma concentration and time, a variance component characterizing between subject variability (BSV) in model parameters, and residual unexplained variability using additive and proportional model. The model had the following form:

$$Cp_{ij} = C(D_i, t_j, \theta_i) + \varepsilon_{ij}$$
$$\theta_i = (\theta_{i1}, \dots, \theta_{im})$$

where  $Cp_{ij}$  is the concentration at  $j^{\text{th}}$  time for subject  $i$ ,  $D_i$  represents dosing history for subject  $i$ ,  $\theta_i$  is the vector of  $m$  model parameters for subject  $i$ , and  $\varepsilon_{ij}$  is random error associated with a concentration at the  $j^{\text{th}}$  time for subject  $i$ . BSV was modeled assuming a log-normal distribution as follows:

$$\theta_{in} = \theta_{TVn} \exp(\eta_{in})$$
$$(\eta_1 \dots \eta_m) \sim MVN(0, \Omega)$$

Where  $\theta_{TVn}$  is the population typical value for the  $n^{\text{th}}$  model parameter, and  $\eta_{in}$  (ETA) is the random inter-subject error or BSV on the  $n^{\text{th}}$  parameter for subject  $i$  that jointly follow a multivariate normal distribution (MVN) with mean zero and variance  $\Omega$ . This model for BSV assumes that estimated parameters are log-normally distributed. Due to the high level of complexity of the model, BSV was incorporated on absorption rate constant  $K_a$  and rate from gallbladder to gut.

Residual variability was assumed to have an additive component and a component proportional to the prediction:

$$y_{ij} = \hat{y}_{ij} * (1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

where  $y_{ij}$  and  $\hat{y}_{ij}$  represent the  $j^{\text{th}}$  observed and predicted plasma drug concentration for the  $i^{\text{th}}$  participant, and  $\varepsilon$  is the random residual variability. Each  $\varepsilon$  ( $\varepsilon_1$  and  $\varepsilon_2$ ) is normally distributed with mean 0 and variance  $\sigma_2$ .

### 3.2. Model evaluation

The model was evaluated using several diagnostic plots [1]:

- Observed total OCA plasma concentration data versus population predicted data (PRED) and individual predicted data (IPRED)
- Observed total OCA data and PRED versus time from the first dose
- Observed OCA, glyco-OCA, tauro-OCA versus PRED and IPRED
- Conditional weighted residual (CWRES) of OCA and conjugates versus PRED and time
- 200 iterations corrected visual predictive check (VPC) on the observed concentrations

### 3.3. CDCA model and assumptions

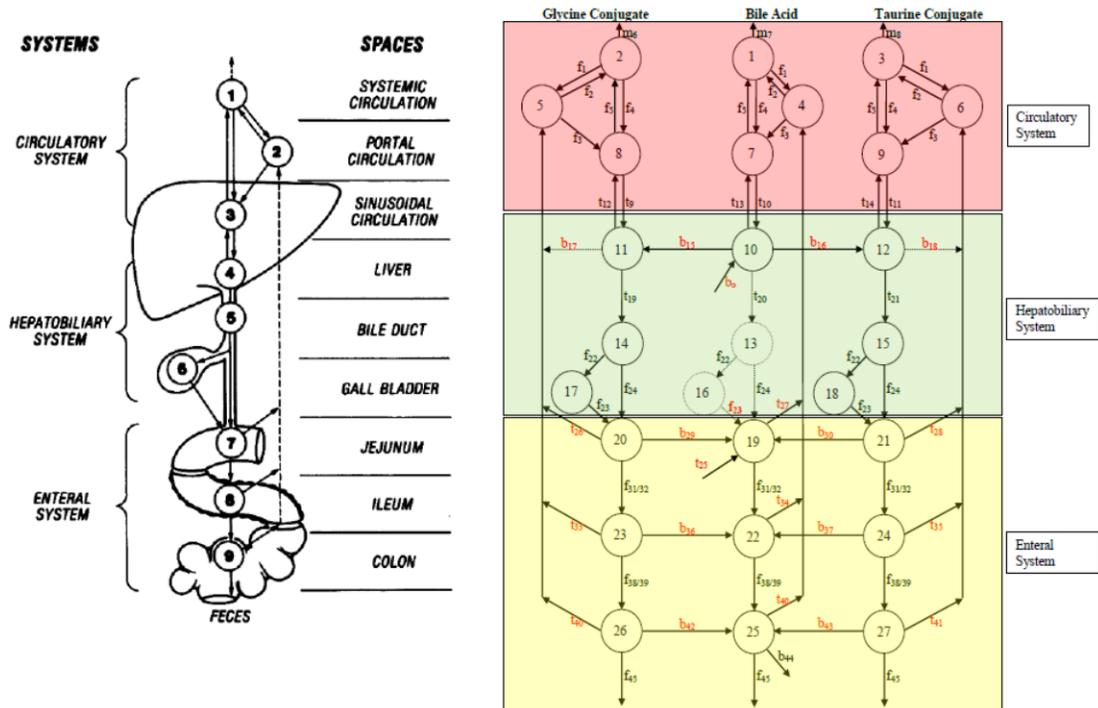
The system model for CDCA and metabolites included three systems: circulatory, hepatobiliary, and enteral systems ([7], **Figure 2**). Within each system, physiology compartments were defined and were interconnected according to either blood flow or kinetic processes relevant to permeation, biotransformation, and active transport of CDCA and its conjugates.

This model was evolved from an earlier model describing cholic acid and conjugates [8]. Key assumptions include:

Circulatory system:

- Total mass of CDCA species was set at 1.9 mmol (0.74 g)
- Portal-systemic shunting is not applicable for healthy individual
- Hepatic first-pass extraction values were 0.8 for conjugates and 0.6 for CDCA. First pass extraction was lower for CDCA than for cholic acid conjugates [8], resulting in higher CDCA serum concentrations

Figure 2: Physiologic PK model for CDCA and conjugates (Source: Figure 1-5, [1])



Dashed lines denote fluxes that do not occur in healthy subjects; “f” refers to a flow rate; “t” refers to a transport rate; “b” refers to a biotransformation; “syn” refers to de novo synthesis of CDCA (set to zero for OCA)

CDCA= chenodeoxycholic acid; OCA= obeticholic acid

#### Hepato-biliary system:

- Synthesis rate was 0.22  $\mu\text{mol}/\text{min}$
- Biotransformation to glycine conjugate was 3 times that of taurine conjugation
- Biliary excretion of unconjugated CDCA was negligible (set to zero)
- Glyco-CDCA in hepatocytes was mainly from reabsorption from duodeno-jejunal and ileal space; minor input was from newly conjugated glycol-CDCA. New, unconjugated CDCA was either from reabsorption or from de novo synthesis from cholesterol
- Tauro-CDCA in hepatocytes was mainly from reabsorption from ileal space; minor input was from newly conjugated tauro-CDCA (See above)
- Both glyco- and tauro-CDCA are actively transported into bile via bile salt excretory pump (BSEP, [1]). This was not specified in the model
- Duration of meal induced gall-bladder contraction was 120 min
- Gall-bladder contraction was delayed until 10 min after the beginning of the meal
- Duration of meal induced (digestive) change in intestinal motility was 210 min
- The ratio between digestive and fasting motility flow rates was 2.4

- Bile exiting from the common duct to duodenum-jejunum space had a rate about twice that of accumulation into the gallbladder
- During gall-bladder contraction all the bile contained in the common duct and in gall-bladder entered directly into the intestine
- Rate of de-conjugation of glycine conjugate was five times higher than that of taurine conjugate
- Negligible conversion of CDCA to ursodeoxycholic acid

Enteral system:

- Passive absorption (proximal intestinal absorption) assumed for CDCA and glyco-CDCA, not for tauro-CDCA within duodeno-jejunal space
- The majority of glyco- and tauro-CDCA are transported in ileum by apical sodium dependent bile acid transporter (ASBT) and then into the portal system via the organic solute transporters (OSTs). These transporters were not specified in the model [1]
- No de-conjugation of CDCA conjugates in duodeno-jejunum
- 15% glyco-CDCA entered ileal space and was de-conjugated to form CDCA, which is effectively absorbed; tauro-CDCA was assumed to be reabsorbed without de-conjugation
- No absorption was assumed in colon. All CDCA are dehydroxylated to lithocholic acid
- No fecal output of CDCA species

### 3.4. OCA model and assumptions

Systems model for OCA and conjugates is simplified by lumping all enteral spaces into a single gut space (**Figure 3**). According to the applicant, values and units for volume of spaces in CDCA model [7] remain unchanged, and volume of gut compartment (0.920 L) corresponds to the sum of duodenum/jejunum, ileum, and colon compartments described by Molino et al [7].

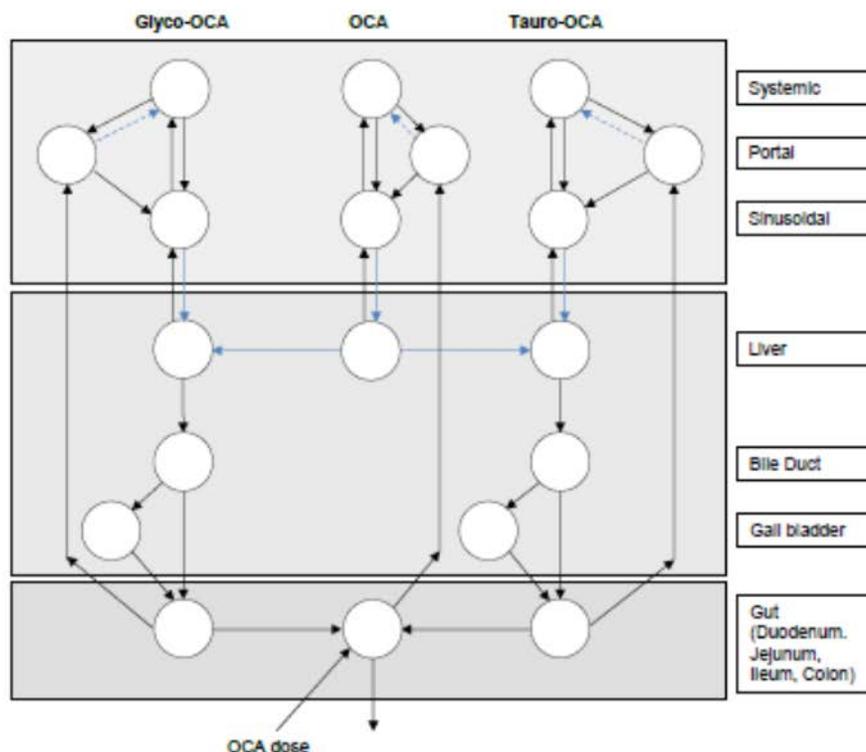
Physiological flow rates from CDCA model were fixed with the exception of flows from bile duct to gallbladder and from bile duct to gut, which were modified to accommodate the simplification of the gut compartment (**Supplementary Tables 3 and 4**, fixed typical values for system parameters).

- Gallbladder emptying time was assumed to be 90 min since the beginning of the meal
- OCA does not have zero order synthesis
- Dehydroxylation of OCA was not assumed because of steric hindrance
- Oral administration of OCA is represented as input into the gut compartment

### 3.5. OCA model for healthy subjects

Biotransformation and transport rates were fitted to observed plasma concentration-time profiles of OCA, glyco-OCA and tauro-OCA (**Figure 1**, Study 747-115). Plasma concentrations below the limit of quantitation (BLQ) of OCA, glyco-OCA and tauro-OCA were imputed to half of the lowest limit of quantitation (LLOQ). Both non-BLQ and inputted data from four Phase 1 studies and one Phase 2 study were used in this analysis (**Supplementary Table 5**).

**Figure 3: Conceptual representation of the models for OCA, glyco-OCA and tauro-OCA (Source: Figure 3-2, [1])**



Solid arrows correspond to flows or rates present in both normal and hepatic impaired subjects; dashed blue arrows correspond to portal systemic shunting (in subjects with hepatic impairment only); blue arrows represent the flows or rates changing with hepatic impairment. In this model, the volume of liver also changes with hepatic impairment.

### 3.6. OCA model adapted for hepatic impairment

Anatomical/physiological changes described by Johnson et al [9] were considered for system parameters of the model to describe OCA disposition in subjects with varying degrees of hepatic impairment. Child-Pugh (CP) A, B, and C were used to categorize mild, moderate, and severe hepatic impairment. These changes include portal-systemic shunting (as a result of increased portal blood pressure) and reduction in liver volume (**Table 2**). The magnitudes of decrease in hepatic uptake (active transport from sinusoidal space to the liver space) and increase in tauro-conjugation rates (decrease in glycine/taurine conjugation ratio) were fitted to observed plasma concentration-time profiles of OCA and conjugates in subjects with hepatic impairment taking a single oral dose of 10 mg OCA in Study 747-103 (**Table 3**).

**Table 2: Effect of cirrhosis on liver volume and hepatic flow fixed in the model (Source: Table 3.2.1, [1])**

| Parameters                         | Percentage change relative to healthy subjects <sup>b</sup> |        |        |
|------------------------------------|---|--------|--------|
|                                    | CP-A  | CP-B   | CP-C   |
| Average liver volume               | -10.9%  | -29.0% | -39.0% |
| Hepatic arterial flow <sup>a</sup> | +40.8%  | +62.5% | +91.5% |
| Hepatic portal flow <sup>a</sup>   | -9.0%   | -36.5% | -44.6% |

<sup>a</sup> The mesenteric arterial flow does not change. The balance of flows was achieved by setting the hepatic venous flow as the sum of hepatic arterial and portal flow, and the portal shunt flow as the mesenteric arterial less the hepatic portal flow.

<sup>b</sup> Numerical values of percentage change in liver volume and blood flows are slightly different from Table III of Johnson et al [9]. CP: Child-Pugh categories

**Table 3: Model parameters associated with anatomical/physiological changes in subjects with hepatic impairment (Source: Table 3.2.2, [1])**

| Parameters                            | Parameters fitted using data in subjects with hepatic impairment in 747-103 |                              |                              |
|---------------------------------------|---|------------------------------|------------------------------|
|                                       | CP-A  | CP-B                         | CP-C                         |
| Decreased hepatic uptake <sup>a</sup> | tvCL_sinu_liver*exp (Hepup2)  | tvCL_sinu_liver*exp (Hepup3) | tvCL_sinu_liver*exp (Hepup4) |
| Increased conjugation <sup>a</sup>    | tvCLf_tauro*exp(tconj2)   | tvCLf_tauro*exp(tconj3)      | tvCLf_tauro*exp(tconj4)      |

<sup>a</sup> tvCL\_sinu\_liver and tvCLf\_tauro are transport rate from sinusoidal space to liver and tauro conjugation rate constant (units: hr<sup>-1</sup>) in healthy subjects

### 3.7. Model verification

Models for OCA and conjugates were verified using plasma OCA pharmacokinetic data from study 747-105 (healthy subjects), 747-116 (healthy subjects), and 747-204 (subjects with hepatic impairment) (**Supplementary Table 5**).

### 3.8. Model application

Total OCA was calculated as the sum of OCA, glyco-OCA and tauro-OCA in nM units. Exposure metrics derived from simulations were AUC, Cmax and average concentration ( $C_{avg}=AUC_{0-24}/24$ ). Simulated liver exposures to total OCA was plotted with changes from baseline of liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) measured systemically at the end of treatment (day 6 to day 12) in the Phase 2 study 747-204.

Based on FDA's request, applicant also used PBPK model to simulate the dosing interval needed to match the steady-state plasma exposures in subjects with mild, moderate, or severe hepatic impairment to those achieved with 5 mg once daily (q.d.) dosing in healthy subjects. Simulated plasma PK profiles of total OCA (every 24 hours) for subjects receiving 5 mg OCA include q.d., every other day (q2d), once weekly (q.w.), every two weeks (q2w), and every 17.3 days (q.17.3.d) [2]. Liver exposures for these dosing regimens were also simulated.

