



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ocaliva

International non-proprietary name: obeticholic acid

Procedure No. EMEA/H/C/004093/II/0038

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Medicinal product no longer authorised



Status of this report and steps taken for the assessment				
Current step ¹	Description	Planned date	Actual Date	Need for discussion ²
☐	Start of procedure	30 Jan 2023	30 Jan 2023	☐
☐	CHMP Rapporteur Assessment Report	06 Mar 2023	20 Mar 2023	☐
☐	CHMP members comments	20 Mar 2023	23 Mar 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	23 Mar 2023	24 Mar 2023	☐
☐	RSI	30 Mar 2023	30 Mar 2023	☐
☐	Submission	11 Aug 2023	11 Aug 2023	☐
☐	Start of procedure	14 Aug 2023	14 Aug 2023	☐
☐	CHMP Rapporteur Assessment Report	18 Sep 2023	29 Sep 2023	☐
☐	CHMP members comments	02 Oct 2023	02 Oct 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Oct 2023	06 Oct 2023	☐
☒	Opinion	12 Oct 2023	12 Oct 2023	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Advanz Pharma Limited submitted to the European Medicines Agency on 22 December 2022 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and IIIB

Update of sections 4.8 and 5.1 of the SmPC in order to update clinical information based on final results from studies 747-302 and 747-401, listed as specific obligations in the Annex II, as well as results from real-world evidence (RWE) studies evaluating analyses of hepatic clinical outcomes. Study 747-302 is a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints, while study 747-401 is a double-blind, randomised, placebo-controlled study evaluating the safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. The Annex II and Package Leaflet are updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

Obeticholic acid (OCA) was granted a conditional marketing authorisation (CMA) in the European Union (EU) in December 2016, for its administration in combination with ursodeoxycholic acid (UDCA) for the treatment of adult patients with primary biliary cholangitis (PBC) who have an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. This initial approval was based on results from the phase 3, randomized, double blind, placebo-controlled Study 747-301, which demonstrated a clinically and statistically significant, sustained reduction in alkaline phosphatase (ALP).

At the time of the CMA granted for Ocaliva, efficacy had only been shown in terms of ALP reductions, with rare cases of normalization. Thus, the main efficacy uncertainty was to what extent those changes in laboratory parameters correlate with a risk reduction in relevant clinical liver outcomes in PBC patients, and thus, on the actual clinical benefit of OCA treatment. Other important uncertainties were the lack of efficacy/safety data in patients with a more advanced stage of the disease, and concerns on long-term (liver and CV) safety data. Given the lack of treatment options in patients unresponsive or unable to tolerate UDCA and the debilitating nature of PBC, a CMA was granted based on incomplete data with the condition to address these limitations, and provide comprehensive data, within two PAES requested as specific obligations (SOBs). Full approval of OCA was contingent on a post-approval requirement to confirm efficacy and safety by assessing the effect of OCA on clinical outcomes such as hepatic decompensation, liver transplant, and death and across the spectrum of liver disease severity.

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the effect of obeticholic acid on clinical outcomes in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the lack of data in a population with more advanced liver disease	Final report: 2023

In the post-authorisation phase the MAH reported enrolment and retention difficulties for study 747-302, and a transition to an open label design versus historic control was proposed, or a revision of the composite primary endpoint. Neither proposal was deemed acceptable at the time to the CHMP.

In 2020, based on a review of a protocol-specified interim analysis of the primary efficacy endpoint of study 747-302, and of *ad hoc* safety and pharmacokinetic data from studies 747-302 and 747-401, the independent data monitoring committee (IDMC) concluded that "*Study 747-302 (COBALT) is unlikely to provide evidence of efficacy for the enrolled PBC population as an aggregate or in any subpopulation*". The IDMC also recommended that there be no further enrolment in either study (747-302 and 747-401), based on feasibility concerns. The MAH considered that it would be no longer feasible to establish the safety and efficacy of Ocaliva in PBC patients with decompensated cirrhosis or a prior decompensation event, from studies 747-302 and 747-401 (the later having been imposed to this aim). Therefore, taking also into account post-marketing data suggesting an association between hepatic events and this treatment in patients with decompensated cirrhosis or a prior decompensation event, a variation was submitted to contraindicate Ocaliva in those patients (EMA/H/C/004093/II/0030), and study 747-401 was prematurely terminated. Study 747-302 was also prematurely terminated.

The MAH has now submitted results of these two SOBs, which constitute the primary evidence of efficacy and safety, aimed to confirm the benefits and risks of Ocaliva across the spectrum of PBC patients after failure or intolerance to UDCA. Unfortunately, none of these two studies have been completed as both were prematurely terminated.

SOB#2 - Interventional study 747-401

This SOB was aimed at assessing the PK and safety profile of OCA in patients with more advanced liver disease and was imposed by CHMP at the time of granting of the initial CMA. The study was prematurely terminated following an SmPC update in 2021 within variation procedure EMA/H/C/004093/II/0030 concluded in May 2022. In this procedure the MAH applied for a contraindication in patients with more advanced liver disease and provided post marketing data suggesting a clear association between hepatic events and PBC patients taking Ocaliva particularly in cirrhosis patients (CP-B and C). At termination of the study, it only included 22 out of the planned 50 subjects. Results of this placebo-controlled study show a significant toxicity and the possible contribution of OCA treatment cannot be ruled out. Despite

testing a reduced dose of OCA (5mg once a week, titrated to 5mg twice a week), treatment was poorly tolerated in both treatment arms. All 22 (100.0%) subjects reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were ascites, oesophageal varices haemorrhage, pneumonia, all of them reported most frequently in OCA treated arm. Treatment-related TEAEs occurred in 4 (40.0%) subjects in the OCA group and 6 (50.0%) subjects in the placebo group. Nine (90.0%) subjects in the OCA group and 9 (75.0%) subjects in the placebo group experienced TEAEs of special interest. Six (60.0%) subjects in the OCA group and 7 (58.3%) subjects in the placebo group experienced severe (Grade 3) TEAEs. Related Grade 3 TEAEs included upper gastrointestinal haemorrhage, hepatic failure, pyrexia, and hepatic function abnormal. Of the Grade 3 TEAEs, 4 subjects experienced a TEAE (multiple organ dysfunction syndrome, cardiac arrest, hepatic encephalopathy, and aortic aneurysm rupture, respectively) that resulted in a fatal outcome, which were all not related or unlikely related to the study treatment. Overall, study treatment discontinuations occurred in 5 (50.0%) subjects in the OCA arm and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) subjects in the OCA and 4 (33.3%) subjects in the placebo groups. Four subjects (3 OCA-treated and 1 placebo-treated) experienced a TEAE of upper gastrointestinal haemorrhage, cardiac arrest secondary to bleeding from oesophageal varices, hepatobiliary disorder, and ascites, respectively) that led to both study drug interruption and study discontinuation. A total of 7 (70.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced serious adverse events (SAEs). Six out of the 7 subjects in OCA reported SAEs of bleeding of oesophageal varices/upper GI haemorrhage (4 cases) or cardiac arrest/MI (2) vs no subjects in placebo. Five subjects died during the study (3 among placebo-treated subjects due to: hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal cell carcinoma; and 2 among OCA-treated subjects due to: multiple organ dysfunction syndrome and cardiac arrest).

Overall, no relevant differences were observed between treatment arms in the incidences of TEAEs, Grade 3 TEAEs, SAEs TEAEs, and those noted can be explained by the low number of subjects in each treatment arm. Indeed, the low number of subjects included and premature study interruption, do not allow reaching sound conclusions on the actual safety profile of OCA in PBC with an advanced liver disease. Nevertheless, a numerical difference between treatment arms, disfavours OCA treatment, is systematically observed for hepatic AESI (9 patients (14 events) OCA vs 8 patients (11 events) placebo), cardiac AESIs (3 patients 5 events in OCA vs 1 subject/event placebo), pruritus (3 OCA vs 1 placebo), and bleeding GI events (both Grade 3 and SAEs were reported in OCA patients while no such cases were reported in placebo (4 in OCA: 3 events of bleeding of oesophageal varices +1 upper GI haemorrhage OCA treated groups), which support the current contraindication in the SmPC.

