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.

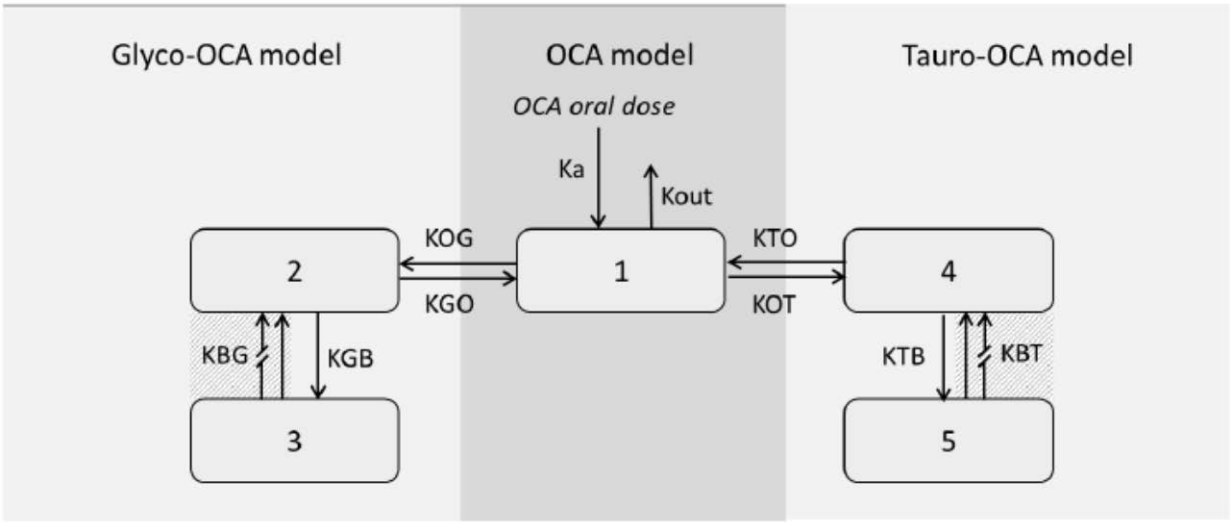
The PK/PD analysis dataset for biomarker C4 included a total of 378 samples of C4 from Studies 747-105 (332 rich samples) and 747-204 (46 sparse samples).

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 (Ka), rates of gallbladder emptying into the central compartment for glyco- and tauro-OCA (KBG 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 (Kout), and volumes of distribution of OCA, glyco-OCA and tauro-OCA (VOCA, Vglyco and Vtauro).

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

Ka = first-order rate of absorption; KBG = rate of gallbladder emptying into the central compartment for glyco-OCA during gallbladder contraction; KBT = rate of gallbladder 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; 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, Vglyco, Vtauro, KBG, KBT, KOG, KOT, KGO and KTO
- Body weight on VOCA, Vglyco, Vtauro, KBG and KBT 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 the 50% higher and in a typical 134-kg is expected to the 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
VOCA (L)	176
Vglyco (L)	195
Vtauro (L)	175
Ka (h^{-1})	0.817
Kout (h^{-1})	0.365
KOG (h^{-1})	0.585
KOT (h^{-1})	0.140
KGO (h^{-1})	0.0475
KTO (h^{-1})	0.0201
KGB (h^{-1})	0.112
KBG (h^{-1})	5.48
KTB (h^{-1})	0.142
KBT (h^{-1})	6.38
gbbl (fraction of tvKBG)	0.00896
Prop Error OCA (%)	74.4
Prop Error Glyco-OCA (%)	50.9
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

Parameter	Estimate	Shrinkage (%)
BSV Ka (%)	70.9	5.6
BSV VOCA (%)	53.9	10.7
Variance between BSV Vglyco and BDV VOCA	0.318	
BSV Vglyco (%)	67.7	7.4
Variance between BSV Vtauro and BDV VOCA	0.400	
Variance between BSV Vtauro and BDV Vglyco	0.547	
BSV Vtauro (%)	89.3	9.4
BSV Kout (%)	60.0	15.6
BSV KGO (%)	24.2	14.9
BSV KTO (%)	53.1	13.5
BSV KOG (%)	17.2	34.7
Variance between BSV KOG and BDV KOT	-0.00139	
BSV KOT (%)	23.3	45.9
BSV KBG (%)	129.5	8.5
Variance between BSV KBG and BDV KBT	1.66	
BSV KBT (%)	129.5	8.3