### 3.9. Additional analyses

Comparisons were made between observed levels of total CDCA in study 747-103 (plasma), Fisher et al [8] (plasma and liver), and applicant's simulations (plasma and liver). In subjects with end-stage cholestasis, subjects with end-stage non-cholestasis cirrhosis, and subjects with normal liver function, mean total endogenous bile acid levels were 215 μM (explant liver samples), 119 μM (reviewer calculated, explant livers), and 57 μM (reviewer calculated) respectively in the liver, and 123 μM, 93 μM, and 5 μM (reviewer calculated), respectively in serum [8]. Reviewer calculated total CDCA based on digitized percentage of total bile acid in liver and serum for each of the three groups [8]. An FDA in house digitizing software was used for these calculations [9].

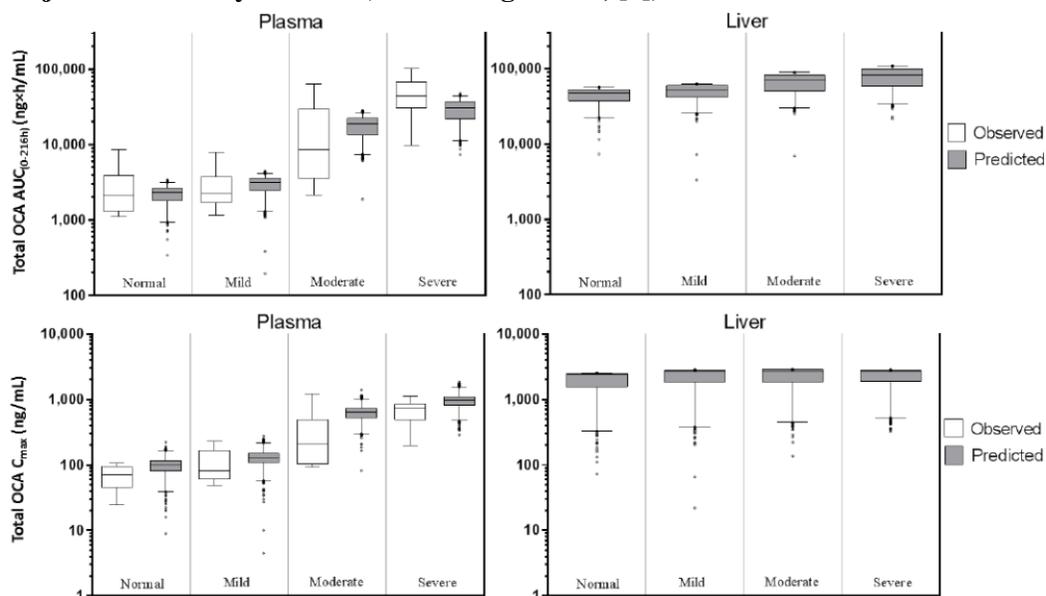
## 4. RESULTS

### 4.1. Does PBPK model adequately describe plasma pharmacokinetics of OCA and metabolites in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment?

Yes, simulated plasma concentration-time profiles of OCA and conjugates in subjects with normal hepatic function and in subjects with portal hypertension generally described observed data.

A comparison of observed plasma exposure data (AUC and C<sub>max</sub>) of total OCA from Study 747-103 and simulated data with best-fit model for OCA after a single dose of 10 mg q.d. is shown in **Figure 4** (left panels) for subjects with normal hepatic function and subjects with various degrees of hepatic impairment. Although there is some over-prediction of plasma total OCA for moderate impairment scenario, the model seems to reasonably characterize the extreme scenarios bracketed by normal and severe hepatic impairment category. The corresponding predictions of liver concentrations for each of these hepatic impairment scenarios are shown on the right panels of **Figure 4** (See more on 4.2 below).

**Figure 4: AUC and C<sub>max</sub> of systemic and liver concentration of total OCA by liver function in subjects from Study 747-103 (Source: Figure 4-2, [1])**



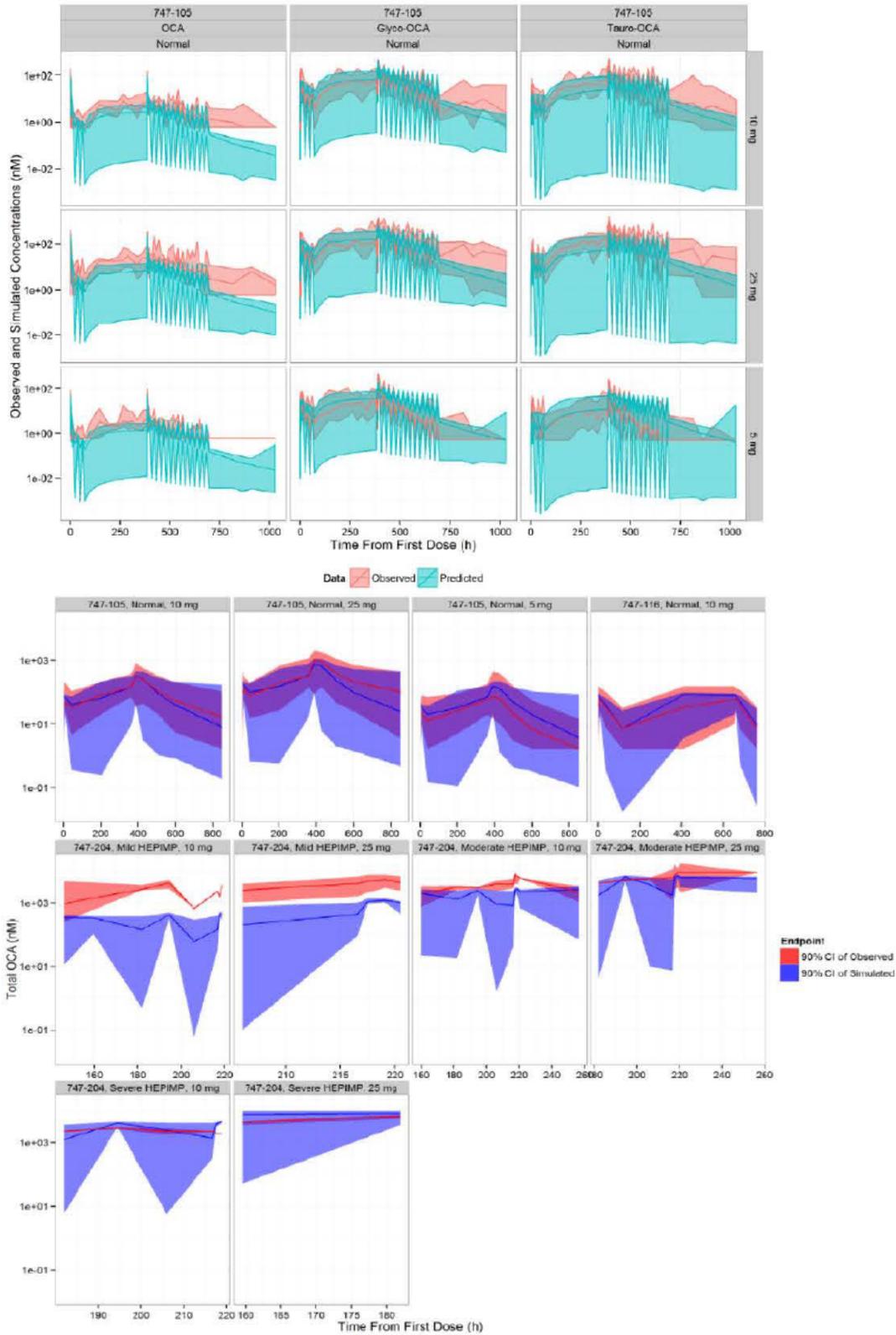
Observed data values are based on n = 8 subjects by group of hepatic impairment; Predicted data values are based on 200 iterations Monte-Carlo simulations in 8 subjects by group of hepatic impairment; Boxplot whiskers represent 1<sup>st</sup> and 99<sup>th</sup> percentile.

AUC = area under the curve; C<sub>max</sub> = maximum concentration; HEPIMP = hepatic impairment; n = number of subjects; OCA = obeticholic acid

**Figure 5** shows VPC plots for verification dataset (Studies 747-105, 106, and 204) that was not being used during model development. For Study 747-105, there is a systematic bias of under-prediction (e.g., predictions for 10 and 25 mg, and OCA PK predictions for 5 mg). For hepatic impairment, there is an apparent under-prediction of total OCA in subjects categorized as mild hepatic impairment based on Child-Pugh score in Study 747-204. The applicant hypothesized that these portal hypertension patients who were categorized CP-A may have physiological changes that are characteristic of moderate-severe hepatic impairment (See 4.4 for more

discussion on target population). **Supplementary Table 4** and **Supplementary Table 6** summarize parameters estimated using Study 747-115 (subjects with normal liver function) and Study 747-103 (subjects with varying degrees of hepatic impairment). Model estimated magnitude of percent decreases in hepatic uptake of OCA species were 12%, 84%, and 91%, (exponential of -0.132, -1.86, and -2.37, respectively for “Hepup”, Table 3) in subjects with mild, moderate, and severe hepatic impairment, respectively; model estimated magnitude of fold-increases in tauro-conjugation were 1.0- (no change), 2.9-, and 4.8-fold (exponential of 0.00481, 1.05, and 1.56, respectively for “tconj”, Table 3) in subjects with mild, moderate, and severe hepatic impairment, respectively. Increases in absorption rate constant ( $K_a$ ) and flow from bile to gall-bladder were also estimated (**Supplementary Table 6**). Of note, VPCs for all model building and verification datasets show high variability in plasma concentrations.

**Figure 5: Visual predictive check (VPC) plots of OCA PBPK model for observed data not used during model development (updated Figures 7.13 and 7.14 [1,2])**



#### 4.2. Can applicant's PBPK models be used to simulate liver exposure of OCA and metabolites?

Yes. However, it has to be acknowledged that both CDCA model and OCA model have many limitations and certain assumptions have not been confirmed (See 4.4). Nonetheless, sufficient evidence seems to support the use of OCA PBPK models to predict hepatic exposures of OCA and metabolites to support dosing recommendations of OCA in subjects with hepatic impairment.

First, the applicant was able to predict systemic and liver CDCA in healthy subjects and subjects with liver dysfunction. In response to FDA's 08242015IR, the applicant first stated that they reproduced modeling results based on Molino's CDCA model using Phoenix software (Phoenix CDCA model, [2]). Using the Phoenix CDCA model, the applicant conducted additional simulations to predict plasma and liver CDCA. For simulations of CDCA in subjects with severe hepatic impairment, effects of severe hepatic impairment on hepatic uptake and taurine conjugation estimated from OCA model (**Supplementary Table 6**) were directly applied for respective pathways for CDCA, and changes in system parameters (e.g., shunting and decreased liver volume) were the same as OCA simulations (**Table 2**). **Table 4** shows that model predicted plasma CDCA exposures are generally consistent with that observed in subjects with normal liver function and subjects with severe liver impairment from several studies [3, 8, 12]. More importantly, the Phoenix CDCA model predictions appear in-line with observed liver CDCA exposure in subjects with normal hepatic function and in subjects with end-stage cholestasis or cirrhosis (non-cholestasis). Of note, systemic CDCA levels seem to vary significantly across different studies.

**Table 4: Comparison of observed and simulated CDCA exposure in plasma and liver**

|                                  | Endogenous bile acid concentrations (µM) | Observed           | Simulated <sup>b</sup> |
|----------------------------------|--|--------------------|------------------------|
| Fisher et al, 1996 [8]           |  |                    |                        |
| Normal hepatic function          | Serum                                    | 1.45 <sup>a</sup>  | -                      |
|                                  | Liver                                    | 23.58 <sup>a</sup> | -                      |
| End-stage chronic cholestasis    | Serum                                    | 53.98 <sup>a</sup> | -                      |
|                                  | Liver                                    | 86.20 <sup>a</sup> | -                      |
| End-stage cirrhosis              | Serum                                    | 57.88 <sup>a</sup> | -                      |
|                                  | Liver                                    | 71.02 <sup>a</sup> | -                      |
| Stiehl et al 1990 [12]           |  |                    |                        |
| Stage I, II cirrhosis            | Serum                                    | 3.1                | -                      |
|                                  | Liver                                    | -                  | -                      |
| Stage IV cirrhosis               | Serum                                    | 38.6               | -                      |
|                                  | Liver                                    | -                  | -                      |
| study 747-103 [3]                |  |                    |                        |
| Normal hepatic function          | Plasma                                   | 3.49               | 5                      |
|                                  | Liver                                    | -                  | 69                     |
| Severe hepatic impairment (CP-C) | Plasma                                   | 61.9               | 47                     |
|                                  | Liver                                    | -                  | 89                     |

<sup>a</sup> Calculated based on the percentage of total endogenous bile acids digitized from Figures 2 (liver) and 5 (serum) from [8]. <sup>b</sup> Simulated using Phoenix CDCA model [2].

Second, modeling of both CDCA and OCA utilizes information of both compounds and a common systems model, which supports PBPK modeling for bile acids in general. The applicant also claimed that absorption, distribution, metabolism, and excretion (ADME) properties are generally comparable between CDCA and OCA, based on in vitro data as well as parameter estimated using respective PBPK models (**Supplementary Tables 7 and 8**).

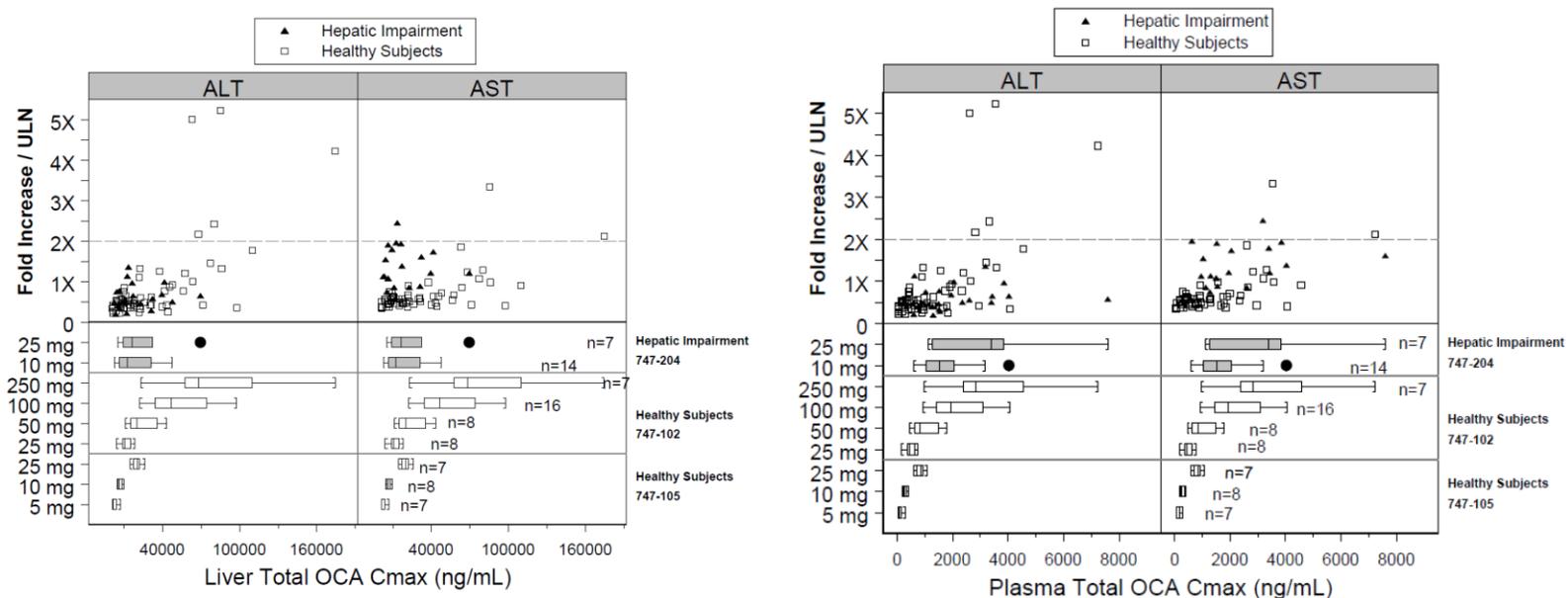
Last but not the least, observed plasma data of OCA and conjugates in subjects with varying degrees of hepatic impairment (Study 747-103) were critical for this analysis.