OCA treatment is contraindicated in "*Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see section 4.4)*", due to the increased risk of hepatic failure/decompensation events, including fatal cases. The worse safety profile of OCA in patients with moderate-severe hepatic impairment is confirmed from the available submitted evidence from clinical trials and the post-marketing experience. Within variation procedure EMEA/H/C/004093/II/0030, measures have been put in place to minimise this risk, i.e. a contraindication in section 4.3 and precautionary wording in section 4.4 of the SmPC to include new information about hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, occurring with obeticholic acid treatment in patients with PBC with cirrhosis, either compensated or decompensated. Section 4.8 ('Undesirable effects') was also updated to include hepatobiliary disorders in the tabulated list of adverse reactions.

Based on the quantitative analysis conducted considering sales data, the data presented shows a continuous downward trend in the reporting rate of hepatic AEs from 2017 until 2023, including fatal cases, although the correlation with relevant RMM milestones is not evident as claimed by the MAH. The decrease in reporting is not a probe of the effectiveness of the current RMM, as this might well be

explained by a shift in the source of data from clinical trials to spontaneous reporting with an obvious risk of under notification with prolonged time on the market aggravated by the fact that these hepatic events would be expected by the progression of the underlying condition. Thus, although the quantitative data provided is reassuring, they do not allow concluding that the current Risk Minimisation Measures have been duly effective.

In relation to SOB 2 the main uncertainty driving this requirement, i.e. lack of safety evidence in patients with more advanced liver disease to establish B/R, is addressed and the safety profile is deemed unfavourable. The available evidence shows a severe toxicity profile of OCA treatment in these patients that led to the inclusion of a contraindication and several precautionary measures to minimise the risk (Variation procedure EMEA/H/C/004093/II/0030).

SOB#1 - Interventional Study 747-302

Efficacy issues

This SOB was imposed at the time of approval to confirm the efficacy and safety, in clinically relevant outcomes/endpoints, associated with OCA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment. According to the MAH, the study has faced enrolment and retention difficulties and a transition to an open label design versus historic control was proposed. This plan was discussed several times with the CHMP and deemed not acceptable as it would not address the remaining uncertainties on the efficacy of Ocaliva. The MAH also proposed a revision of the composite primary endpoint, to extend the list of components adding some less robust components to increase the power of the study, which was not agreed by the CHMP either. The study was prematurely terminated by the Sponsor at the time when the study had randomized nearly 80% of the planned participants (i.e. 334 of the targeted 428 patients) and approximately 67% of the protocol-specified number of clinical events had been observed (last patient last visit Dec 2021). This followed the recommendations of the data monitoring committee due to "feasibility challenges". However, it is noted that with 67% of the planned events, which is not a negligible portion, the study failed to show any differences between treatments for the primary composite endpoint of death, liver transplant, or hepatic decompensation for the ITT population: HR 1.01 (95%CI: 0.68, 1.51), p-value: 0.954. Notably, the results for the primary endpoint according to the liver disease status (compensated vs decompensated) show a numerical increment in the risk of event outcomes in decompensated patients treated with OCA (59.4% OCA vs 54.1% in placebo, HR 1.22 [95% CI: 0.65, 2.28]), though not statistically significant. By contrary, results were nearly identical in both treatment arms in the subgroup of compensated PBC patients (21.3% vs 21.7% OCA and placebo, respectively, HR 0.98 [95% CI: 0.58, 1.64]). Thus, the study has failed to demonstrate any efficacy of OCA treatment in relevant clinical outcomes and across the spectrum of PBC patients.

Secondary endpoint analyses show that only a total of 21 (6.3%) patients enrolled in Study 747-302 met the primary endpoint as defined in the initial pivotal phase 3 Study 747-301 of an ALP $<1.67\times$ ULN and total bilirubin $\leq$ ULN and ALP decrease from baseline of $\geq 15\%$. Indeed, the rate of responders was substantially lower compared to that previously reported and this was the case in both treatment arms, but rather noticeable in the OCA treated group (OCA 10.1% vs 2.4% placebo in Study 747-302 compared to OCA 34.0% vs 7% placebo in Study 747-301). No statistically significant differences were reported, adding even further uncertainties to the actual efficacy of OCA in the treatment of PBC. The MAH was requested to explain the observed differences, considering that Study 747-302 included a more advanced liver disease population likely representative of the actual target population in clinical practice. The MAH argues that the actual target population in clinical practice is more like that included in Study 747-301, based on comparison of baseline disease characteristics of European registries, and much less severe than that included in Study 747-302. It is also argued that subjects with higher values at baseline might unlikely reach normal (or near normal) biochemical ALP/BR values, and that similar absolute changes in ALP values are expected (and thus similar benefits from treatment). However, the actual meaning of the

observed quantitative reductions of ALP/BR values, in the absence of concurrent changes in histological progression, is highly uncertain and of doubtful clinical relevance. Indeed, the predictive value of the changes in biochemical parameters with respect to relevant clinical outcomes in PBC has not been established yet. Summarising, OCA treatment has demonstrated to reduce ALP (and BR) levels, though the effect is of modest magnitude and the actual clinical meaning is uncertain, moreover, the confirmatory trial has failed to demonstrate the efficacy of OCA treatment in clinical outcomes.

While the MAH acknowledges that the SOB studies, as designed, will be considered the primary evidence characterizing the safety and efficacy of OCA in patients with PBC, they have provided additional data (including from real-world sources) as supplementary information. This includes results of the long-term safety extension (LTSE) of the pivotal phase 3 trial submitted with the initial application (Study 747-301), plus results of three real-world evidence (RWE) studies; i.e. two externally controlled analyses of OCA-treated patients from studies 747-301/301 LTSE and 747-302, and a (fully) RWE study (745-405). External controls come from the Global PBC and United Kingdom (UK) PBC registries, as well as from the Komodo Health US Claims database.

The results submitted from the above mentioned external control (EC) studies/analyses, based on RWD, are not considered robust evidence valid to overcome the negative results of well- designed and conducted double-blind, randomised, placebo-controlled trials. The observed differences in the estimation of the treatment effect for the primary endpoint using the primary randomisation and the inverse probability of censoring weighting (IPCW), demonstrate the high risk of bias associated to the provided analysis(es) based on the weighting procedure as compared to the results from Study 747-302. All results based on the EC are considered to have the same problem of bias. Furthermore, in addition to all the issues discussed in this report, the analyses resulting from the *post-hoc* comparisons with EC should be understood in the context of a pivotal trial in which the primary analysis failed, leaving no alpha for confirmatory testing. As a result, any further analyses should be considered exploratory only. The MAH was invited to discuss these issues. Some of the MAH's comments are aimed at justifying the invalidity of the placebo test group, which is also the basis for justifying the use of external controls. However, despite the fact that the current estimation of the treatment effect might be confounded to some extent, should this occur, it would be in both treatment arms and not just in placebo. Therefore, any post-hoc external comparison to overcome the failed trial results is invalid, especially as these RWE results are very far from the results of a randomised comparison. Furthermore, in contrast to the trial, MELD could not be assessed in the EC comparison as a measure of baseline balance and as a component of the primary endpoint, and notably, patients were censored at the occurrence of an ICE (Intercurrent Event), which was handled in the trial using the treatment policy strategy for the primary assessment. Furthermore, propensity score methods are useful tools for balancing for prognostic factors, but unlike randomisation, they only allow adjustment for known and measured factors, so that they will never overcome the effect of randomisation. The MAH states that the treatment effects were remarkably consistent, but the divergence from the trial results only points out that there is a remarkable divergence due to the lack of a randomised comparison and that there is a very high risk of residual confounding in the baseline balance and during the follow-up. As a result of this, the demonstration of efficacy of OCA in the treatment of PBC would be mainly based on the results of the trials, and the RWE is considered only as complementary and exploratory with a much lower level of evidence than the trial results.

Safety issues

From a safety point of view, Study 747-302 shows a more concerning overall safety profile as compared to that reported in the initial submission, given the higher incidence rates of all types of TEAEs overall and as compared to placebo treated patients. OCA treated patients showed a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death, both in the general safety population and the subset of patients with compensated liver disease, which does not speak in favour of

a favourable and well tolerated safety profile. In addition, the higher rates observed in OCA treated patients for some relevant AESI like cardiovascular events (including adjudicated MACE), renal events (including AKI), DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events, both in the overall safety population and for the subset of patients with compensated disease are a matter of major concern.