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

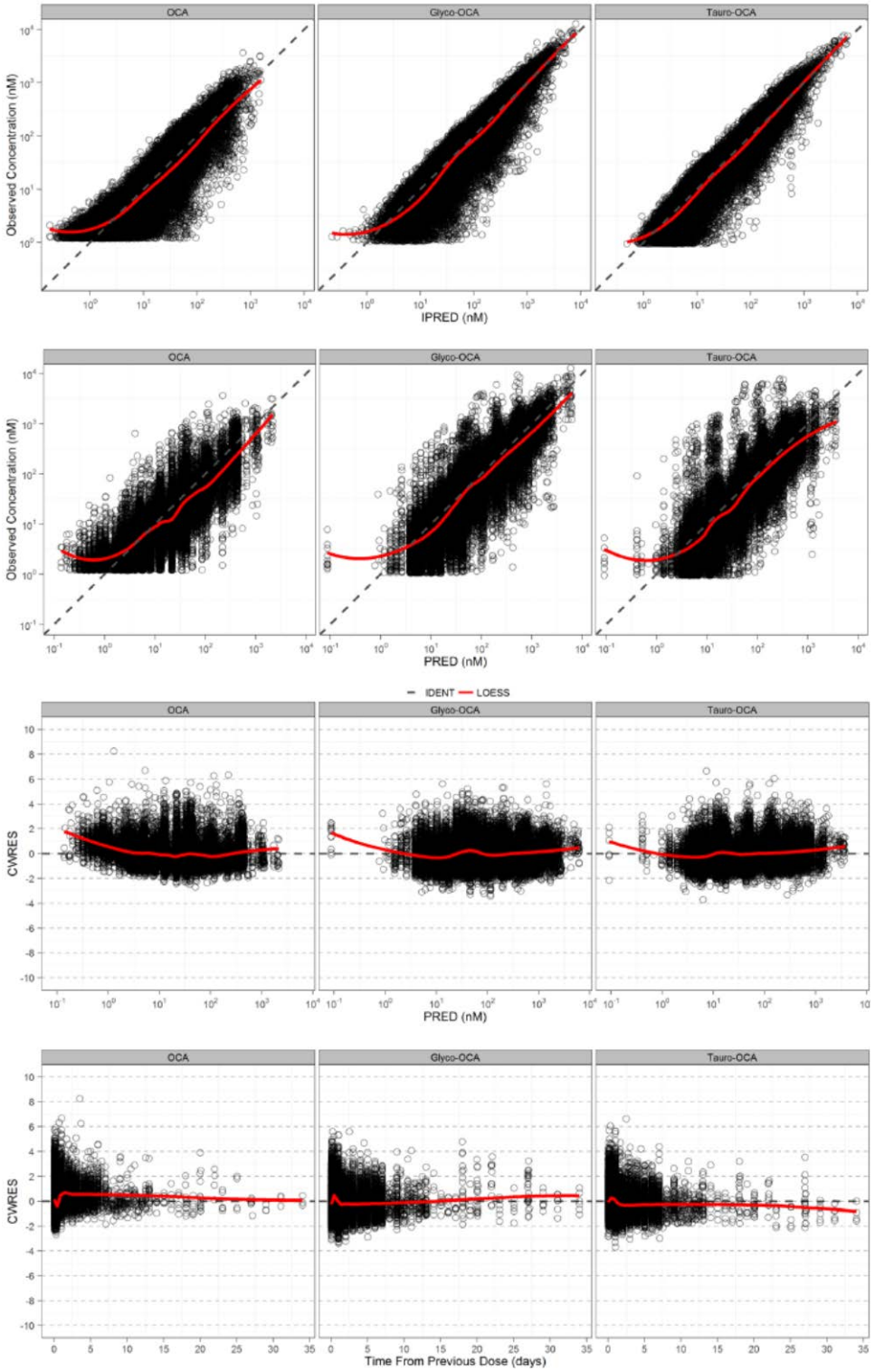


Figure 33: Goodness-of-Fit Diagnostic Plots for the Final Pop-PK Model (*Source: Sponsor's Population PK/PD and Simulation Report, Section 2.2.3)*

Reviewer's comments:

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 cttotoca.xpt ctoca xpt pkparl xpt a1out xpt a2out xpt b3out.xpt b5out.xpt simexp xpt	\\cdsesub1\evsprod\NDA207999\0019\m5\datasets\pk-physiological\analysis\legacy\datasets\ \\CDSESUB1\evsprod\NDA207999\0039\m5\datasets\pk-physiological\analysis\legacy\datasets\
Efficacy/Safety: Demographic Efficacy Responders Vital Status	 Adsl xpt Adeff xpt Adeff2.xpt Adresp xpt Adresp2.xpt Advs xpt	 \\cdsesub1\evsprod\nda207999\0001\m5\datasets\747-301\analysis\adam\datasets\

Table 71: Codes and Output Files

File Name	**Description**	**Location in \\cdsnas\pharmacometrics\Reviews\ Ongoing PM Reviews\ 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

Application Number	NDA207999
Drug Name	Obeticholic Acid
Primary PBPK Reviewer	Ping Zhao, Ph.D., Yuching Yang, Ph.D. and Dhananjay Marathe, Ph.D.
Secondary PBPK Reviewer	Nitin Mehrotra, Ph.D.