#### **4.3. Should OCA dose be adjusted in subjects with hepatic impairment?**

Yes, based on predicted plasma and liver exposures of OCA in subjects with hepatic impairment following different dosing schedules of OCA, and dose-response for pruritus (see main text of Question Based Review), a less frequent dosing schedule is recommended as starting dosing regimen in patients with moderate and severe hepatic impairment. If additional efficacy is desired, patients can be up-titrated via a combination of higher dose and more frequent dosing regimen depending on tolerability.

The applicant presented exposure-response relationship between predicted liver total OCA or observed plasma total OCA and change from baseline AST/ALT (**Figure 6**). Based on this analysis, the applicant suggested that there was no relationship between changes from baseline AST/ALT and plasma drug exposure [1]. The predicted liver concentration needs to be >48,200 ng/mL (black closed circle, left panel (liver), **Figure 6**) to result in increased ALT and AST (e.g., >2-fold increase from upper limit of normal). Model predicted liver total OCA exposures for subjects with portal hypertension (Study 747-204) appeared to be substantially lower than 48,200 ng/mL. As such, the applicant concluded that liver exposure is a more appropriate surrogate for predicting increased ALT and AST by OCA, and the predicted liver levels in patients from Study 747-204 are comparable to healthy subjects at the same dose levels (e.g., 10 or 25 mg q.d.). The applicant also proposed no dose adjustment in patients with hepatic impairment [6].

**Figure 6: Exposure-response relationship for ALT and AST in healthy subjects after daily administration of OCA at 5 mg, 10 mg, 25 mg, 50 mg, 100 mg, and 250 mg from Studies 747-102 and 747-105 and in subject with hepatic impairment after daily administration at 10 mg or 25 mg from Study 747-204. Left, model predicted liver exposure (The predicted liver C<sub>max</sub> was calculated based on liver/plasma ratio of 24.1, 20.3, 4.26, and 2.76 for healthy subjects, subjects with mild hepatic impairment, subjects with moderate hepatic impairment, and subjects with severe hepatic impairment, respectively); right, observed plasma exposure (Source Figures 1-2 and 4-3, ref [1])**



Although exposure-response relationship between plasma total OCA and change in AST/ALT is not apparent (**Figure 5**, right panel), little is known about the safety profiles of OCA (e.g., off-target effects) associated with plasma concentrations of OCA and its conjugates, and differential fold-increases exist among OCA, glyco-OCA and tauro-OCA in subjects with severe hepatic impairment (**Supplementary Table 2**). It is also worth noting here that OCA was dosed for only 7 days in subjects with hepatic impairment (portal hypertension) in study 747-204 and emergence of any hepatotoxicity safety signal with continued dosing cannot be ruled out. The FDA reviewers requested the applicant to provide simulations of plasma and liver OCA exposures in subjects with hepatic impairment following different OCA dosing schedules [2]. Predicted total OCA exposures in plasma and liver for subjects with normal hepatic function and subjects with hepatic impairment receiving 5 mg OCA q.d., q2d, q.w., q2w, and q.17.4.d are presented in **Table 5**, with individual OCA species data summarized in **Supplementary Tables 9-12**.

For patients with severe hepatic impairment, plasma total OCA exposure with 5 mg q.w. dosing is predicted to be similar to that for subjects with normal hepatic function and mild hepatic impairment receiving 5 mg OCA q.d.

**Table 5: PBPK model simulated average plasma and liver steady state concentrations ( $C_{ss,ave}$ ) for total OCA after a 5 mg q.d., q2d, q.w., q2w, and q.17.3.d (QD, Q2D, QW, Q2W, Q17.3D) dose of OCA stratified by hepatic function (Source: Table 2, [2]). Values are median [5<sup>th</sup>, 95<sup>th</sup>]**

| Hepatic Function                            | Dosing Interval     |                     |                     |                     |                     |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|
|   | QD                  | Q2D                 | QW                  | Q2W                 | Q17.3D              |
| Plasma $C_{ss,ave}$ (ng/mL)                 |                     |                     |                     |                     |                     |
| Median [5 <sup>th</sup> -95 <sup>th</sup> ] |                     |                     |                     |                     |                     |
| Normal                                      | 63.3<br>[56.5-64.1] | 31.6<br>[28.4-32.1] | 9.06<br>[8.3-9.2]   | 4.54<br>[4.1-4.6]   | 3.66<br>[3.3-3.7]   |
| Mild Impairment                             | 85.9<br>[77.2-87]   | 43<br>[38.8-43.5]   | 12.3<br>[11-12.4]   | 6.13<br>[5.6-6.2]   | 4.97<br>[4.5-5]     |
| Moderate Impairment                         | 602<br>[511-608]    | 301<br>[256-304]    | 85.9<br>[74.1-86.8] | 43<br>[36.2-43.4]   | 34.7<br>[28.3-35.3] |
| Severe Impairment                           | 1090<br>[899-1100]  | 544<br>[443-551]    | 156<br>[130-157]    | 77.7<br>[63-78.4]   | 63.0<br>[49-63.6]   |
| Liver $C_{ss,ave}$ (ng/mL)                  |                     |                     |                     |                     |                     |
| Normal                                      | 1260<br>[1140-1270] | 627<br>[575-636]    | 180<br>[166-182]    | 89.9<br>[82.1-90.9] | 72.8<br>[65.4-73.7] |
| Mild Impairment                             | 1410<br>[1300-1430] | 706<br>[648-714]    | 202<br>[183-204]    | 101<br>[92.3-102]   | 81.8<br>[74.9-82.8] |
| Moderate Impairment                         | 2180<br>[1890-2210] | 1090<br>[945-1100]  | 312<br>[274-315]    | 156<br>[134-158]    | 126<br>[105-128]    |
| Severe Impairment                           | 2840<br>[2390-2870] | 1420<br>[1180-1440] | 407<br>[346-410]    | 203<br>[168-205]    | 164<br>[131-166]    |

#### 4.4. What are limitations of PBPK model for OCA and CDCA?

Hepatic impairment causes multiple physiological changes that directly or indirectly affect the

ADME processes of a drug [9,11]. Although many changes have been quantitatively or semi-quantitatively incorporated into PBPK modeling framework [9,11], predictive performance of these models in prospectively predicting the effect of varying degrees of hepatic impairment on a drug's pharmacokinetics has not been established [13]. This is further complicated by clinical practice of categorizing hepatic impairment using CP score, which is a composite score of multiple clinical measures. For example, two patients of different liver disease origins may be categorized to have the same CP score. System models for hepatic impairment subjects developed according to CP categorization inherently carry large uncertainty when being used to predict the effect of hepatic impairment on drug exposure.

Molino et. al. [7] acknowledged deficiencies of the CDCA model, including a simplified enterocyte space, a simplified sinusoidal compartment ignoring zonation, the combination of duodeno-jejunum which was not able to explain immediate postprandial increase, pressure changes and fluid absorption by gall-bladder, fixed ratio of conjugation with glycine and taurine whereas taurine conjugation may vary depending on taurine pool, and ignorance of food-bile acid interaction in intestinal lumen. Of note, the CDCA model was used only to simulate total CDCA in small intestine and serum total CDCA during digestion of a meal, of which observed data are available [7]. Thus Molino model did not include some key elements such transporter regulation which is essential to estimate bile acid exposure in liver, and should not be considered as a model that has been fully verified.

Molino's CDCA model was then modified to simulate the pharmacokinetic profiles for OCA and its two conjugates in plasma and liver. However, discrepancies among the terminology and units make it difficult to compare CDCA model parameters listed in Molino's report (Tables 5 and 7, [7]) and that summarized in [1]. For example, one should be able to compare the flow constant ( $f_{22}$ ) in the report (0.003 L/min, [1]) to the transfer coefficient ( $f_{22}$ , 0.003 per min, table 5 of ref [7]) or flow (bile duct to gall-bladder, 0.06 L/min, table 7 of ref [7]) used in Molino's paper [7]. Also related to transparency of the model modification, one should be able to identify how many parameters were actually modified by comparing the original CDCA model parameters (**Supplementary Table 3**) and the updated OCA parameters (**Supplementary Table 4**). For example, transport rates for glyco-CDCA and tauro-CDCA from sinusoidal to liver are the same, but these rates are different for OCA conjugates.

Many assumptions for both CDCA and OCA models, though plausible, cannot be confirmed or adequately justified (i.e., negligible biliary excretion of parent CDCA and OCA, assumption on hepatic first-pass extraction of OCA, rate of de-conjugation of glycine conjugate was 3-times higher than that of taurine conjugate, percentage of glyco-CDCA entering ileum). With regard to hepatic impairment, the model assumed increased tauro-conjugation by hepatic impairment (**Table 3**) that is not bile acid specific. Of note conflicted observations of the total glycine to taurine ratio were reported for patients with liver disease. For example, a decreased total glycine to taurine ratio was reported in PBC patients [14], and Linnet (1982) reported that total glycine to taurine ratio was significantly lower in subjects with extrahepatic cholestasis (median 1.1) than in subjects with cirrhosis (median, 2.0) and in subjects with normal hepatic function (median, 1.7) [15].

Other discrepancies identified include:

- The combined volume of jejunal, ileal, and colonic spaces was 0.9 L, instead of 0.92 L (**Supplementary Table 3**). Flow constants for f1, f3, f4, and f5 are 16.1, 94.3, 5.9, 450 L/h.
- Gallbladder emptying after meal was assumed to be 90 min for OCA model [1] but was stated to be 120 min in response to the information request [2]. The same value was 120 min for CDCA [7].
- The same parameters were tested for the value of 210 min for Phoenix CDCA model [2] to match the original simulation of the effect of food on CDCA pharmacokinetics, whereas the original work reported the use of 120 min [7] (**Supplementary Figure 1**).

## 5. CONCLUSION

The applicant's model was informed by plasma concentrations of OCA and conjugates observed in subjects with varying degrees of hepatic impairment (relatively rich model development dataset) and was able to generally capture OCA exposure observed in subjects with normal hepatic function and with hepatic impairment (verification datasets). The applicant also predicted plasma and liver exposures of CDCA in subjects with normal hepatic function and in subjects with severe hepatic impairment (cholestasis and non-cholestasis). Despite several limitations recognized for modeling of both OCA and CDCA and the lack of predictability of PBPK for hepatic impairment [13], the applicant's prediction of liver OCA exposures using PBPK is considered useful in supporting dosing recommendations of OCA in patients with hepatic impairment.

Although the magnitude of elevation in liver OCA concentrations in subjects with severe hepatic impairment was predicted to be less than that in plasma concentrations, there were significantly higher plasma OCA exposures in subjects with moderate and severe hepatic impairment compared to patients with normal liver function. With the evidence of dose-response relationship for pruritus (and related discontinuations, see main text of Question Based Review) and unknown relationship of plasma/liver exposures to pruritus, a conservative approach of adjustment of starting dose in subjects with severe hepatic impairment to match plasma exposures to those subjects with normal hepatic function, followed by subsequent up-titrations of dose and dosing frequency, appears reasonable.

## 6. SUPPLEMENTARY INFORMATION

### 6.1. Abbreviations

ADME, absorption, distribution, metabolism, and excretion; ALT, alanine aminotransferase; ASBT, apical sodium dependent bile acid transporter; AST, aspartate aminotransferase; AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; b.i.d., twice daily dosing; B/P, blood to plasma ratio; BLQ, below the limit of quantification; BSEP, bile salt excretory pump; BSV, between subject variability; CDCA, chenodeoxycholic acid;  $C_{avg}$ , average concentration; CI, confidence interval;  $C_{max}$ , maximal concentration in plasma;  $C_{maxR}$ , the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the

perpetrator; CP, Child-Pugh score; CV, coefficient of variation; CWRES, conditional weighted residuals; EC50, concentration to achieve 50% of the maximum effect; ETA, individual random effect; FXR, farnesoid X receptor; Glyco-CDCA, glycine conjugate of CDCA; glyco-OCA, glycine conjugate of OCA;  $f_{up}$ , fraction unbound in plasma; IPRED, individual prediction;  $K_a$ , first order absorption rate constant;  $K_p$ , tissue/plasma partitioning; LLOQ, lower limit of quantification; LOESS, locally weighted scatterplot smoothing; MVN, multivariate normal distribution;  $\text{Log}P_{o:w}$ , logarithm of the octanol-water partition coefficient; NA, not applicable; NDA: new drug application; OCA, obeticholic acid; OST, organic solute transporters; PBC, primary biliary cirrhosis; PRED, population prediction; PSC, primary sclerosing cholangitis; q.d., once daily; q2d, once every other day; q.w., once weekly; q2w, once every two weeks; q.17.3.d, once every 17.3 days; RSE, relative standard error, SD, standard deviation, tauro-CDCA, taurine conjugate of CDCA; tauro-OCA, taurine conjugate of OCA; s, population value of a model parameter for a given effect; ULN, upper limit of normal; VPC, visual predictive check;  $P_{app}$ , apparent passive permeability; PBPK: Physiological-based Pharmacokinetic; ursodeoxycholic acid, UDCA.

## **6.2. Information requests**

### 6.2.1. Clinical Pharmacology (dated Sep 09, 2015)

In regard to your PBPK report “Modeling and simulations to support liver safety of obeticholic acid” (report):

- a. Clarify if you reproduced Molino’s 1986 results using the model you constructed in Phoenix.
- b. Compare in detail ADME properties of OCA and CDCA, and their respective conjugates. Such details include quantitative, protein level activities of drug metabolism, diffusion, and transport in each system/space.
- c. Introduction of the report (page 7) summarized fold-increase values of bile acids in serum and liver in patients with cirrhosis or PBC/PSC versus healthy subjects. You also stated that taurine conjugation of CDCA may be greater in hepatic impaired subjects (page 27). For these conditions, adjust your physiology model by considering known physiology changes and simulate plasma and liver levels of respective bile acids. Estimates of the effect of hepatic impairment on OCA hepatic uptake and taurine conjugation (Table 7.10) can be referenced/ modified in the model for the new simulations. Compare simulated plasma and liver bile acid levels with observed data mentioned above:
- d. Figure 4.3 of the report shows ER relationship using predicted liver total OCA levels. These liver levels are indirectly calculated using model predicted plasma/liver  $C_{max}$  ratios. Justify the adequacy of this calculation.
- e. Overlay 90% CI of both predicted and observed data on the same plot for figures 7.13 and 7.14.

Additional requests regarding population pharmacokinetic analysis were sent to the applicant.

### 6.3. Supplementary Tables and Figures

**Supplementary Table 1: Geometric mean exposure values of OCA, glyco-OCA, tauro-OCA, and total OCA in subjects with normal liver function and in subjects with varying degrees of hepatic impairment (Source: Tables 14.2.1.1-4,[4])**

| Hepatic function <sup>a</sup> | Parameters (units) <sup>b</sup> | OCA      | Glyco-OCA | Tauro-OCA | Total-OCA |
|-------------------------------|---------------------------------|----------|-----------|-----------|-----------|
| Normal                        | AUCt (ng/ml h)                  | 145.098  | 1507.93   | 603.632   | 2032.27   |
|                               | AUC 24(ng/ml h)                 | 81.036   | 478.622   | 152.288   | 641.106   |
|                               | Cmax (ng/mL)                    | 50.428   | 43.975    | 15.552    | 62.437    |
| Mild                          | AUCt (ng/ml h)                  | 199.855  | 1915.909  | 427.776   | 2289.451  |
|                               | AUC 24(ng/ml h)                 | 118.401  | 630.473   | 116.202   | 788.647   |
|                               | Cmax (ng/mL)                    | 68.036   | 62.774    | 13.558    | 92.816    |
| Moderate                      | AUCt (ng/ml h)                  | 349.568  | 5019.448  | 4138.842  | 8545.281  |
|                               | AUC 24(ng/ml h)                 | 255.237  | 1883.237  | 1009.972  | 2822.473  |
|                               | Cmax (ng/mL)                    | 96.357   | 164.194   | 87.62     | 234.596   |
| Severe                        | AUCt (ng/ml h)                  | 1020.141 | 17163.4   | 22236.99  | 35116.47  |
|                               | AUC 24(ng/ml h)                 | 672.267  | 5465.626  | 5022.804  | 9789.211  |
|                               | Cmax (ng/mL)                    | 237.258  | 357.094   | 333.049   | 608.568   |

<sup>a</sup> Mild (Child-Pugh A); moderate (Child-Pugh B); severe (Child-Pugh C) and normal hepatic function. <sup>b</sup>AUCt AUC from time zero to the time of the last measurable concentration. The PK parameters of OCA, glyco-OCA, and tauro-OCA were determined using unadjusted concentrations (direct weight equivalents). Prior to calculating total OCA concentrations, the plasma concentrations of glyco-OCA and tauro-OCA were adjusted for mass equivalence to OCA as follows Glyco-OCA adjusted = unadjusted glyco-OCA concentration × 0.8805; Tauro-OCA adjusted = unadjusted tauro-OCA concentration × 0.7969. The resulting total OCA concentrations (sum of plasma OCA, glyco-OCA adjusted, and tauro-OCA adjusted) were used to calculate total OCA PK parameters.