The MAH recognizes there is some potential safety risk given the imbalance observed in the overall safety population of Study 747-302 and cannot exclude a contributory role of OCA. Therefore, the MAH has proposed to further restrict the SmPC indicated population to patients with PBC without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or a prior decompensation event. Comparative safety data in the restricted indication have been presented, though this analysis was not pre-specified and the newly proposed target population for OCA is data driven by an otherwise limited subset of early stage PBC subjects of Study 747-302 (68 OCA vs 61 placebo), which hampers the interpretation of the reported results. Thus, it is uncertain if the observed results in this subset of the study population represent an accurate estimation of their safety profile and thus if a "more benign" safety profile can be firmly concluded in them.

The MAH addressed the Major objection in an oral explanation to the CHMP reiterating largely previous argumentation that the failure of study 742-302 could be explained by bias also referring to results generated in RWE studies. The MAH agreed that the switch from a conditional to a full marketing authorisation is not approvable at present and proposed a registry study as a follow up specific obligation, a drug utilisation study and the implementation of further risk minimisation measures to maintain the benefit risk balance positive within this CMA. The oral explanation did not change the CHMPs negative opinion on the outcome of this variation procedure as outlined in the assessment report.

In conclusion, the confirmatory study 747-302 has failed to demonstrate the clinical benefit of OCA treatment in reducing the risk of relevant clinical outcomes in patients with PBC, regardless of liver disease severity. The clinical effect on liver outcomes is absent in the ITT population (HR 1.01) and even might be detrimental in decompensated patients (HR 1.22). Further, the results submitted from the external control studies/analyses are not valid evidence to overcome the failed RCT. The absence of improvement of liver histology further correlates these findings. The MAH's attempt to restrict post-hoc OCA use to an early stage PBC sub-population cannot be an acceptable strategy given that the results were nearly identical in both treatment arms (HR 0.98). The proposals to amend the SmPC including also a restriction of the indication and updates applied to the SmPC cannot be agreed with in view of the concerns raised on the demonstration of efficacy and safety in the whole target population. As a consequence, the SOB#1, aimed to address the main efficacy uncertainty at the time of granting a Conditional Marketing Authorisation (CMA), i.e. to what extent those changes in biochemical parameters correlate with a risk reduction in relevant clinical liver outcomes in PBC patients and thus, the actual clinical benefit of OCA treatment, is not fulfilled.

These results do not allow to update the product information and to convert the CMA to a standard MA. Therefore, the type II variation is not approvable.

The lack of a demonstrated benefit in relevant clinical outcomes in PBC patients and the confirmed increased risk of CV events (including MACE), liver DILI, renal, transplant death events, and poor treatment tolerability, both in the overall study population and in the restricted mildly symptomatic early-stage subset, raise question on the actual benefit/risk balance of OCA in the treatment of PBC patients that will need to be addressed in the appropriate procedure.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II and III B

Update of sections 4.8 and 5.1 of the SmPC in order to update clinical information based on final results from studies 747-302 and 747-401, listed as specific obligations in the Annex II, as well as results from real-world evidence (RWE) studies evaluating analyses of hepatic clinical outcomes. Update of Annex II of the Product information to remove studies 747-302 and 747-401, listed as specific obligations,

Study 747-302 is a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints, while study 747-401 is a double-blind, randomised, placebo-controlled study evaluating the safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. The Annex II and Package Leaflet are updated accordingly.

Is not approvable.

Grounds for refusal

Whereas

- The confirmatory study 747-302 has failed to demonstrate the clinical benefit of OCA treatment in reducing the risk of relevant clinical outcomes in patients with PBC, regardless of liver disease severity and the absence of improvement of liver histology is further corroborating these findings.
- The results submitted from the external control studies/analyses, based on RWD, are not considered to provide a sufficient level of evidence valid to demonstrate the efficacy of Ocaliva. The observed differences in the estimation of the treatment effect for the primary endpoint using the primary randomisation and the inverse probability of censoring weighting (IPCW), demonstrate the high risk of bias associated to the provided analysis(es) based on the weighting procedure as compared to the results from Study 747-302. All results based on the external controls are considered to have the same problem of bias. Besides, the analyses resulting from the *post-hoc* comparisons with external controls should be understood in the context of a pivotal trial in which the primary analysis failed, leaving no alpha for confirmatory testing. As a result, any further analyses should be considered exploratory only. Therefore, due to methodological limitations these RWE cannot be considered a robust demonstration of efficacy, in the context of the negative results of the well-designed and conducted double-blind, randomised, placebo-controlled trial 747-302.
- In view of the concerns raised on the demonstration of efficacy and the safety observed in the whole target population based on the provided data including Study 747-302, 747-401 and results from real-world evidence (RWE) studies, the proposed amendments of the SmPC (including restriction of the indication) cannot be agreed. The evidence submitted do not allow to consider that the uncertainties on the efficacy of Ocaliva were addressed and to convert

the conditional marketing authorisation to a standard marketing authorisation.

the CHMP has recommended the refusal of the variation to the terms of the Marketing Authorisation.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion 'Ocaliva - EMEA/H/C/004093/II/0038'.

Annex: Rapporteur's assessment comments on the type II variation

Medicinal product no longer authorised

5. Introduction

Initial MAA filing

Efficacy and safety data that supported a conditional approval in the EU of Ocaliva included three randomized, double-blind, placebo-controlled, multi-center, international studies in patients with PBC:

- **Study 747-201** was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in patients with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses of 10 mg and 50 mg were evaluated as monotherapies.
- **Study 747-202** was a Phase 2, 3-month, international, double-blind, placebo-controlled, parallel-group study in patients with a proven or likely diagnosis of PBC who were suboptimally controlled. OCA doses of 10 mg, 25 mg, and 50 mg were evaluated as add-on therapy to UDCA, the current standard of care for PBC.
- **Study 747-301** was the pivotal Phase 3, 12-month, international, double-blind, placebo-controlled study in patients with a proven or likely diagnosis of PBC who were suboptimally controlled. In this study, OCA doses evaluated were 10 mg or a titration approach (i.e., 5 mg for the initial 6 months, with uptitration to 10 mg for the last 6 months if the patient did not meet the primary composite endpoint and had no tolerability issues).

Studies 747-201, 747-202, and 747-301 included open-label, uncontrolled, LTSE phases to evaluate the long-term effects of OCA treatment. For the initial marketing authorization application (MAA), the LTSEs of Studies 747-201 and 747-202 were completed, while the LTSE for 747-301 remained ongoing.

An additional, 8-week, open-label study was also included in the initial MAA filing; however, efficacy data from this study was not integrated with Studies 747-201, 747-202, and 747-301 due to differences in study design and endpoints:

- **Study 747-205** assessed the safety, tolerability, and PD effects of OCA on HDLc metabolism in patients with PBC on a stable dose of UDCA. This study included an LTSE which was completed after the initial marketing authorization.

New Data to Support Fulfilment of Specific Obligations of the CMA and PAES

Efficacy and safety data to support fulfilment of the requirements of the Specific Obligations of the CMA and support the grant of a Marketing Authorization without conditions include completed postmarketing requirement (PMR)/SOB/PAER studies in patients with PBC included the following:

- **Study 747-401** was a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in patients with PBC and moderate to severe hepatic impairment.
- **Study 747-302** was a double-blind, randomized, placebo-controlled, multicenter study designed to prospectively obtain evidence to confirm clinical benefit and further evaluate the benefit-risk profile of OCA treatment in patients with PBC.

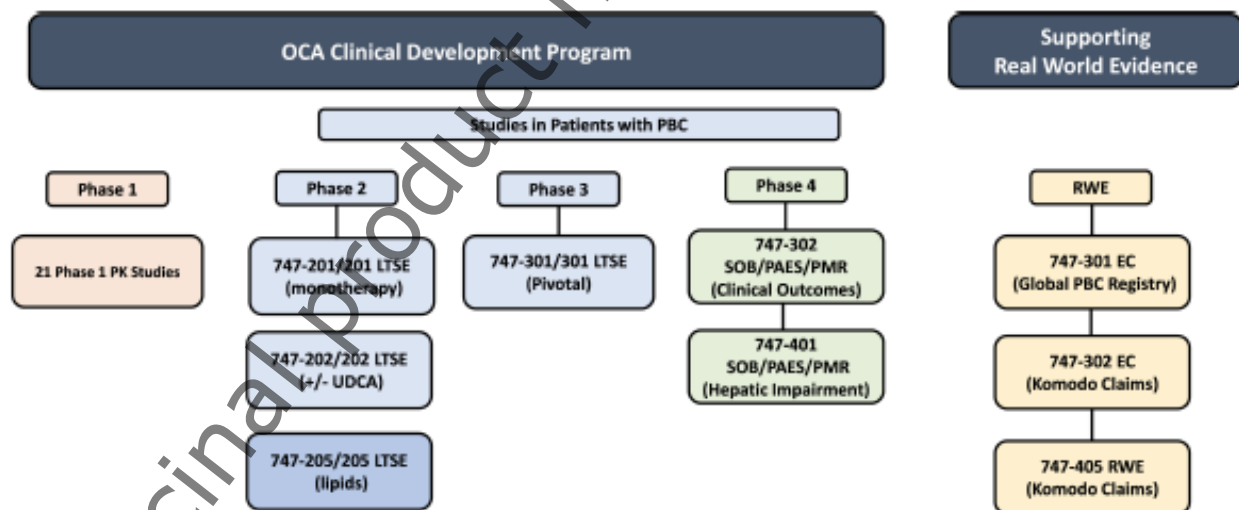
In addition to Studies 747-401 and 747-302, the LTSE of Study 747-301 is completed and provides long-term durability and safety data of OCA for up to 6 years (with median exposure of 5.3 years in 193 patients).