**Supplementary Table 2: Comparison of total endogenous bile acid (sum of bile acid, glyco- and tauro-conjugates) exposures between Study 747-103 (hepatic impairment study [4]) and Fisher et al [5]. (Source: Table 14.2.1.7.8-13, [4])**

|                   |                                | Ursodeoxycholic acid | Chenodeoxycholic acid | Deoxycholic acid | Cholic acid | Lithocholic acid | Iso bile acids | Total  |
|-------------------|--------------------------------|----------------------|-----------------------|------------------|-------------|------------------|----------------|--------|
| Study 747-103 [4] | Severe hepatic impairment CP-C | 2.02                 | 65.19                 | 3.24             | 23.25       | 0.23             |                | 93.92  |
|                   | Control                        | 0.18                 | 3.27                  | 2.32             | 1.52        | 0.11             |                | 7.40   |
|                   | ratio                          | 11.32                | 19.95                 | 1.40             | 15.31       | 1.98             |                | 12.70  |
|                   | Liver                          |                      |                       |                  |             |                  |                |        |
|                   | CP-C                           | NA                   | NA                    | NA               | NA          | NA               |                | NA     |
|                   | Control                        | NA                   | NA                    | NA               | NA          | NA               |                | NA     |
|                   | ratio                          | NA                   | NA                    | NA               | NA          | NA               |                | NA     |
| Fisher 1996 [5]   | Serum                          |                      |                       |                  |             |                  |                |        |
|                   | Cholestasis                    | 3.01                 | 53.98                 | 2.36             | 57.02       | 3.46             | 5.66           | 123.00 |
|                   | Control                        | 0.60                 | 1.45                  | 0.82             | 0.84        | 0.37             | 1.17           | 5.35   |
|                   | ratio                          | 4.99                 | 37.29                 | 2.87             | 68.02       | 9.22             | 4.85           | 23.00  |
|                   | Liver                          |                      |                       |                  |             |                  |                |        |
|                   | Cholestasis                    | 6.01                 | 86.20                 | 3.67             | 109.25      | 6.96             |                | 215.00 |
|                   | Control                        | 0.91                 | 23.58                 | 15.28            | 14.44       | 2.95             |                | 56.58  |
|                   | ratio                          | 6.62                 | 3.66                  | 0.24             | 7.57        | 2.36             |                | 3.80   |
| Fisher 1996 [5]   | Serum                          |                      |                       |                  |             |                  |                |        |
|                   | non-cholestasis                | 8.11                 | 57.88                 | 0.63             | 14.16       | 0.00             | 12.45          | 92.80  |
|                   | Control                        | 0.60                 | 1.45                  | 0.82             | 0.84        | 0.37             | 1.17           | 5.35   |
|                   | ratio                          | 13.47                | 39.99                 | 0.77             | 16.89       | 0.00             | 10.67          | 17.35  |
|                   | Liver                          |                      |                       |                  |             |                  |                |        |
|                   | non-cholestasis                | 1.92                 | 71.02                 | 0.15             | 46.06       | 0.09             |                | 119.44 |
|                   | Control                        | 0.91                 | 23.58                 | 15.28            | 14.44       | 2.95             |                | 56.58  |
|                   | ratio                          | 2.12                 | 3.01                  | 0.01             | 3.19        | 0.03             |                | 2.11   |

<sup>a</sup> Severe (Child-Pugh C) and normal hepatic function. Units are micromolar (plasma,  $\mu\text{M}$ ) or nmol/g liver (hepatic). Study 747-103 Concentrations are geometric mean time-averaged (across the 5, 6, 10, and 11 hours time-points after single oral dose of 10 mg OCA). Ratios are CP-C/control. Fisher et al concentration values were approximated by digitizing figures that summarized % contribution of each bile acid to total endogenous bile acids for each study group. Geometric least square mean total bile acid concentration in subjects with hepatic impairment to that in subjects with normal hepatic function.

**Supplementary Table 3: Values of volumes spaces and flux constants used in the CDCA model  
(Source: Table 7.1, [1], Tables 5 and 6, [7])**

Note: In reference [7] values for the following processes were different:

B45 was 1.0 (dihydroxylation in colon), b0 >0; t26 was 0.0015, t28 was 0, and t27 was 0; Synthesis rate was 0.22 umol/min (b0)

| Volume Spaces                                   | Compartment    | Value (L)  |                       |
|---|----------------|--|-----------------------|
| Systemic Space                                  | 1.1, 1.2, 1.3  | 2.46   |                       |
| Portal Space                                    | 2.1, 2.2, 2.3  | 0.420  |                       |
| Sinusoidal Space                                | 3.1, 3.2, 3.3  | 0.120  |                       |
| Hepatic Space                                   | 4.1, 4.2, 4.3  | 0.950  |                       |
| Bile Duct Space                                 | 5.1, 5.2, 5.3  | 0.020  |                       |
| Gallbladder Space                               | 6.1, 6.2, 6.3  | 0.020  |                       |
| Jejunal Space                                   | 7.1, 7.2, 7.3  | 0.300  |                       |
| Ileal Space                                     | 8.1, 8.2, 8.3  | 0.150  |                       |
| Colonic Space                                   | 9.1, 9.2, 9.3  | 0.450  |                       |
| Flow Constants                                  | Value (L/min)  | Parameter  | Value (L/min)         |
| Mesenteric (f <sub>1</sub> )                    | 0.26829        | Bile duct → jejunum (f <sub>24</sub> )                   | 0.00700               |
| Portal-systemic shunt (f <sub>2</sub> )         | 0 <sup>a</sup> | Duodenum/Jejunum → ileum (fasting; f <sub>31</sub> )     | 0.00300               |
| Portal (f <sub>3</sub> )                        | 1.5714         | Duodenum/Jejunum → ileum (fed; f <sub>32</sub> )         | 0.0 1200              |
| Hepatic Arterial (f <sub>4</sub> )              | 0.098          | Ileum → colon (fasting; f <sub>38</sub> )                | 0.0020                |
| Hepatic Venous (f <sub>5</sub> )                | 7.5000         | Ileum → colon (fed; f <sub>39</sub> )                    | 0.00800               |
| Bile duct → gallbladder (f <sub>22</sub> )      | 0.00300        | Colon → out (f <sub>46</sub> )                           | 5.000 <sup>c</sup>    |
| Gallbladder → jejunum (f <sub>23</sub> )        | 0.0200         |  |                       |
| Biotransformation Constants                     | Value (L/min)  | Parameter  | Value (L/min)         |
| CDCA → glyco-CDCA (b <sub>15</sub> )            | 0.06           | glyco-CDCA → CDCA (b <sub>42</sub> )                     | 5.0000                |
| CDCA → tauro-CDCA (b <sub>16</sub> )            | 0.02           | tauro-CDCA → CDCA (b <sub>43</sub> )                     | 5.0000                |
| glyco-CDCA → CDCA (b <sub>35</sub> )            | 0.04000        | CDCA → Lithocholic Acid (b <sub>45</sub> ) <sup>d</sup>  | 0                     |
| tauro-CDCA → CDCA (b <sub>36</sub> )            | 0.00800        | syn (b <sub>0</sub> ) de novo synthesis                  | NA                    |
| Transport Constants                             | Value (L/min)  | Parameter  | Value (L/min)         |
| glyco-CDCA: Sinusoid → liver (t <sub>9</sub> )  | 17.500         | glyco-CDCA: Duodenum/jejunum → portal (t <sub>26</sub> ) | 0                     |
| CDCA: Sinusoid → liver (t <sub>10</sub> )       | 11.250         | CDCA: Duodenum/jejunum → portal (t <sub>27</sub> )       | 0. 20000 <sup>e</sup> |
| tauro-CDCA: Sinusoid → liver (t <sub>11</sub> ) | 17.500         | tauro-CDCA: Duodenum/jejunum → portal (t <sub>28</sub> ) | 0                     |
| glyco-CDCA: Liver → sinusoid (t <sub>12</sub> ) | 0.027          | glyco-CDCA: Ileum → portal (t <sub>33</sub> )            | 0.16000               |
| CDCA: Liver → sinusoid (t <sub>13</sub> )       | 0.027          | CDCA: Ileum → portal (t <sub>34</sub> )                  | 0.20000               |
| tauro-CDCA: Liver → sinusoid (t <sub>14</sub> ) | 0.027          | tauro-CDCA: Ileum → portal (t <sub>35</sub> )            | 0. 15200              |
| glyco-CDCA: Liver → bile (t <sub>19</sub> )     | 0.15000        | glyco-CDCA: Colon → portal (t <sub>40</sub> )            | 0                     |
| CDCA: Liver → bile (t <sub>20</sub> )           | 0 <sup>a</sup> | CDCA: Colon → portal (t <sub>41</sub> )                  | 0                     |
| tauro-CDCA: Liver → bile (t <sub>21</sub> )     | 0.15000        | tauro-CDCA: Colon → portal (t <sub>42</sub> )            | 0                     |

<sup>a</sup> Fluxes that do not occur in healthy subjects

<sup>b</sup> Assumed values taken from cholic acid PK model (Molino et al., 1986)

<sup>c</sup> Values originally zero; however, this value was fixed to 5

<sup>d</sup> b<sub>45</sub> was fixed to zero

<sup>e</sup> Fixed to the ileum rate constant for CDCA

<sup>f</sup> NA: Not applicable (no *de novo* synthesis of OCA)

CDCA = chenodeoxycholic acid

**Supplementary Table 4: Typical values of the physiological population PK model parameters for OCA and its conjugates in subjects with normal hepatic function (Source: Table 7.7, [1])**

| Parameter                                | Typical value |       | BSV (RSE%)    |
|--|---------------|-------|---------------|
|  | Estimate      | RSE%  |               |
| tvQha (L/h)                              | 14.4          | Fixed | NA            |
| tvQportal (L/h)                          | 39.6          | Fixed |               |
| tvCLsinu_liver_OCA (h <sup>-1</sup> )    | 1698          | 1.0   |               |
| tvCLsinu_liver_gly (h <sup>-1</sup> )    | 1210          | 2.0   |               |
| tvCLsinu_liver_tau (h <sup>-1</sup> )    | 1615          | 1.9   |               |
| tvCLliver_sinu_OCA (h <sup>-1</sup> )    | 1.62          | Fixed |               |
| tvCLliver_sinu_glytau (h <sup>-1</sup> ) | 1.62          | Fixed |               |
| tvQbile_gut (L/h)                        | 7.29          | 4.5   |               |
| tvQbile_gb (L/h)                         | 0.856         | 4.4   | 78.1 % (19.3) |
| tvCLgb_gut (h <sup>-1</sup> )            | 1.2           | Fixed | NA            |
| tvKout_OCA (L/h)                         | 0.612         | 5.5   |               |
| tvCLf_glyco (h <sup>-1</sup> )           | 1.44          | 4.5   |               |
| tvCLf_tauro (h <sup>-1</sup> )           | 0.312         | 1.9   |               |
| tvKdeconj_gutglyco (h <sup>-1</sup> )    | 0.0431        | 4.5   |               |
| tvKdeconj_guttauro (h <sup>-1</sup> )    | 0.0200        | 1.8   |               |
| tvKa_gutOCA (h <sup>-1</sup> )           | 0.857         | 3.4   |               |
| tvKa_gutglyco (h <sup>-1</sup> )         | 0.904         | 1.1   |               |
| tvKa_guttauro (h <sup>-1</sup> )         | 1.62          | 2.2   | 195 % (2.21)  |
| tvKa (h <sup>-1</sup> )                  | 5.32          | 1.0   |               |
| tvCLliver_bile_glyco (h <sup>-1</sup> )  | 7.44          | 0.7   | NA            |
| tvCLliver_bile_tauro (h <sup>-1</sup> )  | 9.28          | 1.0   |               |
| Prop Error OCA (%)                       | 88.0          | 33.9  |               |
| Prop Error Glyco-OCA (%)                 | 62.6          | 32.7  |               |
| Prop Error Tauro-OCA (%)                 | 71.6          | 70.4  |               |
| Additional Error OCA (nM)                | 0.546         | 16.5  |               |
| Additional Error Glyco-OCA (nM)          | 0.675         | 21.8  |               |
| Additional Error Tauro-OCA (nM)          | 0.469         | 50.3  |               |

BSV = between-subject variability; glyco-OCA = glycine conjugate of OCA; OCA= obeticholic acid; NA = not applicable; Prop. = proportional; RSE%= relative standard error (%); tauro-OCA = taurine conjugate of OCA; tvCLf\_glyco = OCA rate of conjugation with glycine; tvCLf\_tauro= OCA rate of conjugation with taurine; tvCLgb\_gut = rate of output from gallbladder to gut; tvCLliver\_bile\_glyco = glyco-OCA transport rate from liver to bile duct; tvCLliver\_bile\_tauro = tauro-OCA transport rate from liver to bile duct; tvCLliver\_sinu\_glytau = glyco-OCA and tauro-OCA transport rate from liver to sinusoidal space; tvCLliver\_sinu\_OCA = OCA transport rate from liver to sinusoidal space; tvCLsinu\_liver\_gly = glyco-OCA transport rate from sinusoidal space to liver; tvCLsinu\_liver\_OCA = OCA transport rate from sinusoidal space to liver; tvCLsinu\_liver\_tau = tauro-OCA transport rate from sinusoidal space to liver; tvKa = OCA first order rate constant of oral absorption; tvKa\_gutglyco = glyco-OCA rate of absorption from gut to portal space; tvKa\_gutOCA = OCA rate of absorption from gut to portal space; tvKa\_guttauro = tauro-OCA rate of absorption from gut to portal space; tvKdeconj\_gutglyco = glyco-OCA rate of deconjugation to OCA; tvKdeconj\_guttauro = tauro-OCA rate of deconjugation to OCA; tvKout\_OCA = rate of fecal elimination of OCA; tvQbile\_gb = flow from bile duct to gallbladder; tvQbile\_gut = flow from bile duct to gut; tvQha = hepatic arterial flow; tvQportal = hepatic portal flow.

**Supplementary Table 5: Data source for PBPK modeling of OCA and conjugates (Modified from Table 3.1-1, [1])**

| Study number       | Dosing  | subjects  | Notes  | Purpose                                  |
|--------------------|---|---|--|--|
| 747-115<br>Phase 1 | Single dose day 1 and day 28, 10 mg. Two different formulations: commercial image or clinical development tablets | 160 healthy subjects  | Open label, two-way crossover  | Model development – healthy subjects     |
| 747-103<br>Phase 1 | Single dose 10 mg, commercial tablets   | 8 healthy subjects, 24 (8 each) hepatic impairment subjects of different degrees (hepatic impairment study)   | Open label. Hepatic impairment study   | Model development – hepatic impairment   |
| 747-105<br>Phase 1 | Single dose followed by once daily (q.d.) for 14 days. 5, 10, or 25 mg, commercial tablets                        | 24 healthy subjects, 8 per arm  | Open label, randomized, single and multiple dose study. Exposure levels of OCA, conjugates, and total OCA were near dose proportional after a single dose. Following multiple dose administration, dose-proportionality was concluded for parent drug only. For conjugates and total OCA, C <sub>max</sub> and AUC increased more than proportionally with dose. | Model verification – healthy subjects    |
| 747-116<br>Phase 1 | Single dose at day 1 and day 28, 10 mg Two different formulations: commercial image tablet or capsule             | 160 healthy subjects  | Open label, two-way crossover  | Model verification in healthy subjects   |
| 747-204<br>Phase 2 | 10 or 25 mg q.d., capsule or tablet   | 23 subjects with cirrhosis (15 in 10 mg, 8 in 25 mg arm) (portal hypertension study). The numbers of mild, moderate, and severe hepatic impairment subjects were 8, 12, and 3, respectively | Portal hypertension study  | Model verification in hepatic impairment |

**Supplementary Table 6: Typical values of the model parameters for OCA and conjugates in subjects with impaired hepatic function (Source: Table 7.10, [1])**

| Parameter                       | Estimate     | RSE%  |
|---------------------------------|--------------|-------|
| Hepup2                          | -0.132       | 9.11  |
| Hepup3                          | -1.86        | 44.3  |
| Hepup4                          | -2.37        | 24.9  |
| tconj2                          | 0.00481      | 0.341 |
| tconj3                          | 1.05         | 15.8  |
| tconj4                          | 1.56         | 109   |
| Residual Errors Parameter       | Estimate     | RSE%  |
| Prop Error OCA (%)              | 122          | 77.1  |
| Prop Error Glyco-OCA (%)        | 112          | 384   |
| Prop Error Tauro-OCA (%)        | 123          | 636   |
| Additional Error OCA (nM)       | 0.993        | 77.1  |
| Additional Error Glyco-OCA (nM) | 0.273        | 383   |
| Additional Error Tauro-OCA (nM) | 0.532        | 627   |
| BSV                             |              |       |
| Parameter                       | Estimate (%) | RSE%  |
| tvKa                            | 246          | 9.87  |
| tvQbile_gb                      | 168          | 299   |

BSV = between-subject variability; HEPIMP = hepatic impairment; Prop. = proportional; Hepup2= effect of HEPIMP for mild group in hepatic uptake for OCA, glyco-OCA, and tauro-OCA; Hepup3= effect of HEPIMP for moderate group in hepatic uptake for OCA, glyco-OCA, and tauro-OCA; Hepup4= effect of HEPIMP for severe group in hepatic uptake for OCA, glyco-OCA and tauro-OCA; RSE%= relative standard error (%); tconj2= effect of HEPIMP for mild group on rate of OCA tauro-conjugation; tconj3 = effect of HEPIMP for moderate group on rate of OCA tauro-conjugation; tconj4= effect of HEPIMP for severe group on rate of OCA tauro-conjugation; tvKa = OCA first order rate constant of oral absorption.

**Supplementary Table 7: Comparison of the hepatobiliary uptake, metabolism and excretion of deuterated CDCA (d4-CDCA) and OCA in Sandwich Cultured Human Hepatocytes (SCHH) (adopted and modified from Table 2, ref [2])**

| Compound Administered <sup>a</sup> | Test Compound | Intracellular Conc. (μM) | Bile Conc. (μM) | Intracellular conc/dose concentration (Kp) | BEI <sup>c</sup> (%) |
|------------------------------------|---------------|--------------------------|-----------------|--|----------------------|
| d4-CDCA (5 μM)                     | d4-CDCA       | 5.3 ± 1.1                | BLQ             | 1.1 ± 0.2                                  | ND <sup>c</sup>      |
|                                    | d4-Tauro-CDCA | BLQ <sup>b</sup>         | BLQ             | NA <sup>d</sup>                            | ND <sup>c</sup>      |
|                                    | d4-Glyco-CDCA | 4.2 ± 1.1                | 23.7 ± 12.5     | NA <sup>d</sup>                            | 42.1 ± 23.4          |
| OCA (5 μM)                         | OCA           | 7.23 ± 1.32              | BLQ             | 1.45 ± 0.26                                | ND                   |
|                                    | Tauro-OCA     | 1.20 ± 0.45              | 0.75 ± 3.53     | NA <sup>d</sup>                            | 7.57 ± 35.47         |
|                                    | Glyco-OCA     | 7.86 ± 1.90              | 53.8 ± 31.8     | NA <sup>d</sup>                            | 47.1 ± 30.2          |

<sup>a</sup> SCHH were treated with d4-CDCA or OCA at 5 μM for 20 minutes at 37°C; <sup>b</sup> Below the limit of quantitation (1.53 μM, versus 0.77 μM for Tauro-OCA); <sup>c</sup> ND: Not determined due to concentrations being below the limit quantitation (BLQ), of note, no information on BLQ was available in [2]; <sup>d</sup> NA: Not applicable since only CDCA or OCA was dosed in the media; eBEI(%), biliary excretion index, fraction of the parent or metabolite that is excreted into the bile

**Supplementary Table 8: Comparison of ADME Parameters of OCA and CDCA using the Physiologic PK Model for OCA and the Original CDCA Model (Source: Table 1, ref [2])**

| Parameter                                     | Description  | Model for OCA  | Reported from CDCA model <sup>c</sup>   |
|---|--|--|---|
| <b>Hepatobiliary system</b>                   |  |  |   |
| Hepatic Uptake (h <sup>-1</sup> )             | First order uptake rate constant from the sinusoidal space to the liver  | OCA: 1698<br>Glyco-OCA: 1210<br>Tauro-OCA: 1615  | CDCA: 675<br>Glyco-CDCA: 1050<br>Tauro-CDCA: 1050   |
| Conjugation to Glycine (h <sup>-1</sup> )     | First order conjugation rate constant for glycine  | OCA: 1.44  | CDCA: 3.6   |
| Conjugation to Taurine (h <sup>-1</sup> )     | First order conjugation rate constant for taurine  | OCA: 0.312   | CDCA: 1.2   |
| Basolateral Hepatic Efflux (h <sup>-1</sup> ) | First order efflux rate constant from the liver to the sinusoidal blood space  | OCA: 1.62 <sup>a</sup><br>Glyco-OCA: 1.62 <sup>a</sup><br>Tauro-OCA: 1.62 <sup>a</sup> | CDCA: 1.62<br>Glyco-CDCA: 1.62<br>Tauro-CDCA: 1.62  |
| Apical Hepatic Efflux (h <sup>-1</sup> )      | First order efflux rate constant from the liver to the bile duct   | OCA: 0 <sup>b</sup><br>Glyco-OCA: 7.44<br>Tauro-OCA: 9.28                              | CDCA: 0<br>Glyco-CDCA: 9<br>Tauro-CDCA: 9   |
| <b>Enteral system <sup>b</sup></b>            |  |  |   |
| K <sub>a</sub> (h <sup>-1</sup> )             | First order absorption rate constant   | <i>Gut</i><br>OCA: 0.857<br>Glyco-OCA: 0.904<br>Tauro-OCA: 1.62                        | <i>Duodenum/Jejunum</i><br>CDCA: 0; Glyco-CDCA: 0.09; Tauro-CDCA: 0<br><i>Ileum</i><br>CDCA: 12; Glyco-CDCA: 9.6; Tauro-CDCA: 12<br><i>Colon</i><br>CDCA: 0; Glyco-CDCA: 0; Tauro-CDCA: 0 |
| K <sub>deconjugation</sub> (h <sup>-1</sup> ) | First order rate constant for the conversion (de-conjugation) of glyco-OCA or tauro-OCA to OCA in the gastrointestinal tract | <i>Gut</i> <sup>b</sup><br>Glyco-OCA: 0.0431<br>Tauro-OCA: 0.0200                      | <i>Duodenum/Jejunum</i><br>Glyco-CDCA: 0; Tauro-CDCA: 0<br><i>Ileum</i><br>Glyco-CDCA: 2.4; Tauro-CDCA: 1.2<br><i>Colon</i><br>Glyco-CDCA: 300; Tauro-CDCA: 300                           |

<sup>a</sup> Values were fixed to Molino et al. CDCA model [7]; <sup>b</sup> The enteral compartments of the Molino et al. model (CDCA) was simplified in OCA physiologic PK model to a single compartment; <sup>c</sup> Parameter values from Molino et al. model (CDCA) were converted from minute units to hours to allow direct comparison to the OCA Physiologic PK Model

**Supplementary Table 9: PBPK model simulated OCA at 5 mg of OCA (Source: Table 1, parameter document from [2])**

| Matrix | Hepatic                     | Exposure                             | Mean (CV%)                            |  |  |                                       |                                       |                                       |
|--------|-----------------------------|--------------------------------------|---------------------------------------|--|--|---------------------------------------|---------------------------------------|---------------------------------------|
|        |                             |                                      | Median (5th-95th)                     |  |  |                                       |                                       |                                       |
|        |                             |                                      | SD                                    | QD                                     | Q2D                                    | QW                                    | Q2W                                   | Q414h                                 |
| Plasma | Healthy                     | AUC <sub>tau</sub> (ng·h/mL)         | 356(1%)<br>356[353-361]               | 55(6.2%)<br>54[51-60]                  | 55(6.4%)<br>54[50-60]                  | 64(5.7%)<br>63[60-69]                 | 105(4.1%)<br>104[101-110]             | 123(3.4%)<br>123[120-129]             |
|        |                             | C <sub>avg</sub> (ng/mL)             | 0.27(1%)<br>0.26[0.3-0.3]             | 2.29(6.2%)<br>2.26[2.1-2.5]            | 1.14(6.4%)<br>1.13[1-1.2]              | 0.38(5.7%)<br>0.38[0.4-0.4]           | 0.31(4.1%)<br>0.31[0.3-0.3]           | 0.3(3.4%)<br>0.3[0.3-0.3]             |
|        |                             | C <sub>max</sub> (ng/mL)             | 11.14(31.6%)<br>12.3[2.6-14.2]        | 11.83(29.1%)<br>13.25[3.9-15.2]        | 11.44(31.1%)<br>12.69[3.2-14.6]        | 10.83(34.4%)<br>12.28[2-14.2]         | 10.57(38.5%)<br>12.24[1.4-14.2]       | 10.55(38.4%)<br>12.21[1.5-14.1]       |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 0.64(62.4%)<br>0.6[0.2-1.2]            | 0.26(26.1%)<br>0.25[0.2-0.2]           | 0.25(0%)<br>0.25[0.2-0.2]             | 0.25(0%)<br>0.25[0.2-0.2]             | 0.25(0%)<br>0.25[0.2-0.2]             |
|        |                             | AUC <sub>tau</sub> (ng·h/mL)         | 364(1.6%)<br>363[358-371]             | 72(6.7%)<br>71[66-78]                  | 71(6.6%)<br>70[65-78]                  | 75(6.5%)<br>74[69-82]                 | 112(4.6%)<br>111[107-120]             | 131(3.6%)<br>131[125-139]             |
|        |                             | C <sub>avg</sub> (ng/mL)             | 0.27(1.6%)<br>0.27[0.3-0.3]           | 2.98(6.7%)<br>2.96[2.7-3.3]            | 1.48(6.6%)<br>1.46[1.4-1.6]            | 0.45(6.5%)<br>0.44[0.4-0.5]           | 0.33(4.6%)<br>0.33[0.3-0.4]           | 0.32(3.6%)<br>0.32[0.3-0.3]           |
|        | Mild                        | C <sub>max</sub> (ng/mL)             | 14.22(34.2%)<br>15.82[3-18.6]         | 15.33(29.9%)<br>17.07[5.6-19.8]        | 15.1(29.1%)<br>16.4[4.2-19.2]          | 14.24(33.6%)<br>15.82[2.6-18.6]       | 14.29(33.3%)<br>15.83[2.5-18.4]       | 14.04(34.1%)<br>15.65[2.7-18.6]       |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 0.81(66.8%)<br>0.78[0.2-1.6]           | 0.37(49.6%)<br>0.25[0.2-0.6]           | 0.25(0%)<br>0.25[0.2-0.2]             | 0.25(0%)<br>0.25[0.2-0.2]             | 0.25(0%)<br>0.25[0.2-0.2]             |
|        |                             | AUC <sub>tau</sub> (ng·h/mL)         | 568(5.5%)<br>569[516-618]             | 355(6.2%)<br>352[324-387]              | 355(6%)<br>352[321-387]                | 356(5.7%)<br>354[328-385]             | 355(5.6%)<br>354[328-384]             | 360(5.7%)<br>359[331-390]             |
|        |                             | C <sub>avg</sub> (ng/mL)             | 0.42(5.5%)<br>0.42[0.4-0.5]           | 14.8(6.2%)<br>14.6[13.5-16.1]          | 7.4(6%)<br>7.33[6.7-8.1]               | 2.12(5.7%)<br>2.11[2-2.3]             | 1.06(5.6%)<br>1.05[1-1.1]             | 0.87(5.7%)<br>0.87[0.8-0.9]           |
|        |                             | C <sub>max</sub> (ng/mL)             | 73.05(36.1%)<br>83.9[11.7-96.3]       | 80.96(29.8%)<br>91.17[27.3-102.9]      | 76.72(32.6%)<br>87.16[18.7-98.8]       | 74.08(35.1%)<br>84.71[13.6-96.7]      | 75.1(33%)<br>84.65[14.5-96.4]         | 73.57(35.3%)<br>84.22[12.1-96.4]      |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 3.93(76.2%)<br>3.76[0.2-8]             | 1.76(71.9%)<br>1.72[0.2-3.5]           | 0.29(41.6%)<br>0.25[0.2-0.5]          | 0.25(0%)<br>0.25[0.2-0.2]             | 0.25(0%)<br>0.25[0.2-0.2]             |
|        | Moderate                    | AUC <sub>tau</sub> (ng·h/mL)         | 704(6.2%)<br>707[628-773]             | 532(5.8%)<br>531[480-573]              | 530(5.9%)<br>528[479-574]              | 531(5.5%)<br>528[488-573]             | 527(5.1%)<br>526[492-564]             | 525(5.4%)<br>521[489-563]             |
|        |                             | C <sub>avg</sub> (ng/mL)             | 0.52(6.2%)<br>0.53[0.5-0.6]           | 22.17(5.8%)<br>22.14[20-23.9]          | 11.04(5.9%)<br>11.01[10-12]            | 3.16(5.5%)<br>3.14[2.9-3.4]           | 1.57(5.1%)<br>1.57[1.5-1.7]           | 1.27(5.4%)<br>1.26[1.2-1.4]           |
|        |                             | C <sub>max</sub> (ng/mL)             | 107.51(39.9%)<br>129.12[16-144.5]     | 121.04(31.9%)<br>139.78[37.6-155.5]    | 115.54(35.5%)<br>134.43[23-149.7]      | 113.04(35.4%)<br>131.07[21.5-146]     | 112.18(35%)<br>130.11[22.5-145.5]     | 107.75(40.4%)<br>129.75[12.2-145]     |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 5.86(78.4%)<br>5.36[0.2-12.1]          | 2.73(74.6%)<br>2.9[0.2-5.4]            | 0.53(53.4%)<br>0.56[0.2-0.9]          | 0.25(11.3%)<br>0.25[0.2-0.2]          | 0.25(15%)<br>0.25[0.2-0.2]            |
|        |                             | AUC <sub>tau</sub> (ng·h/mL)         | 3777(3.7%)<br>3767[3546-3986]         | 3655(3.3%)<br>3656[3492-3814]          | 3653(3.1%)<br>3649[3497-3818]          | 3648(3.3%)<br>3647[3477-3809]         | 3660(3.2%)<br>3674[3488-3809]         | 3631(3.4%)<br>3627[3448-3791]         |
|        |                             | C <sub>avg</sub> (ng/mL)             | 2.81(3.7%)<br>2.8[2.6-3]              | 152.31(3.3%)<br>152.4[145.5-158.9]     | 76.11(3.1%)<br>76.02[72.8-79.5]        | 21.72(3.3%)<br>21.71[20.7-22.7]       | 10.89(3.2%)<br>10.93[10.4-11.3]       | 8.77(3.4%)<br>8.76[8.3-9.2]           |
|        | Severe                      | C <sub>max</sub> (ng/mL)             | 743.97(33.8%)<br>882.83[168.4-928.4]  | 784.82(31.6%)<br>942.86[244.8-992.5]   | 762.47(33.5%)<br>917.05[200.4-954.2]   | 728.84(36.8%)<br>892.6[126.3-931.8]   | 704.71(40.6%)<br>882.3[86.2-929]      | 712.76(40.5%)<br>887.78[96.4-929.2]   |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 39.03(72.6%)<br>39.38[0.2-76.2]        | 16.31(71.3%)<br>16.4[0.2-31.6]         | 2.3(71.6%)<br>2.62[0.2-3.6]           | 0.46(92.9%)<br>0.51[0.2-0.6]          | 0.43(49.3%)<br>0.25[0.2-0.7]          |
|        |                             | AUC <sub>tau</sub> (ng·h/mL)         | 4223(4.5%)<br>4225[3978-4444]         | 4106(3.1%)<br>4105[3921-4290]          | 4092(3.1%)<br>4081[3918-4279]          | 4091(3.2%)<br>4086[3906-4267]         | 4082(3.1%)<br>4068[3904-4267]         | 4086(3.2%)<br>4108[3877-4246]         |
|        |                             | C <sub>avg</sub> (ng/mL)             | 3.14(4.5%)<br>3.14[3-3.3]             | 171.1(3.1%)<br>171.04[163.4-178.7]     | 85.25(3.1%)<br>85.02[81.6-89.1]        | 24.35(3.2%)<br>24.32[23.2-25.4]       | 12.15(3.1%)<br>12.11[11.6-12.7]       | 9.87(3.2%)<br>9.92[9.4-10.3]          |
|        |                             | C <sub>max</sub> (ng/mL)             | 820.84(36.5%)<br>993.75[166.7-1041.4] | 874.32(32.5%)<br>1056.27[294.2-1104.8] | 874.15(31.5%)<br>1033.26[227-1069.9]   | 828.73(36.1%)<br>1005[142.6-1045.7]   | 836.94(35.6%)<br>999.61[134.4-1042.5] | 808.01(36.7%)<br>991.99[146-1042.1]   |
|        |                             | C <sub>trough</sub> (ng/mL)          | 0.25(8.1%)<br>0.25[0.2-0.2]           | 43.39(73.6%)<br>43.75[0.5-86]          | 18.46(72.8%)<br>19.37[0.2-35.5]        | 2.61(78.9%)<br>2.8[0.2-4.1]           | 0.5(66.1%)<br>0.56[0.2-0.7]           | 0.48(47.2%)<br>0.54[0.2-0.8]          |
| Liver  | Healthy                     | AUC <sub>tau</sub> (ng·h/mL)         | 3983(3.7%)<br>3979[3730-4187]         | 3885(3.5%)<br>3891[3654-4054]          | 3885(3.4%)<br>3896[3637-4051]          | 3885(3.3%)<br>3894[3672-4039]         | 3886(3.3%)<br>3894[3677-4038]         | 3855(3.5%)<br>3856[3610-4028]         |
|        |                             | C <sub>avg</sub> (ng/mL)             | 2.96(3.7%)<br>2.96[2.8-3.1]           | 161.87(3.5%)<br>162.14[152.2-168.9]    | 80.94(3.4%)<br>81.17[75.8-84.4]        | 23.12(3.3%)<br>23.18[21.9-24]         | 11.57(3.3%)<br>11.59[10.9-12]         | 9.31(3.5%)<br>9.31[8.7-9.7]           |
|        |                             | C <sub>max</sub> (ng/mL)             | 790.8(38.3%)<br>990.02[122-1031.9]    | 873(32%)<br>1048.52[285-1097.3]        | 835.93(34.9%)<br>1021.32[192.2-1061.2] | 807.24(37.3%)<br>995.52[142.4-1036.3] | 817.12(35.2%)<br>991.88[152-1033.4]   | 804.21(37.5%)<br>992.64[126.9-1033.6] |
|        | Mild                        | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]             | 41.53(76.2%)<br>40.27[0.2-83.4]        | 18.36(74.1%)<br>18.36[0.2-36.3]        | 3.1(70.2%)<br>3.38[0.2-5.4]           | 0.78(55.7%)<br>0.95[0.2-1.1]          | 0.79(39.5%)<br>0.83[0.2-1.1]          |
|        |                             | AUC <sub>tau</sub> (ng·h/mL)         | 3665(3.9%)<br>3676[3401-3864]         | 3600(3.7%)<br>3625[3339-3752]          | 3592(3.8%)<br>3615[3323-3753]          | 3600(3.6%)<br>3607[3365-3746]         | 3592(3.8%)<br>3609[3320-3743]         | 3566(4.1%)<br>3571[3266-3732]         |
|        |                             | C <sub>avg</sub> (ng/mL)             | 2.73(3.9%)<br>2.74[2.5-2.9]           | 150(3.7%)<br>151.02[139.1-156.3]       | 74.83(3.8%)<br>75.3[69.2-78.2]         | 21.43(3.6%)<br>21.47[20-22.3]         | 10.69(3.8%)<br>10.74[9.9-11.1]        | 8.61(4.1%)<br>8.62[7.9-9]             |
| Severe | C <sub>max</sub> (ng/mL)    | 723.78(41.7%)<br>919.78[104.4-971.8] | 804.37(33.7%)<br>980.28[245.3-1036.6] | 778.39(37.1%)<br>959.14[149.2-999.3]   | 763.81(37.3%)<br>940.66[140.3-976.9]   | 756.61(37%)<br>937.66[147.3-973.1]    | 733.3(42.3%)<br>937.43[79.3-973.9]    |                                       |
|        | C <sub>trough</sub> (ng/mL) | 0.25(0%)<br>0.25[0.2-0.2]            | 38.6(78.1%)<br>35.73[0.2-78.8]        | 17.94(75.3%)<br>19.23[0.2-35.6]        | 3.36(63%)<br>3.7[0.2-5.8]              | 0.92(59.5%)<br>1.05[0.2-1.4]          | 0.99(48.5%)<br>1.03[0.2-1.3]          |                                       |