The SOB studies provide primary evidence characterizing the safety and efficacy of OCA in patients with PBC and are supplemented by three **real-world evidence (RWE) studies** evaluating analyses of hepatic clinical outcomes (i.e., time to death, liver transplant and hepatic decompensation) to provide supplementary evidence in this data package. These studies include:

- The **747-301/301 LTSE external control (EC)** analysis was conducted in OCA-treated patients from Study 747-301/301 LTSE compared to external-weighted controls (Global PBC and United Kingdom [UK] PBC Registries) consisting of PBC patients who had failed UDCA but had not been prescribed Ocaliva from the Global PBC Registry). As UK-PBC only analyzed only death and liver transplant (and not hepatic decompensation), the efficacy results in Section 4.2.3 are based on Global PBC only, which evaluated the primary composite endpoint of time to death, liver transplant or hepatic decompensation.
- The **747-302 EC analysis** was conducted in OCA-treated patients in Study 747-302 compared to external-weighted controls from the Komodo Health US Claims database consisting of PBC patients who had failed UDCA or discontinued UDCA for 3 or more months but had not been prescribed Ocaliva. Both guidelines and the standard of care in PBC in the EU are similar to those in the US, supporting the relevance of these data for EU patients with PBC.
- **Study 747-405** is a fully RWE study that compared the incidence of hepatic clinical outcomes in patients with PBC initiating Ocaliva to a standardized mortality/morbidity ratio (SMR)-weighted control group of patients with PBC who would otherwise be eligible for, but who are not prescribed, Ocaliva. Administrative US claims data linked (Komodo Health US Claims database) to additional data sources were used. The MAH states that these US data are relevant to European patients with PBC because US diagnostic criteria, patient demographics, and treatment patterns for PBC are similar.

A summary of the clinical development program for OCA in the treatment of patients with PBC and supporting real-world evidence in patients with PBC is summarized in Figure 1.

Figure 1: Overview of the OCA Clinical Development Program for PBC and Supporting Real-World Evidence



EC=external control; LTSE=long-term safety extension; OCA=obeticholic acid; PAES=prior approval efficacy study; PBC=primary biliary cholangitis; PK=pharmacokinetic; PMR=postmarketing requirement; RWE=real-world evidence; SOB=scientific obligation

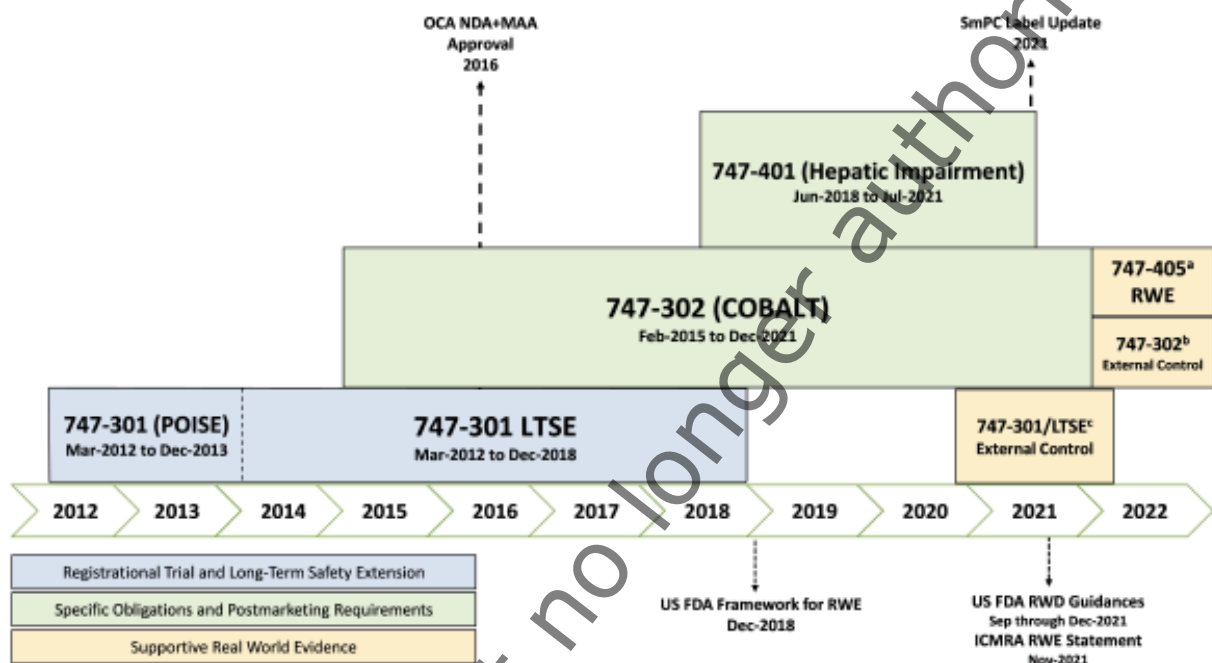
The chronology of studies conducted postmarketing authorization to support fulfilment of the SOBs for conditional approval is presented in Figure 2.

Of note, during the conduct of Studies 747-401 and 747-302, the EU SmPC was updated (Variation submitted 01 Jul 2021 and EC approved 24 Jun 2022) to include a contraindication in patients with decompensated cirrhosis (e.g., CP- B or C) or a prior decompensation event. At the time of submission, for Study 747-302, the Sponsor discontinued investigational product in all patients with decompensated

liver cirrhosis globally and additionally, excluded patients with compensated cirrhosis and evidence of portal hypertension in the US. A total of 21% of patients enrolled in Study 747-302 met the criteria for contraindication per SmPC.

The MAH terminated Study 747-401 as the study enrolled patients with moderate or severe hepatic impairment (n=22), all of whom had decompensated liver disease; following the SmPC restriction update, the study was no longer relevant.

Figure 2: Chronology of Studies Conducted



EC=external control; FDA=Food and Drug Administration; ICMRA=International Coalition of Medicines Regulatory Authorities; LTSE=long-term safety extension; OCA=obeticholic acid; RWD=real world data; RWE=real world evidence; US=United States

^a Study 747-405 (HEROES) began in October 2021 and concluded in August 2022.

^b The study for the 747-302 EC analyses began in October 2021 and concluded in September 2022.

^c The study for the 747-301/301 LTSE EC analyses began in January 2021 and concluded in January 2022.

In summary:

- Registrational study and long-term safety extension (LTSE) – Study 747-301 LTSE
- European Union (EU) specific obligations (SOBs) and post marketing requirement (PMR)
 - Study 747-401
 - Study 747-302
- Supportive real-world evidence (RWE) Studies – Studies 747-301 EC, 747-302 EC, and 747-405.