For SD (single dose), AUC<sub>tau</sub>; For QD AUC<sub>tau</sub> from 1320 to 1344 hours; For Q2D AUC<sub>tau</sub> from 1296 to 1344 hours; For QW AUC<sub>tau</sub> from 1176 to 1344 hours; For Q2W AUC<sub>tau</sub> from 1008 to 1344 hours; For Q414h AUC<sub>tau</sub> from 828 to 1242 hours

**Supplementary Table 10: PBPK model simulated glyco-OCA at 5 mg of OCA (Source: Table 2, parameter document from [2])**

| Matrix | Hepatic                      | Exposure                             | Mean (CV%)<br>Median [5th-95th]        |                                       |                                       |                                      |                                      |                                      |
|--------|------------------------------|--------------------------------------|--|---------------------------------------|---------------------------------------|--------------------------------------|--------------------------------------|--------------------------------------|
|        |                              |                                      | SD                                     | QD                                    | Q2D                                   | QW                                   | Q2W                                  | Q414h                                |
| Plasma | Healthy                      | AUC <sub>tau</sub> (ng·h/mL)         | 1210(5.1%)<br>1220[1098-1284]          | 1032(2.8%)<br>1040[966-1056]          | 1034(2.5%)<br>1041[972-1057]          | 1036(2.2%)<br>1043[987-1057]         | 1034(2.1%)<br>1042[991-1051]         | 1032(2.2%)<br>1034[986-1059]         |
|        |                              | C <sub>avg</sub> (ng/mL)             | 0.9(5.1%)<br>0.91[0.8-1]               | 43(2.8%)<br>43.3[40.3-44]             | 21.54(2.5%)<br>21.69[20.2-22]         | 6.17(2.2%)<br>6.21[5.9-6.3]          | 3.08(2.1%)<br>3.1[2.9-3.1]           | 2.49(2.2%)<br>2.5[2.4-2.6]           |
|        |                              | C <sub>max</sub> (ng/mL)             | 12.93(16.5%)<br>13.33[9.3-15.5]        | 71.31(30%)<br>63.01[50.7-118.3]       | 39.08(25.1%)<br>35.6[29.8-60.7]       | 17.33(12.1%)<br>17.12[13.4-20.9]     | 13.98(12.9%)<br>14.25[10.3-15.7]     | 12.77(12.5%)<br>12.32[10.2-15.4]     |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]              | 16.86(73.9%)<br>16.77[0.2-35.6]       | 7.24(72.2%)<br>7.28[0.2-14.7]         | 0.99(60.5%)<br>1.15[0.2-1.6]         | 0.26(36%)<br>0.25[0.2-0.2]           | 0.25(5.1%)<br>0.25[0.2-0.2]          |
|        |                              | AUC <sub>tau</sub> (ng·h/mL)         | 1540(5.6%)<br>1554[1407-1624]          | 1372(2.5%)<br>1384[1290-1403]         | 1373(2.6%)<br>1386[1293-1404]         | 1374(2.6%)<br>1383[1292-1405]        | 1373(2.1%)<br>1383[1306-1399]        | 1371(2.2%)<br>1379[1310-1402]        |
|        |                              | C <sub>avg</sub> (ng/mL)             | 1.15(5.6%)<br>1.16[1-1.2]              | 57.17(2.5%)<br>57.67[53.8-58.5]       | 28.61(2.6%)<br>28.88[26.9-29.2]       | 8.18(2.6%)<br>8.23[7.7-8.4]          | 4.09(2.1%)<br>4.12[3.9-4.2]          | 3.31(2.2%)<br>3.33[3.2-3.4]          |
|        | Mild                         | C <sub>max</sub> (ng/mL)             | 17.09(17%)<br>17.66[12.2-20.4]         | 95.21(29.9%)<br>83.96[67.1-155]       | 52.08(26.2%)<br>46.53[39.6-80.4]      | 23.11(13%)<br>22.66[18-28.4]         | 18.7(10.6%)<br>18.9[15-20.8]         | 17.14(10.8%)<br>16.4[14.4-20.4]      |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]              | 22.3(75.9%)<br>22.78[0.2-47.3]        | 9.83(72.7%)<br>10.15[0.2-19.6]        | 1.31(67.1%)<br>1.45[0.2-2.1]         | 0.26(39.1%)<br>0.25[0.2-0.2]         | 0.25(0%)<br>0.25[0.2-0.2]            |
|        |                              | AUC <sub>tau</sub> (ng·h/mL)         | 5756(3.6%)<br>5835[5296-5964]          | 5671(3.5%)<br>5747[5245-5820]         | 5677(3.3%)<br>5759[5251-5814]         | 5679(3.2%)<br>5760[5291-5817]        | 5682(3.3%)<br>5760[5230-5821]        | 5634(4%)<br>5740[5118-5809]          |
|        |                              | C <sub>avg</sub> (ng/mL)             | 4.28(3.6%)<br>4.34[3.9-4.4]            | 236.29(3.5%)<br>239.46[218.5-242.5]   | 118.27(3.3%)<br>119.97[109.4-121.1]   | 33.8(3.2%)<br>34.28[31.5-34.6]       | 16.91(3.3%)<br>17.14[15.6-17.3]      | 13.61(4%)<br>13.87[12.4-14]          |
|        |                              | C <sub>max</sub> (ng/mL)             | 63.9(16.6%)<br>65.95[45.6-76.5]        | 376.3(26.1%)<br>344.24[273.9-572.2]   | 204.5(22.5%)<br>189.78[158.6-295.1]   | 89.29(10.8%)<br>88.11[71.3-102.4]    | 71.77(9.5%)<br>72.66[60.3-78.6]      | 64.8(10.7%)<br>62.5[54.3-76.2]       |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]              | 98.3(73.8%)<br>100.4[0.7-202.9]       | 43.51(69.7%)<br>45.43[0.2-85.7]       | 6.65(65%)<br>7.7[0.2-11]             | 1.57(53.9%)<br>2.01[0.2-2.3]         | 1.5(38.3%)<br>1.58[0.2-2.1]          |
|        | Moderate                     | AUC <sub>tau</sub> (ng·h/mL)         | 7265(4.2%)<br>7366[6520-7540]          | 7227(3.8%)<br>7351[6612-7452]         | 7231(4%)<br>7373[6558-7456]           | 7263(3.7%)<br>7383[6653-7446]        | 7233(4%)<br>7365[6543-7434]          | 7192(4.7%)<br>7363[6401-7423]        |
|        |                              | C <sub>avg</sub> (ng/mL)             | 5.41(4.2%)<br>5.48[4.9-5.6]            | 301.13(3.8%)<br>306.29[275.5-310.5]   | 150.64(4%)<br>153.61[136.6-155.3]     | 43.23(3.7%)<br>43.95[39.6-44.3]      | 21.53(4%)<br>21.92[19.5-22.1]        | 17.37(4.7%)<br>17.78[15.5-17.9]      |
|        |                              | C <sub>max</sub> (ng/mL)             | 75.31(17.8%)<br>78.06[51.8-90.9]       | 473.83(24.6%)<br>439.96[348-697.7]    | 255.34(22.2%)<br>233.7[192.2-366.8]   | 109.26(10.5%)<br>108.1[86.2-127.1]   | 87.14(9.3%)<br>88.82[74-94.6]        | 78.03(13.4%)<br>76.58[58.9-91.9]     |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]              | 128.07(72.5%)<br>127.61[1.2-263.1]    | 58.65(69.7%)<br>63.12[0.2-113.6]      | 10.04(56.7%)<br>11.66[0.2-16]        | 2.54(57.1%)<br>3.16[0.2-3.7]         | 2.57(43%)<br>2.65[0.5-3.4]           |
|        |                              | AUC <sub>tau</sub> (ng·h/mL)         | 18254(2.4%)<br>18366[17296-18671]      | 18151(2.4%)<br>18273[17192-18491]     | 18180(2.1%)<br>18289[17230-18513]     | 18209(2%)<br>18310[17405-18514]      | 18203(2.3%)<br>18344[17281-18522]    | 18144(2.5%)<br>18284[17085-18494]    |
|        |                              | C <sub>avg</sub> (ng/mL)             | 13.58(2.4%)<br>13.66[12.9-13.9]        | 756.28(2.4%)<br>761.36[716.3-770.4]   | 378.76(2.1%)<br>381.01[359-385.7]     | 108.39(2%)<br>108.99[103.6-110.2]    | 54.18(2.3%)<br>54.59[51.4-55.1]      | 43.83(2.5%)<br>44.16[41.3-44.7]      |
| Severe | C <sub>max</sub> (ng/mL)     | 258(16.3%)<br>269.63[173-301.5]      | 1245.8(27.5%)<br>1115.48[914.4-1992.1] | 698.01(22.9%)<br>644.43[527.7-1045.1] | 329.54(14.7%)<br>332.52[237-405.9]    | 271.93(16.1%)<br>291.23[181.8-306.9] | 256.54(16.2%)<br>269.9[178.8-301.5]  |                                      |
|        | C <sub>trough</sub> (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]            | 292.63(73.6%)<br>291.79[1.1-615.4]     | 125.39(72.3%)<br>126.49[0.6-253.4]    | 16.87(65.5%)<br>19.95[0.2-27.3]       | 3.13(72.3%)<br>3.58[0.2-4.4]         | 2.98(43.7%)<br>3[1-4.5]              |                                      |
|        | AUC <sub>tau</sub> (ng·h/mL) | 20482(3.6%)<br>20596[19462-20920]    | 20373(2%)<br>20508[19396-20744]        | 20388(2.1%)<br>20530[19425-20748]     | 20388(2.3%)<br>20496[19332-20766]     | 20396(2.1%)<br>20508[19402-20768]    | 20370(2.2%)<br>20502[19392-20745]    |                                      |
|        | C <sub>avg</sub> (ng/mL)     | 15.24(3.6%)<br>15.32[14.5-15.6]      | 848.88(2%)<br>854.5[808.2-864.3]       | 424.74(2.1%)<br>427.72[404.7-432.2]   | 121.36(2.3%)<br>122[115.1-123.6]      | 60.7(2.1%)<br>61.03[57.7-61.8]       | 49.2(2.2%)<br>49.52[46.8-50.1]       |                                      |
|        | C <sub>max</sub> (ng/mL)     | 286.71(17.6%)<br>302.23[180.5-335.9] | 1400.85(27.2%)<br>1251.46[1002-2182.9] | 784.64(23.7%)<br>713.94[592.3-1171.1] | 370.86(15.3%)<br>371.6[268.9-477]     | 309.97(13.8%)<br>327.71[219.2-342.5] | 288.4(14.5%)<br>301.1[207.7-335.8]   |                                      |
|        | C <sub>trough</sub> (ng/mL)  | 0.25(41.5%)<br>0.25[0.2-0.2]         | 326.53(75.5%)<br>333.94[2.5-688.7]     | 143.68(72.7%)<br>148.81[0.7-285.7]    | 18.83(70.8%)<br>21.28[0.2-30.6]       | 3.34(68.1%)<br>3.96[0.2-4.8]         | 3.34(40.2%)<br>3.31[1.4-5.1]         |                                      |
| Liver  | Moderate                     | AUC <sub>tau</sub> (ng·h/mL)         | 19283(2.9%)<br>19524[17921-19742]      | 19209(3.1%)<br>19431[17946-19662]     | 19227(2.9%)<br>19469[17943-19622]     | 19459[18072-19638]                   | 19242(2.9%)<br>19469[17872-19647]    | 19088(3.6%)<br>19421[17500-19611]    |
|        |                              | C <sub>avg</sub> (ng/mL)             | 14.35(2.9%)<br>14.53[13.3-14.7]        | 800.37(3.1%)<br>809.61[747.7-819.2]   | 400.57(2.9%)<br>405.61[373.8-408.8]   | 114.48(2.8%)<br>115.83[107.6-116.9]  | 57.27(2.9%)<br>57.94[53.2-58.5]      | 46.11(3.6%)<br>46.91[42.3-47.4]      |
|        |                              | C <sub>max</sub> (ng/mL)             | 248.72(17%)<br>263.67[160.4-289.5]     | 1288.21(25.8%)<br>1170.09[934.4-1975] | 714.57(22.2%)<br>660.83[539.6-1039.2] | 330.53(13.9%)<br>331.24[242.2-399.7] | 274.75(12.8%)<br>290.58[203.7-302.4] | 254.34(14.9%)<br>270.49[183.1-291.5] |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(0%)<br>0.25[0.2-0.2]              | 328.49(73.5%)<br>335.76[2.5-675.1]    | 145.4(69.5%)<br>151.97[1.1-285.6]     | 22.25(65.2%)<br>25.82[0.2-36.8]      | 5.21(55.8%)<br>6.75[0.2-7.7]         | 5.08(38.4%)<br>5.35[1-7.2]           |
|        |                              | AUC <sub>tau</sub> (ng·h/mL)         | 17737(3.8%)<br>18019[16018-18251]      | 17727(3.5%)<br>18002[16348-18229]     | 17734(3.6%)<br>18052[16225-18239]     | 18072[16441-18214]                   | 17738(3.6%)<br>18033[16176-18183]    | 17635(4.4%)<br>18022[15823-18161]    |
|        |                              | C <sub>avg</sub> (ng/mL)             | 13.2(3.8%)<br>13.41[11.9-13.6]         | 738.61(3.5%)<br>750.11[681.2-759.5]   | 369.45(3.6%)<br>376.08[338-380]       | 105.98(3.4%)<br>107.57[97.9-108.4]   | 52.79(3.6%)<br>53.67[48.1-54.1]      | 42.6(4.4%)<br>43.53[38.2-43.9]       |
|        | Severe                       | C <sub>max</sub> (ng/mL)             | 214.2(18.9%)<br>231.73[130.1-250.5]    | 1174.17(25%)<br>1079.36[863.8-1767]   | 645.98(22.7%)<br>590.71[468.8-945.9]  | 292.57(13.6%)<br>294.41[214.1-350.9] | 242.11(13.1%)<br>257.38[182.2-271.2] | 223(17.6%)<br>242.02[143.2-254.8]    |
|        |                              | C <sub>trough</sub> (ng/mL)          | 0.25(11.5%)<br>0.25[0.2-0.2]           | 310.07(72.2%)<br>309.04[3.6-635.4]    | 142.01(69.5%)<br>152.85[1-274.2]      | 24.37(56.6%)<br>28.29[0.5-38.9]      | 6.15(58.1%)<br>7.68[0.2-9]           | 6.29(43.1%)<br>6.48[1.3-8.2]         |