6. Clinical Efficacy aspects

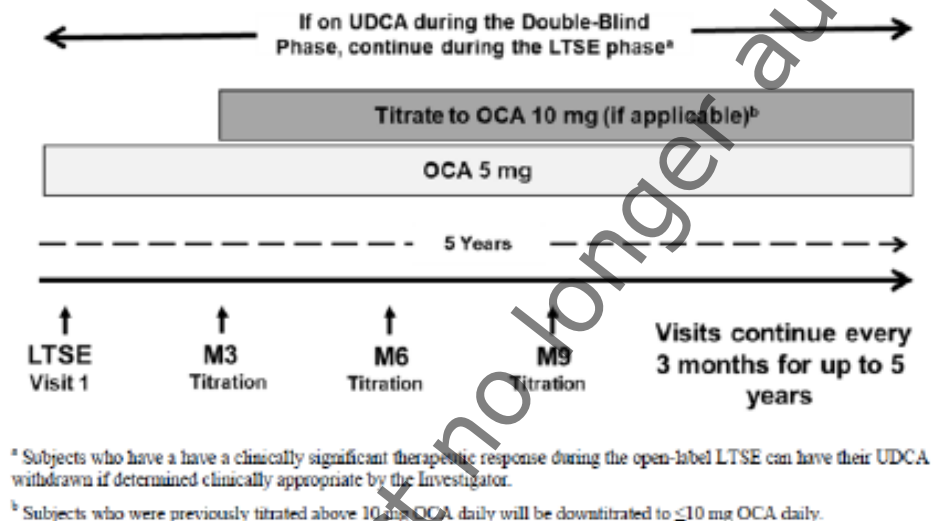
Study 747-301 was the Phase 3, 12-month, double-blind, placebo-controlled trial to meet requirements of accelerated approval in the US and conditional marketing approval via the EU centralized procedure based on establishing a reduction in serum ALP. Following the 12-month double-

blind, placebo-controlled period of Study 747-301, patients randomized to placebo crossed over to OCA treatment and all patients were followed for up to an additional 5 years (747-301 LTSE).

Methods – analysis of data submitted

Study 747-301 LTSE (uncontrolled study)

Study 747-301 was the Phase 3, 12-month, double-blind, placebo-controlled trial to support accelerated approval based on establishing a reduction in serum ALP. Following the 12-month double-blind, placebo-controlled period of Study 747-301, all patients, including those who received placebo, were eligible to participate in an open-label LTSE and were followed for up to an additional 5 years (747-301 LTSE). The Month 12 Visit from the Double-Blind Phase served as the Day 1 Visit of the LTSE Phase as shown in the figure below.



LTSE = long-term safety extension; M = month; OCA = obeticholic acid; UDCA = ursodeoxycholic acid

Key study design aspects of 747-301 LTSE included:

- Patient treatment allocation in the Double-Blind Phase was not made available until the entire study was unblinded. Accordingly, all patients starting in the LTSE Phase were initially started on the 5 mg dose, i.e., patients who received placebo started OCA therapy, those already on 5 mg continued on the same dose, while those who received 10 mg at the end of the Double-Blind Phase were titrated down to 5 mg. Using this approach, blinding of the entire study was maintained and data on the effects of down titrating from 10 mg to 5 mg were also obtained.
- All patients continued at a 5 mg dose for a minimum of 3 months. Subsequent to the LTSE Month 3 visit, OCA doses could be titrated (incrementally from 5 mg to 10 mg to 15 mg, up to 25 mg OCA at a frequency of no more than one up-titration every 3 months). However, effective with Protocol Version 5 (21 Mar 2018), the protocol was amended to align with marketing doses (i.e., 5 mg or 10 mg once daily). Any patient receiving a dose higher than 10 mg was down titrated to ≤10 mg daily.
- Any of the patients who had a clinically significant therapeutic response during the LTSE Phase could have had their UDCA withdrawn if determined clinically appropriate by the Investigator. Patients who received investigational product as a monotherapy in the Double-Blind Phase were to receive OCA as a monotherapy in the LTSE Phase.

Results

747-301 LTSE - Study Population

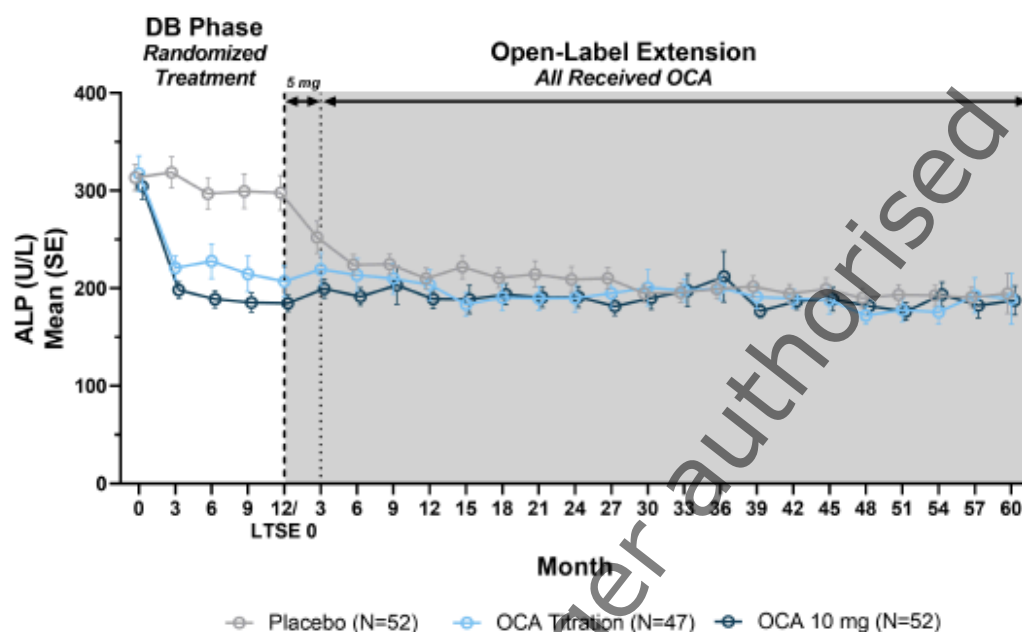
A total of 217 patients were enrolled into the 12-month double-blind phase of the study; of the 198 patients who completed the double-blind phase, 193 patients (97.5%) enrolled into the LTSE phase. Overall, there was good retention in the study: 146 (76%) patients completed the protocol as specified following administrative termination/closure of the study, and 47 (24%) patients discontinued the LTSE prematurely. The majority of patients discontinued due to study closure by the Sponsor. Twenty (10%) patients discontinued due to an AE (either pruritus or other AE), and 12 (6%) patients withdrew consent. Two patients (one during the study and another after the study was closed) died during the LTSE; both deaths were considered by the Investigator as unrelated to OCA.

For the total population, the mean age was 55.4 years, with a range from 29 to 83 years. A total of 83% of patients were <65 years of age. As expected with PBC, the study population was predominantly female (92%) and white (94%). The majority (93%) of the population was on UDCA at baseline. In general, key demographic and PBC baseline disease characteristics were well balanced across weighted average daily dose (WADD) categories.

747-301 LTSE - Efficacy Summary

The efficacy associated with continued treatment with OCA was durable and consistent with the effects observed in the double-blind phase. For patients originally randomized to OCA, continued treatment was associated with sustained improvements in liver biochemistry. For patients originally randomized to placebo, there were clinically significant improvements in liver biochemistry following the initiation of OCA nearly identical to the changes observed in patients randomized to OCA in the double-blind phase. Specifically, long-term treatment with OCA, up to 6 years in patients with PBC resulted in clinically meaningful improvements as assessed by the primary efficacy endpoint—the composite ALP and total bilirubin endpoint that supported initial approval of OCA for the treatment of PBC. In addition, improvements in markers of cholestasis (ALP and GGT) and hepatocellular injury (ALT and AST) were observed along with improvement or no worsening of histologic fibrosis. Total bilirubin levels remained stable and within the normal range throughout the duration of the study (see Section 5 for durability of liver biochemistry over time). Improvements in markers of fibrosis and apoptosis observed during the double-blind phase were all maintained with long-term treatment.

Figure 12: Mean (SE) ALP Over Time (747-301 LTSE)



ALP = alkaline phosphatase; LTSE = long-term safety extension.

A biopsy substudy (n=17) was performed in patients assessing baseline biopsies (up to 1 year before the start of the double-blind phase) and after 3 years of OCA treatment (LTSE Month 24 for OCA randomized patients and LTSE Month 36 for placebo randomized patients) (Bowlus 2020). Overall, the results of the post hoc reanalysis were indicative that long-term OCA treatment in patients with PBC is associated with improvement or stabilization across a spectrum of histologic features of PBC.

747-301 LTSE - Safety Summary

Overall, administration of OCA was safe and generally well tolerated over the 5-year LTSE phase in patients with PBC; the safety profile during the LTSE phase was similar to that in the double-blind phase as well as other PBC studies with OCA, and no new safety signals were noted.

A total of 193 patients received at least 1 dose of OCA during the LTSE. The median number of days on OCA was 1944.0 days (5.3 years) from initiation of OCA regardless if it were in the double-blind or LTSE phase. The median weighted average daily OCA dose was 8.3 mg. Forty-two (22%) patients received OCA >10 mg daily at some point during the study.

The most common treatment-emergent adverse event (TEAE) was pruritus. With the exception of pruritus, diarrhea, and dyspepsia, the distribution of TEAEs was generally similar across weighted average daily dose (WADD) categories, and most TEAEs were considered resolved at the end of the LTSE. There was a dose-related pattern of pruritus across WADD categories, and most patients experienced TEAEs of pruritus that were mild or moderate in severity. Pruritus frequency and severity remained steady after approximately 3 months of OCA treatment.

Overall, 61 (32%) patients experienced a serious TEAE. There was no apparent pattern to the types of serious TEAEs nor dose-relationship of serious TEAEs across WADD categories. The majority of serious TEAEs were considered not related to OCA. Two (1%) deaths occurred during the LTSE (one was attributed to sepsis complications from a heart valve replacement and the other was due to jaundice associated with acute alcohol hepatitis); and both deaths were assessed as unrelated to OCA.

The hepatic-related safety was consistent with that reported in previous studies with OCA, and no new findings were noted following long-term treatment with OCA. Markers of liver injury and cholestasis improved with long-term OCA treatment.

Low-density lipoprotein cholesterol remained unchanged with long-term OCA treatment and the modest decrease in high-density lipoprotein cholesterol observed during the double-blind phase plateaued during the LTSE phase, with median values remaining above the LLN.

747-301 LTSE - Overall Conclusions (as provided by the MAH)

- The efficacy associated with continued treatment with OCA was durable and consistent with the effects observed in the double-blind phase.
- The safety profile remained consistent with the known safety profile of OCA in patients with PBC, with no new safety signals apparent with long-term treatment.
- Overall, these findings support the long-term efficacy and safety of OCA treatment for patients with PBC who are intolerant or inadequately responsive to UDCA.

Discussion

Only top line LTSE results have been provided, which do not allow to formally assess and conclude on the long-term safety of Ocaliva. Of note, 61 (32%) patients experienced a serious TEAE (according to the MAH, the majority not considered OCA related), and a substantial proportion (47/198 (24%)) of patients discontinued the LTSE prematurely: 20 (10%) patients discontinued due to an AE (either pruritus or other AE), and 12 (6%) patients withdrew consent; although the reduction in ALP achieved with OCA appears to remain in the long-term, these data do not speak in favour of the claimed good tolerability in the long-term, also considering the lack of alternative treatment options. A more comprehensive presentation of the relevant efficacy and safety results of this study was requested and provided. Overall, long term efficacy data support the maintenance of the effect of OCA treatment in liver biochemical and inflammatory parameters. A high proportion of patients had a severe TEAE (54%), and SAEs (32%), though the overall rate of treatment discontinuation was relatively low (13%). The safety profile remains unchanged, with pruritus being the most common bothersome TEAEs, largely responsible for the severe TEAEs. CV (21%) and hepatic events (24%) were commonly reported during the trial, though the incidence of serious CV and hepatic events was relatively low (around 4% both), and most of these cases occurred in patients with underlying conditions or in whom treatment with OCA is currently contraindicated. Overall, these data do not raise major concerns, although the absence of a control arm does not allow drawing firm conclusions on the actual role of OCA in the incidence of these events.

7. Post-Authorisation efficacy study (PAES) results

European Union Specific Obligations (EU SOBs)

Studies 747-401 and 747-302 were imposed as a part of the accelerated approval of Ocaliva by FDA and SOBs imposed as a part of the Conditional Marketing Authorization (CMA) of Ocaliva in the EU.

Study 747-401

Study 747-401 was a Phase 4, double-blind, randomized, placebo-controlled study evaluating the safety and pharmacokinetics (PK) of Ocaliva in patients with PBC and moderate to severe hepatic impairment. A total of 22 patients with moderate or severe hepatic impairment were enrolled. Study 747-401 was terminated upon the updates to the Core Company Datasheet (CCDS), EU Summary of Product

Characteristics (SmPC), and the US Prescribing Information (USPI), with last-patient-last-visit on 09 Jul 2021. As patients with moderate or severe hepatic impairment are contraindicated per the revised EU SmPC, the data from this study are of limited value to prescribers for Ocaliva in PBC.

Study 747-302

Study 747-302 was a Phase 3b/4, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA on clinical outcomes in patients with PBC to confirm clinical outcomes with Ocaliva as required in multiple jurisdictions. Both Committee for Medicinal Products for Human Use (CHMP) and FDA provided input into the design of Study 747-302, and per requirements, Study 747-302 was ongoing at the time of marketing authorizations.

The primary objective of the study was to assess the effects of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in patients with PBC as derived as a composite event endpoint (defined below).

Most patients enrolled into Study 747-302 were at a more advanced disease stage compared to Study 747-301 and only a subpopulation of patients (79%) reflected the currently indicated (e.g., with compensated cirrhosis) population in the revised EU SmPC.

Study 747-302 encountered enrolment and retention challenges, which were discussed on several occasions with both FDA and CHMP. The Sponsor proposed a transition to an open-label design versus historic control; however, at the time of the CHMP Positive Opinion in October 2016, CHMP explicitly required that no analysis utilizing an external control be conducted without advanced agreement from regulators.

In alignment with the FDA and EMA and upon recommendation from the Data Monitoring Committee (DMC), the Sponsor decided to terminate Study 747-302 early due to feasibility challenges in the setting of commercially available Ocaliva, with last-patient-last-visit on 23 Dec 2021. The study was underpowered to detect a hazard ratio (HR) of 0.6 for the original primary composite endpoint of death, liver transplant, or hepatic decompensation. At the time of study termination by the Sponsor, approximately 67% of the clinical events had been observed of the total estimated to provide 80% power to demonstrate a statistically significant difference in clinical progression between OCA and placebo.

To better evaluate the benefit-risk ratio, the composite endpoint was expanded in alignment with FDA to include additional components that occur earlier in the progression of PBC. The revised expanded endpoint from FDA was not agreed by CHMP. It was requested that the Sponsor continue assessing the composite endpoint as originally defined in the protocol and described in the statistical analysis plan (SAP). The resulting difference in feedback from EMA and FDA on the composite endpoint led to the Sponsor analyzing both endpoints.

Methods – analysis of data submitted

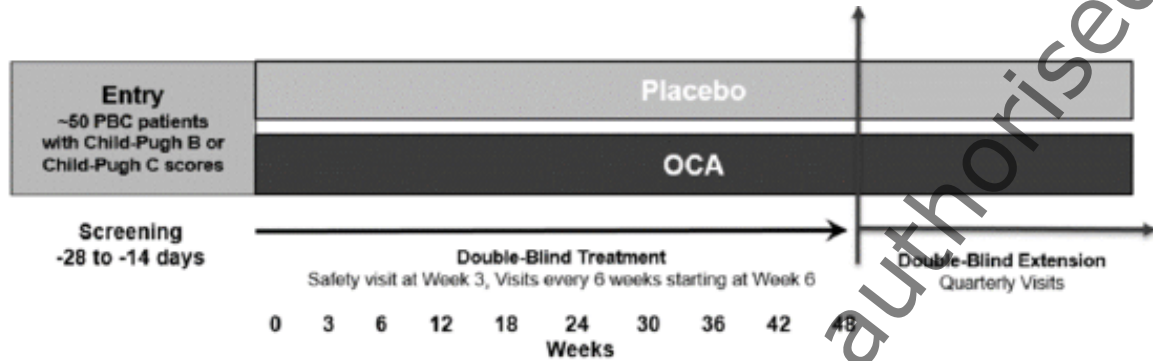
Study 747-401 (double-blind, placebo-controlled)

As outlined above, study 747-401 was a Phase 3b/4, double-blind, randomized, placebo-controlled study evaluating the safety and PK of Ocaliva in patients with PBC and moderate to severe hepatic impairment. Efficacy was considered as a secondary objective. Patients with definite or probable PBC and Child-Pugh Class B (CP-B) or Child-Pugh Class C (CP-C) cirrhosis with Model for End Stage Liver Disease (MELD) scores of 6 to 24 were enrolled in the study.

Enrolled patients who met all eligibility requirements were randomized in a 1:1 ratio to 1 of 2 treatment groups: placebo or OCA at Screening and Day 1. The study included a Double-Blind Treatment Phase of 48 weeks, followed by a Double-Blind Extension Phase (see figure below).