For SD (single dose), AUC<sub>tau</sub>; For QD AUC<sub>tau</sub> from 1320 to 1344 hours; For Q2D AUC<sub>tau</sub> from 1296 to 1344 hours; For QW AUC<sub>tau</sub> from 1176 to 1344 hours; For Q2W AUC<sub>tau</sub> from 1008 to 1344 hours; For Q414h AUC<sub>tau</sub> from 828 to 1242 hours

**Supplementary Table 11: PBPK model simulated tauro-OCA at 5 mg of OCA (Source: Table 3, parameter document from [2])**

| Matrix | Hepatic  | Exposure         | Mean (CV%)                          |  |   |                                      |                                      |                                     |  |
|--------|----------|------------------|-------------------------------------|--|---|--------------------------------------|--------------------------------------|-------------------------------------|--|
|        |          |                  | Median [5th-95th]                   |  |   |                                      |                                      |                                     |  |
|        |          |                  | SD                                  | QD                                       | Q2D                                     | QW                                   | Q2W                                  | Q414h                               |  |
| Plasma | Healthy  | AUCtau (ng·h/mL) | 838(7.1%)<br>842[737-913]           | 669(6%)<br>684[569-696]                  | 671(5.4%)<br>685[579-696]               | 675(4.7%)<br>686[605-696]            | 675(4.2%)<br>685[610-693]            | 671(4.5%)<br>681[599-692]           |  |
|        |          | Cavg (ng/mL)     | 0.62(7.1%)<br>0.63[0.5-0.7]         | 27.87(6%)<br>28.5[23.7-29]               | 13.98(5.4%)<br>14.26[12.1-14.5]         | 4.02(4.7%)<br>4.08[3.6-4.1]          | 2.01(4.2%)<br>2.04[1.8-2.1]          | 1.62(4.5%)<br>1.64[1.4-1.7]         |  |
|        |          | Cmax (ng/mL)     | 3.92(17.5%)<br>4.01[2.7-4.8]        | 52.2(35.5%)<br>46.15[31.7-90]            | 26.94(33.4%)<br>23.96[17.45.1]          | 8.93(24.8%)<br>8.13[6.6-13.4]        | 5.55(14.3%)<br>5.19[4.9-7.3]         | 4.99(8.2%)<br>4.86[4.6-5.9]         |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 9.31(93.4%)<br>6.86[0.2-24.8]            | 4.39(92.5%)<br>3.15[0.2-11.3]           | 0.85(72.3%)<br>0.73[0.2-1.8]         | 0.25(24.7%)<br>0.25[0.2-0.2]         | 0.25(6.5%)<br>0.25[0.2-0.2]         |  |
|        |          | AUCtau (ng·h/mL) | 1102(7%)<br>1112[961-1189]          | 943(5.6%)<br>965[813-981]                | 944(5.8%)<br>968[817-982]               | 946(5.7%)<br>964[816-982]            | 949(4.7%)<br>964[839-981]            | 945(4.8%)<br>962[844-975]           |  |
|        |          | Cavg (ng/mL)     | 0.82(7%)<br>0.83[0.7-0.9]           | 39.3(5.6%)<br>40.23[33.9-40.9]           | 19.67(5.8%)<br>20.17[17-20.5]           | 5.63(5.7%)<br>5.74[4.9-5.8]          | 2.82(4.7%)<br>2.87[2.5-2.9]          | 2.28(4.8%)<br>2.32[2-2.4]           |  |
|        | Mild     | Cmax (ng/mL)     | 5.51(16.8%)<br>5.64[3.9-6.7]        | 74.1(35.7%)<br>64.53[45-125.4]           | 37.91(34.5%)<br>33.38[23.9-63.2]        | 12.7(25.9%)<br>11.65[9.2-19.2]       | 7.92(14.1%)<br>7.42[6.9-10.1]        | 7.03(7.6%)<br>6.82[6.6-8.2]         |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 13.14(94.4%)<br>10.17[0.2-34.3]          | 6.43(91.3%)<br>4.91[0.2-16.1]           | 1.19(79.6%)<br>0.92[0.2-2.5]         | 0.26(33.8%)<br>0.25[0.2-0.2]         | 0.25(4.9%)<br>0.25[0.2-0.2]         |  |
|        |          | AUCtau (ng·h/mL) | 11014(6.7%)<br>11359[9194-11533]    | 10930(6.9%)<br>11293[9176-11421]         | 10947(6.8%)<br>11319[9202-11441]        | 10951(6.6%)<br>11304[9377-11427]     | 10962(6.8%)<br>11314[9100-11436]     | 10772(6.6%)<br>11231[8654-11428]    |  |
|        |          | Cavg (ng/mL)     | 8.19(6.7%)<br>8.45[6.8-8.6]         | 455.41(6.9%)<br>470.54[382.3-475.9]      | 228.06(6.8%)<br>235.8[191.7-238.3]      | 63.18(6.6%)<br>67.28[55.8-68]        | 32.62(6.8%)<br>33.67[27.1-34]        | 26.02(6.6%)<br>27.13[20.9-27.6]     |  |
|        |          | Cmax (ng/mL)     | 56.02(17.4%)<br>58.68[38.7-68.3]    | 807.08(31.6%)<br>739.22[510.8-1297.2]    | 414.12(29.8%)<br>384.15[273.4-655.7]    | 137.01(22.7%)<br>127.66[103.5-192.9] | 84.49(12.4%)<br>80.63[74.3-105.9]    | 74.79(7.4%)<br>72.87[69.4-85.6]     |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 166.05(92.4%)<br>134.08[0.2-423.4]       | 78.38(88.4%)<br>63.73[0.2-188.3]        | 16.02(83.1%)<br>14.35[0.2-34.4]      | 4.18(73.1%)<br>4.69[0.2-7.4]         | 4.04(53.4%)<br>4.66[0.2-6.5]        |  |
|        | Moderate | AUCtau (ng·h/mL) | 22996(8%)<br>23878[18203-24205]     | 22997(7.4%)<br>23855[19143-24215]        | 23011(7.7%)<br>23953[18808-24270]       | 23216(6.9%)<br>23994[19425-24228]    | 23030(7.7%)<br>23926[18692-24174]    | 22781(9.2%)<br>23913[17827-24149]   |  |
|        |          | Cavg (ng/mL)     | 17.11(8%)<br>17.77[13.5-18]         | 958.21(7.4%)<br>993.95[797.6-1009]       | 479.39(7.7%)<br>499.03[391.8-505.6]     | 138.19(6.9%)<br>142.82[115.6-144.2]  | 68.54(7.7%)<br>71.21[55.6-71.9]      | 53.03(9.2%)<br>57.76[43.1-58.3]     |  |
|        |          | Cmax (ng/mL)     | 106.89(18.3%)<br>110.34[72.5-131.9] | 1653.52(28.3%)<br>1570.33[1074.1-2490.5] | 842.71(27.7%)<br>779.92[563.6-1271.4]   | 272.14(19.7%)<br>258.38[212.3-373.5] | 169.5(11.5%)<br>164.67[148.2-205.4]  | 146.56(8.3%)<br>144.16[131.4-164.7] |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 355.54(91.3%)<br>276.09[0.2-901.5]       | 176.46(87.4%)<br>153.63[0.2-418.9]      | 38.83(74.8%)<br>39.21[0.2-79.3]      | 10.73(74.1%)<br>11.53[0.2-19.6]      | 11.25(51.1%)<br>12.97[0.2-16.4]     |  |
|        |          | AUCtau (ng·h/mL) | 12791(5.7%)<br>13047[11102-13314]   | 12699(5.6%)<br>12964[10937-13159]        | 12731(5.1%)<br>12976[11070-13170]       | 12774(4.8%)<br>13003[11360-13172]    | 12762(5.3%)<br>13039[11151-13172]    | 12663(6.1%)<br>12981[10825-13167]   |  |
|        |          | Cavg (ng/mL)     | 9.52(5.7%)<br>9.71[8.3-9.9]         | 529.12(5.6%)<br>540.16[455.7-548.3]      | 265.23(5.1%)<br>270.34[230.6-274.4]     | 76.04(4.8%)<br>77.4[67.6-78.4]       | 37.98(5.3%)<br>38.81[33.2-39.2]      | 30.59(6.1%)<br>31.36[26.1-31.8]     |  |
|        | Severe   | Cmax (ng/mL)     | 74.26(17.8%)<br>76.57[51.2-91.3]    | 975.66(34.6%)<br>870.83[598.7-1664.1]    | 503.59(32.6%)<br>453.4[320.6-834.5]     | 167.66(24.2%)<br>153.33[124.2-250.5] | 104.78(13.9%)<br>98.27[92.1-136.1]   | 93.67(7.4%)<br>91.65[86.8-108.6]    |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 175.51(93.7%)<br>131.23[0.2-466.8]       | 82.31(93.8%)<br>59.94[0.2-212.8]        | 15.06(84.9%)<br>13.87[0.2-33.2]      | 3.39(75.7%)<br>4.05[0.2-5.6]         | 3.3(52.6%)<br>3.63[0.2-5.2]         |  |
|        |          | AUCtau (ng·h/mL) | 14468(5.7%)<br>14701[12638-14984]   | 14324(5.1%)<br>14621[12527-14839]        | 14356(5.3%)<br>14654[12565-14835]       | 14333(5.6%)<br>14611[12390-14840]    | 14345(5.2%)<br>14635[12568-14841]    | 14301(5.6%)<br>14631[12528-14838]   |  |
|        |          | Cavg (ng/mL)     | 10.77(5.7%)<br>10.94[9.4-11.1]      | 596.84(5.1%)<br>609.23[522-618.3]        | 298.67(5.3%)<br>305.3[261.8-309.1]      | 85.31(5.6%)<br>86.97[73.8-88.3]      | 42.69(5.2%)<br>43.56[37.4-44.2]      | 34.54(5.6%)<br>35.34[30.3-35.8]     |  |
|        |          | Cmax (ng/mL)     | 83.43(17%)<br>85.78[57.6-101.6]     | 1104.36(34.6%)<br>972.78[679.5-1845.2]   | 565.78(33.5%)<br>503.73[359.7-931.8]    | 190.28(25.2%)<br>176.68[139.9-287.6] | 119.38(13.7%)<br>112.42[104.6-152.5] | 105.38(6.5%)<br>102.74[100.2-120.5] |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 198.19(94.5%)<br>154.63[0.2-516.2]       | 96.48(92.2%)<br>74.68[0.2-242.4]        | 17.03(88.9%)<br>13.99[0.2-38]        | 3.6(78.9%)<br>3.97[0.2-6.4]          | 3.73(50.6%)<br>4.06[0.2-5.9]        |  |
| Liver  | Healthy  | AUCtau (ng·h/mL) | 38322(6.3%)<br>39494[32357-39812]   | 38186(6.3%)<br>39297[32566-39745]        | 38240(6.3%)<br>39392[32638-39789]       | 38248(6%)<br>39361[33199-39741]      | 38281(6.3%)<br>39394[32276-39766]    | 37647(8%)<br>39170[30705-39735]     |  |
|        |          | Cavg (ng/mL)     | 28.51(6.3%)<br>29.39[24.1-29.6]     | 1591.07(6.3%)<br>1637.38[1356.9-1656]    | 796.68(6.3%)<br>820.68[680-828.9]       | 227.67(6%)<br>234.29[197.6-236.6]    | 113.93(6.3%)<br>117.24[96.1-118.4]   | 90.94(8%)<br>94.61[74.2-96]         |  |
|        |          | Cmax (ng/mL)     | 198.9(16.1%)<br>207.87[140.3-237.9] | 2779.92(30.4%)<br>2571.86[1777.1-4353.3] | 1428.23(28.7%)<br>1338.28[948-2200.3]   | 474.98(22.1%)<br>445.54[359.8-655.8] | 296.1(12.6%)<br>282.92[258.7-364.2]  | 258.24(6.3%)<br>254.21[241.7-287.5] |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)<br>0.25[0.2-0.2]           | 577.42(92.1%)<br>468.92[0.2-1465.7]      | 272.47(88.1%)<br>222.83[0.2-652.1]      | 55.56(83%)<br>50.1[0.2-118.8]        | 14.44(73.9%)<br>16.35[0.2-25.7]      | 14.08(53.4%)<br>16.23[0.2-22.7]     |  |
|        |          | AUCtau (ng·h/mL) | 58831(7.5%)<br>61015[47199-61637]   | 58868(6.8%)<br>60880[49664-61752]        | 58895(7.2%)<br>61131[48843-61875]       | 59382(6.4%)<br>61230[50329-61765]    | 58938(7.2%)<br>61033[48531-61598]    | 58308(8.7%)<br>60994[46301-61532]   |  |
|        |          | Cavg (ng/mL)     | 43.77(7.5%)<br>45.4[35.1-45.9]      | 2452.82(6.8%)<br>2536.68[2069.3-2573]    | 1226.98(7.2%)<br>1273.56[1017.6-1289.1] | 353.46(6.4%)<br>364.47[299.6-367.7]  | 175.41(7.2%)<br>181.65[144.4-183.3]  | 140.84(8.7%)<br>147.33[111.8-148.6] |  |
|        | Moderate | Cmax (ng/mL)     | 281.03(16%)<br>290.84[197.2-336.1]  | 4202.4(27.7%)<br>4015.77[2742.1-6104.5]  | 2142.2(27.1%)<br>1986.97[1439.3-3124.4] | 696.69(20%)<br>659.97[541.7-941.7]   | 438.15(12.6%)<br>423.89[378.1-524.2] | 373.34(8%)<br>367.74[337-408.2]     |  |
|        |          | Ctrough (ng/mL)  | 0.26(34.6%)<br>0.25[0.2-0.2]        | 906.53(90.8%)<br>708.1[0.9-2287.9]       | 449.64(87%)<br>393.33[0.2-1064.3]       | 98.85(74.5%)<br>100.2[0.2-201.1]     | 27.28(74.2%)<br>29.5[0.2-49.7]       | 28.76(50.8%)<br>33.07[0.8-41.8]     |  |