Study 747-401 was terminated upon the EU SmPC update in 2021, with last-patient-last-visit on 09 Jul 2021. A total of 22 patients with moderate or severe hepatic impairment were enrolled. As patients with moderate or severe hepatic impairment are contraindicated per the revised EU SmPC, the data from this study are of limited value to prescribers for Ocaliva in PBC.

Study design



OCA = obeticholic acid; PB = primary biliary cholangitis.

Notes: Initial dose titration of investigational product was considered as early as the Week 12 Visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and safety laboratory tests from the previous visit. Subsequent dose titration(s) may have occurred no earlier than 6 weeks after the previous dose titration and was based on tolerability. Patients who completed Week 48 continued double-blind treatment until all randomized patients had completed their participation in the 48-week treatment period and the database for that period was locked.

Key study aspects of Study 747-401 included the following:

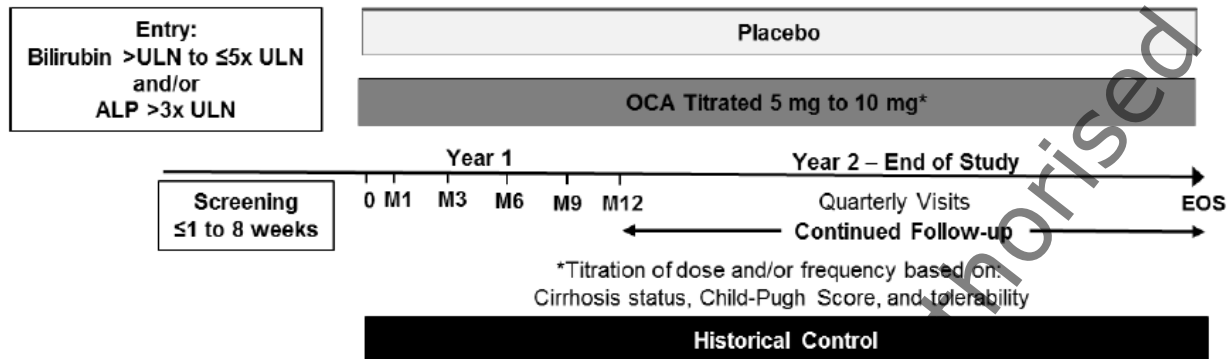
- A 48-week study designed to characterize the PK and safety of OCA in patients with PBC with moderate to severe hepatic impairment.
- PK and safety parameters were evaluated as primary objectives. Efficacy parameters were evaluated as secondary and additional objectives.
- Study site personnel, patients, and the Sponsor were blinded to treatment allocations.
- Based on results from previous Phase 1 and 2 studies, doses of OCA administered to patients with moderate or severe hepatic impairment should be lower than those for patients with normal hepatic function to achieve similar hepatic exposure.
- All patients initiated investigational product once weekly with OCA 5 mg or matching placebo. At Week 12, if the investigational product was tolerated and laboratory assessments did not indicate a safety concern, the patient could be up titrated to OCA 5 mg twice weekly and no earlier than 2 days after they took their last dose. Following titration, dosing was to occur at least 3 days apart. Every 6 weeks thereafter, based on tolerability assessments, patients could be considered for further up titration.
- There was no primary efficacy endpoint in the study; data were described under clinical outcome events efficacy endpoints and additional efficacy endpoints. The study was not designed to detect differences between treatments for efficacy endpoints.
- Missing data for patients were considered as non-informative missing data and were not imputed.

Study 747-302 (double-blind, placebo-controlled)

Study 747-302 was a Phase 3b/4, double-blind, randomized, placebo-controlled, multicenter study evaluating the effect of OCA on clinical outcomes in patients with PBC to confirm clinical outcomes with Ocaliva. Most patients enrolled into Study 747-302 were more advanced disease stage (i.e., higher risk

for liver-related clinical complications) compared to previous studies and only a subpopulation of patients is reflective of the compensated population in the revised SmPC.

Study design



ALP = alkaline phosphatase; CP-B = Child-Pugh Class B cirrhosis; CP-C = Child-Pugh Class C cirrhosis; EOS = end of study; M = month; OCA = obeticholic acid; ULN = upper limit of normal

* Initial dose titration of investigational product should have occurred at the Month 3 visit, or any study visit thereafter for patients on all dosing regimens, based on tolerability and biochemical response (Up-titration should have been considered when ALP and/or total bilirubin were >ULN). Subsequent dose titration(s) for patients classified as CP-B or CP-C and following a modified dosing schedule may have occurred no earlier than 6 weeks after the previous dose titration

With the exception of liver transplant or death, if a patient experienced a suspected or confirmed clinical outcomes event, the patient may have continued the regular visit schedule and taking investigational product as long as the patient had not met any of the criteria for discontinuation including:

- Patient began treatment with commercially available OCA.
- The Investigator or Sponsor considered that it was advisable or in the best interest of the patient.
- The occurrence of clinical or laboratory AEs considered by the Investigator to be clinically important safety concerns and related to investigational product.
- Withdrawal of consent

Patients who discontinued investigational product were expected to be followed through to study closure (or at the discretion of the Sponsor).

Discussions with both FDA and CHMP regarding recruitment and retention challenges with Study 747-302 occurred from 2019 until study termination. The transition to an open-label design versus historic control was proposed previously, although at the time of the CHMP Positive Opinion in October 2016, CHMP explicitly required deletion of reference to the use of a historic control as exploratory endpoint analysis in the study protocol.

Rationale for Study Design

Study 747-302 was a clinical outcomes study, designed to confirm the clinical benefit of OCA treatment in patients with PBC. Data from a retrospective observational database of patients with PBC (Global PBC Study Group) were utilized to inform the design of Study 747-302.

Patient Eligibility

Given the low prevalence of PBC, combined with the slow but inevitable progression of the disease, the study was designed to balance scientific rigor with feasibility of execution. Hence, the 747-302 study

population purposely recruited more advanced PBC patients compared to the Study 747-301 population that served as the basis for accelerated/conditional approval.

Patient eligibility required a diagnosis of PBC with bilirubin levels $>ULN$ and $\leq 5 \times ULN$ and/or ALP levels $>3 \times ULN$, which were tested twice during the screening period. Enrolled patients were randomized in a 1:1 ratio across sites and were stratified by UDCA treatment (yes/no) and baseline bilirubin categories ($>ULN/\leq ULN$), as specified by the central laboratory. A minimum of 30% of patients were required to have elevated bilirubin at Screening.

Rationale for Dose

In Phase 2 studies, OCA 10 mg demonstrated equivalent efficacy to OCA 25 mg and 50 mg with better tolerability. Study 747-301 demonstrated that titration from OCA 5 mg to OCA 10 mg based on clinical response improved tolerance, minimized dropouts due to pruritus, and showed comparable efficacy to OCA 10 mg after 1 year. Thus, in alignment with the EU SmPC, the dosing regimen for all 747-302 study patients initially was OCA 5 mg once daily with titration to OCA 10 mg once daily at 6 months, if tolerated. Following Protocol Version 3.0 dated 07 Sep 2016, dose and frequency were modified according to the SmPC for patients with CP-B or CP-C cirrhosis; these patients are now contraindicated in the current EU SmPC.

Determination of Sample Size

The following assumptions were used for sample size calculations:

- Exponential survival curves, placebo survival estimate of 0.6 at 8 years with a HR of 0.60, and total study duration of 10 years (from first patient enrolled), allowing for 4 years of patient accrual and 6 years of follow up.
- Patients were randomized in a 1:1 ratio to placebo or OCA.
- The two treatment groups were compared using a 2-sided log rank test at the 5% level of significance.
- Two interim analyses and one final analysis were planned, with interim analyses to occur after the accrual of 50% and 75% of clinical outcome events, respectively.
- A dropout rate equally distributed between treatment arms of 10% was assumed.

Based on the randomization ratio, significance level, and assumed HR, a total of 127 events (both groups combined) was to provide 80% power to demonstrate a statistically significant difference between OCA and placebo on time to liver-related outcomes, including all-cause mortality.

In addition, based on the remaining assumptions stated above, it was estimated that approximately 428 patients would be enrolled to attain 127 events.

Sample size calculations were based on the following composite endpoint: time to first occurrence of death, liver transplant, MELD ≥ 15 , uncontrolled ascites, or hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.