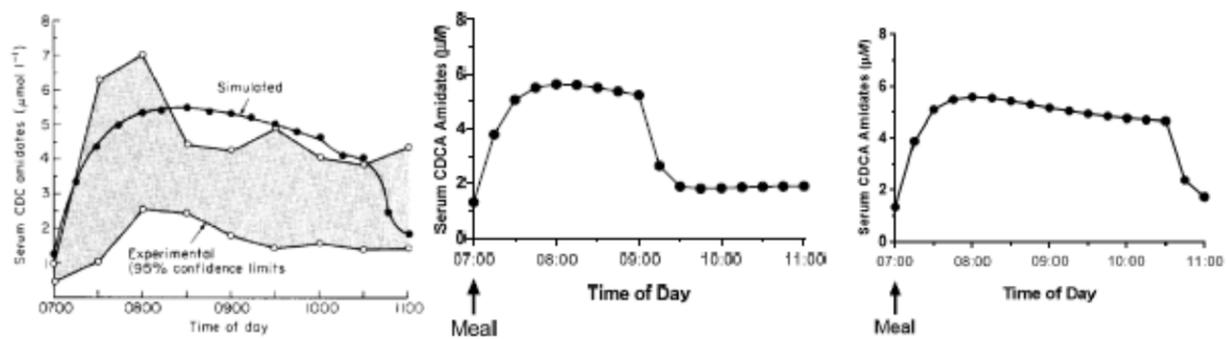
For SD (single dose), AUClast; For QD AUCtau from 1320 to 1344 hours; For Q2D AUCtau from 1296 to 1344 hours; For QW AUCtau from 1176 to 1344 hours; For Q2W AUCtau from 1008 to 1344 hours; For Q414h AUCtau from 828 to 1242 hours

**Supplementary Table 12: PBPK model simulated total OCA at 5 mg of OCA (Source: Table 3, parameter document from [2])**

| Matrix | Hepatic  | Exposure         | Mean (CV%)         |                      |                       |                       |                       |                       |  |
|--------|----------|------------------|--------------------|----------------------|-----------------------|-----------------------|-----------------------|-----------------------|--|
|        |          |                  | Median [5th-95th]  |                      |                       |                       |                       |                       |  |
|        |          |                  | SD                 | QD                   | Q2D                   | QW                    | Q2W                   | Q414h                 |  |
| Plasma | Healthy  | AUCtau (ng×h/mL) | 1646(5.4%)         | 1496(3.9%)           | 1499(3.5%)            | 1503(3.3%)            | 1503(3.4%)            | 1494(3.6%)            |  |
|        |          | Cavg (ng/mL)     | 1.22(5.4%)         | 62.35(3.9%)          | 31.24(3.5%)           | 8.95(3.3%)            | 4.47(3.4%)            | 3.61(3.6%)            |  |
|        |          | Cmax (ng/mL)     | 18.1(21.6%)        | 107.64(31.5%)        | 58.63(28.1%)          | 25.67(18.7%)          | 20.03(17%)            | 18.48(15.2%)          |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 22.85(79.9%)         | 10.1(79.2%)           | 1.55(69.2%)           | 0.27(58.9%)           | 0.26(22.9%)           |  |
|        |          | AUCtau (ng×h/mL) | 2173(5.6%)         | 2031(3.6%)           | 2032(3.8%)            | 2033(3.9%)            | 2035(3.5%)            | 2030(3.6%)            |  |
|        |          | Cavg (ng/mL)     | 1.62(5.6%)         | 84.63(3.6%)          | 42.34(3.8%)           | 12.1(3.9%)            | 6.06(3.5%)            | 4.9(3.6%)             |  |
|        | Mild     | Cmax (ng/mL)     | 1.63[1.5-1.7]      | 85.86[77.2-87]       | 43[38.8-43.5]         | 12.26[11-12.4]        | 6.13[5.6-6.2]         | 4.97[4.5-5]           |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 30.86(81.8%)         | 14.08(79.4%)          | 2.1(75.3%)            | 0.43(55.1%)           | 0.37(43.2%)           |  |
|        |          | AUCtau (ng×h/mL) | 2194[1967-2290]    | 2061[1852-2088]      | 2064[1860-2089]       | 2060[1846-2091]       | 2059[1868-2092]       | 2058[1872-2086]       |  |
|        |          | Cavg (ng/mL)     | 1.63[1.5-1.7]      | 85.86[77.2-87]       | 43[38.8-43.5]         | 12.26[11-12.4]        | 6.13[5.6-6.2]         | 4.97[4.5-5]           |  |
|        |          | Cmax (ng/mL)     | 23.35(16.5%)       | 146.79(31.7%)        | 79.24(29.4%)          | 34.21(19.5%)          | 26.8(14.1%)           | 24.17(12.1%)          |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 30.86(81.8%)         | 14.08(79.4%)          | 2.1(75.3%)            | 0.43(55.1%)           | 0.37(43.2%)           |  |
|        | Moderate | AUCtau (ng×h/mL) | 14139(5.5%)        | 14058(5.6%)          | 14077(5.5%)           | 14081(5.3%)           | 14092(5.5%)           | 13894(6.8%)           |  |
|        |          | Cavg (ng/mL)     | 10.78(9.1-10.9)    | 601.82[510.8-607.9]  | 301.1[255.5-303.8]    | 85.9[74.1-86.8]       | 43[36.2-43.4]         | 34.69[28.3-35.3]      |  |
|        |          | Cmax (ng/mL)     | 116.33(14.6%)      | 990.82(29.3%)        | 521.21(27.2%)         | 199.94(19.3%)         | 145.57(13.2%)         | 128.38(9.1%)          |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 222.78(84.6%)        | 102.49(80.8%)         | 18.89(76.8%)          | 4.76(67.4%)           | 4.61(47.4%)           |  |
|        |          | AUCtau (ng×h/mL) | 14494[12276-14694] | 14444[12259-14591]   | 14453[12266-14580]    | 14431[12453-14587]    | 14449[12170-14599]    | 14361[11729-14594]    |  |
|        |          | Cavg (ng/mL)     | 10.78(9.1-10.9)    | 601.82[510.8-607.9]  | 301.1[255.5-303.8]    | 85.9[74.1-86.8]       | 43[36.2-43.4]         | 34.69[28.3-35.3]      |  |
|        | Severe   | Cmax (ng/mL)     | 123.43[77.5-130.9] | 905.55[674.6-1553.2] | 481.48[372.1-807.1]   | 186.75[155.1-276.4]   | 142.03[115.9-183.1]   | 132.68[105.7-140.1]   |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 198.86(0.7-523.6)    | 92.85(0.2-229.4)      | 18.59(0.2-37.7)       | 5.61(0.2-7.9)         | 5.16(0.2-7.1)         |  |
|        |          | AUCtau (ng×h/mL) | 2521(76.9%)        | 25222(6.4%)          | 25233(6.7%)           | 25426(6%)             | 25250(6.7%)           | 25011(7.9%)           |  |
|        |          | Cavg (ng/mL)     | 18.76(6.9%)        | 1051(6.4%)           | 525.69(6.7%)          | 151.34(6%)            | 75.15(6.7%)           | 60.41(7.9%)           |  |
|        |          | Cmax (ng/mL)     | 171.61(15.6%)      | 1756.04(26.8%)       | 910.39(26%)           | 326.67(18.2%)         | 230.03(13.3%)         | 198.41(10.4%)         |  |
|        |          | Ctrough (ng/mL)  | 0.25(0.2-0.2)      | 337.51[1.7-961]      | 183.18[0.2-443.4]     | 42.02[0.2-78.5]       | 12.13[0.2-19]         | 12.77[0.7-16.1]       |  |
| Liver  | Healthy  | AUCtau (ng×h/mL) | 29840(3.4%)        | 29756(3.3%)          | 29806(3%)             | 29860(2.9%)           | 29853(3.2%)           | 29696(3.6%)           |  |
|        |          | Cavg (ng/mL)     | 22.47[20.5-22.8]   | 1239.85(3.3%)        | 620.95(3%)            | 177.74(2.9%)          | 88.85(3.2%)           | 71.73(3.6%)           |  |
|        |          | Cmax (ng/mL)     | 985.55(31.2%)      | 2537.5(24%)          | 1699.52(23.1%)        | 1103.39(30.3%)        | 979.78(35.5%)         | 962.17(36%)           |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 436.53(79.1%)        | 192.28(78.8%)         | 29.12(72.7%)          | 5.89(73%)             | 5.72(43.8%)           |  |
|        |          | AUCtau (ng×h/mL) | 30200[27575-30655] | 30122[27351-30464]   | 30120[27586-30517]    | 30172[27872-30514]    | 30210[27577-30546]    | 30138[27070-30527]    |  |
|        |          | Cavg (ng/mL)     | 22.47[20.5-22.8]   | 1239.85(3.3%)        | 620.95(3%)            | 177.74(2.9%)          | 88.85(3.2%)           | 71.73(3.6%)           |  |
|        | Mild     | Cmax (ng/mL)     | 1166.8[288-1215.3] | 2381.05[1647.5-3775] | 1697.91[980.1-2426.3] | 1268.33[386.6-1460.8] | 1201.71[262.1-1278.3] | 1179.94[257.3-1224.6] |  |
|        |          | Ctrough (ng/mL)  | 0.25(0%)           | 436.53(79.1%)        | 192.28(78.8%)         | 29.12(72.7%)          | 5.89(73%)             | 5.72(43.8%)           |  |
|        |          | AUCtau (ng×h/mL) | 33594(4.1%)        | 33459(2.9%)          | 33467(3.1%)           | 33463(3.3%)           | 33470(3%)             | 33417(3.3%)           |  |
|        |          | Cavg (ng/mL)     | 25.25[23.2-25.6]   | 1394.13(2.9%)        | 697.22(3.1%)          | 199.18(3.3%)          | 99.61(3%)             | 80.72(3.3%)           |  |
|        |          | AUCtau (ng×h/mL) | 33936[31115-34428] | 33861[31094-34272]   | 33878[31093-34271]    | 33880[30778-34295]    | 33850[31005-34299]    | 33856[30993-34285]    |  |
|        |          | Cavg (ng/mL)     | 25.25[23.2-25.6]   | 1394.13(2.9%)        | 697.22(3.1%)          | 199.18(3.3%)          | 99.61(3%)             | 80.72(3.3%)           |  |
|        | Moderate | Cmax (ng/mL)     | 1088.37(33.5%)     | 2841.06(24.3%)       | 1925.62(22.9%)        | 1252.51(29.7%)        | 1156.53(31.4%)        | 1085.76(32.9%)        |  |
|        |          | Ctrough (ng/mL)  | 0.25(0.2-0.2)      | 396.28[1.3-993.2]    | 175.23[0.7-425.3]     | 31.48[0.2-53.8]       | 7.11[0.2-8.8]         | 5.95[1.1-8.4]         |  |
|        |          | AUCtau (ng×h/mL) | 52565[45287-52999] | 52417[45437-52939]   | 52490[45345-52904]    | 52427[45966-52943]    | 52491[45111-52960]    | 52192[43572-52932]    |  |
|        |          | Cavg (ng/mL)     | 38.22[4.8%]        | 2134.49(4.9%)        | 1068.49(4.8%)         | 305.35(4.7%)          | 152.77(4.9%)          | 122.37(6.1%)          |  |
|        |          | Cmax (ng/mL)     | 1099.03(33.6%)     | 3951.25(24.4%)       | 2437.6(22.1%)         | 1392.74(26.8%)        | 1221.02(29%)          | 1147.03(32%)          |  |
|        |          | Ctrough (ng/mL)  | 0.25(0.2-0.2)      | 707.85[3.2-1843.9]   | 333.37[1.3-810.2]     | 66.15[0.5-132.8]      | 16.83(67.8%)          | 16.48(46.9%)          |  |
|        | Severe   | AUCtau (ng×h/mL) | 66071(6.4%)        | 66119(5.8%)          | 66139(6.1%)           | 66596(5.5%)           | 66175(6.2%)           | 65556(7.4%)           |  |
|        |          | Cavg (ng/mL)     | 49.16(6.4%)        | 2754.96(5.8%)        | 1377.89(6.1%)         | 396.41(5.5%)          | 196.95(6.2%)          | 158.35(7.4%)          |  |
|        |          | Cmax (ng/mL)     | 1057.87(35.7%)     | 4873.55(23.9%)       | 2821.34(22.7%)        | 1468.93(24.8%)        | 1231.38(28.7%)        | 1130.76(33.4%)        |  |
|        |          | Ctrough (ng/mL)  | 0.25(0.2-0.2)      | 707.85[3.2-1843.9]   | 333.37[1.3-810.2]     | 66.15[0.5-132.8]      | 16.83(67.8%)          | 16.48(46.9%)          |  |
|        |          | AUCtau (ng×h/mL) | 68153[55040-68769] | 68076[57376-68878]   | 68277[56608-68983]    | 68359[58043-68874]    | 68173[56307-68773]    | 68094[54086-68695]    |  |
|        |          | Cavg (ng/mL)     | 49.16(6.4%)        | 2754.96(5.8%)        | 1377.89(6.1%)         | 396.41(5.5%)          | 196.95(6.2%)          | 158.35(7.4%)          |  |

For SD (single dose), AUClast; For QD AUCtau from 1320 to 1344 hours; For Q2D AUCtau from 1296 to 1344 hours; For QW AUCtau from 1176 to 1344 hours; For Q2W AUCtau from 1008 to 1344 hours; For Q414h AUCtau from 828 to 1242 hours

**Supplementary Figure 1: Comparison of simulated serum profile of total CDCA conjugates (CDCA amidates: glycol-CDCA and tauro CDCA) by the original CDCA Model [7] (left), the Phoenix CDCA Model (middle), and the updated Phoenix Model with Extended Gallbladder Emptying (right) (Source Figure 1 in [2])**



*The applicant assumed a longer gallbladder emptying time after a meal from 2 hours to 3.5 hours.*

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