Due to enrolment challenges and difficulties to keep patients in the study, and in alignment with the FDA, EMA, and the recommendations of the DMC, the study was terminated early by the Sponsor. To better evaluate the benefit-risk ratio, the primary composite endpoint was revised in alignment with FDA to include additional components that occur earlier in the progression of PBC (referred to as expanded primary endpoint). The revised expanded endpoint from FDA was not agreed by CHMP. It was requested that the Sponsor continue assessing the composite endpoint as originally defined in the protocol and assessed in the SAP. The resulting difference in feedback from EMA and FDA on the

composite endpoint led to the Sponsor analyzing both endpoints as described in the clinical study report and elsewhere.

Duration of Treatment

The study was event driven and total duration was determined on the time required to accrue approximately 127 adjudicated primary endpoint events (based on the assumed HR of 0.6 and to provide 80% power), estimated to be approximately 10 years. Patients were expected to have a minimum follow-up time of approximately 6 years.

Primary Endpoint

Per the most recent protocol at the time of database lock (Version 6), the primary analysis was a log rank test comparing the OCA-treated arm to the placebo arm on time to first occurrence of an adjudicated event in the composite endpoint (referred to as primary composite endpoint) as summarized in the table below.

Definition of Primary Composite Endpoint

Primary Composite Endpoint
• Death (all-cause) • Liver transplant • MELD score ≥ 15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥ 2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) – Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

Expanded Primary Endpoint

Due to enrollment and retention challenges, and in alignment with the FDA, EMA and on recommendation of the DMC, the study was terminated early by the Sponsor, with approximately 67% of the protocol-specified number of events necessary to provide 80% power to demonstrate a statistically significant difference between OCA and placebo (84 adjudicated Protocol Version 6 endpoints observed), with 171 (51.2%) patients actively on study at time of Sponsor termination. To increase the number of endpoint events and power to detect a difference between treatment arms, the primary efficacy endpoint was expanded based on recommendation from the FDA, to include:

- Portal hypertension syndromes (hepatorenal, portopulmonary, or hepatopulmonary)
- Progression to decompensated liver disease (for patients without decompensation at baseline)
- Progression to clinical evidence of portal hypertension without decompensation (for patients without decompensation or clinical evidence of portal hypertension at baseline)

A detailed definition of the expanded composite endpoint is presented in the following table.

Definition of Expanded Primary Endpoint

Expanded Primary Endpoint
Group 1 (applies to all patients)
• Death (all-cause) • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of $>250/\text{mm}^3$ polymorph leucocytes [PMNs] in the ascitic fluid), or bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid) • Uncontrolled or refractory ascites (requiring large volume paracentesis) • Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club [Angel 2019]), portopulmonary syndrome, or hepatopulmonary syndrome • Model for End Stage Liver Disease-Sodium (MELD-Na) score ≥ 15 if MELD-Na < 12 at baseline • MELD score ≥ 15 if MELD-Na ≥ 12 at baseline
Group 2 (applies to patients without decompensation at Baseline)
Progression to decompensated liver disease (for patients without decompensation at baseline), prioritized as follows: • New onset of hepatic hydrothorax, variceal bleeding, or ascites requiring treatment with sodium restriction, diet modification, or diuretics • Hepatic encephalopathy requiring lactulose and/or rifaximin • New onset of Child-Pugh (CP) ≥ 7 or total bilirubin > 3 mg/dL
Group 3 (applies to patients without decompensation or clinical evidence of portal hypertension at Baseline)
Progression to clinical evidence of portal hypertension without decompensation (for patients without decompensation or clinical evidence of portal hypertension at baseline) as defined as: • Endoscopic evidence of portal hypertension without bleeding (i.e. gastroesophageal varices [requiring banding or progression to large varices if no or small varices were observed at baseline]) or portal hypertensive gastropathy • Platelets $< 150 \times 10^9/\text{L}$ with splenomegaly and/or with transient elastography (TE) > 15 kPa

The primary efficacy analysis remained the stratified log rank test. With the inclusion of additional endpoints that occurred earlier in the course of the disease, the log rank test was limited to each patient's first event, which was likely to be an outcome of lesser clinical importance.

As noted in the CHMP/PRAC 2021 annual renewal assessment report (EMA/H/C/004093/R/0027), CHMP did not agree to the proposed changes to the primary endpoint.

Number of Interim Analyses

Although the protocol did originally plan for 2 interim analyses, one at $\sim 50\%$ (64 events) and the other at $\sim 75\%$ (96 events) information fraction, the first interim analysis was postponed to after regulatory authority review of the interim SAP. As a result, the first interim analysis occurred after the accrual of approximately 65% (83 events) of the required total clinical outcome events. It was agreed that the second interim analysis would be omitted. O'Brien-Fleming Boundaries were used for superiority in the interim analysis. The table below provides the relevant estimates both for the original 2-interim analyses and revised single-interim analysis scenarios.

Stopping criteria based on O'Brien-Fleming Boundaries

Type I Error	Power	Information Fraction	Number of Clinical Events	Incremental α Spend	Cumulative α Spend	Reject for Efficacy if Hazard Ratio
Two Interim Analyses (Originally Planned)						
		50%	64	0.003	0.003	≤ 0.473
0.05	0.80	75%	96	0.018	0.019	≤ 0.611
		End of Study (100%)	127	0.044	0.050	≤ 0.695
Single Interim Analysis						
		65%	83	0.011	0.011	≤ 0.564
0.05	0.80	End of Study (100%)	127	0.047	0.050	≤ 0.697

Results

Study 747-401: A Phase 4, Double-Blind, Randomized, Placebo-Controlled Study Evaluating the Pharmacokinetics and Safety of Obeticholic Acid in Patients with Primary Biliary Cholangitis and Moderate to Severe Hepatic Impairment

Patients with moderate or severe hepatic impairment are contraindicated per the revised EU SmPC; therefore, the data from this study are of limited value to prescribers for Ocaliva in PBC.

747-401 - Study Population

A total of 22 patients were randomized in the study (10 patients in the OCA group and 12 in the placebo group) and comprised the Randomized, ITT, and Safety populations. Of these, 10 (45.5%) patients (6 patients in the OCA group and 4 patients in the placebo group) completed the Double-Blind Phase. The majority of patients were White (95.5%) and female (72.7%). The median age of patients was 63 (range: 45 to 79 years old).

In general, baseline characteristics, including Child-Pugh (CP) and MELD scores, were well balanced across treatment arms. The majority of patients had CP Class B (100.0% [OCA] and 91.7% [placebo]) whereas 0.0% (OCA) and 8.3% (placebo) patients had CP Class C. Mean (SD) Baseline CP score was 7.7 (0.67) in the OCA and 7.9 (0.90) in the placebo groups. Mean (SD) Baseline MELD score was 12.7 (3.47) in the OCA and 12.4 (2.97) in the placebo groups. The mean (SD) age at time of consent was 60.5 (10.19) years in the OCA and 62.5 (9.10) years in the placebo groups, and the percentage of females was 60.0% (OCA) and 83.3% (placebo).

747-401 - Safety Summary

In the Double-Blind Phase and Double-Blind Extension Phase, the overall mean duration of exposure to study treatment was 296.5 days in the OCA and 233.4 days in the placebo groups. In the Safety Population, all patients in the OCA and placebo groups reported at least 1 TEAE during the Double-Blind Phase and Double-Blind Extension Phase of the study. The most frequently reported TEAEs ($\geq 30\%$) were ascites, oesophageal varices haemorrhage, pneumonia, urinary tract infection, pruritus, and anaemia.

The majority of TEAEs in both treatment groups were reported to be mild (Grade 1) or moderate (Grade 2) in severity.

Study treatment or study discontinuations occurred in 5 (50.0%) patients in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) patients in the OCA and 4

(33.3%) patients in the placebo group. The most common TEAE leading to study treatment interruption was ascites (2 [20.0%] patients in OCA and 1 [8.3%] in placebo groups).

A total of 7 (70.0%) patients in the OCA and 9 (75.0%) patients in the placebo groups experienced serious adverse events (SAEs). In general, the nature of SAEs is consistent with the underlying advanced liver disease in this patient population.

A total of 5 deaths were reported (3 patients in the placebo group [hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal carcinoma] and 2 patients in the OCA group [multiple organ dysfunction syndrome and cardiac arrest]), which were all considered by the Investigator as not related or unlikely related to the study treatment. The case of death from clear cell renal cell carcinoma occurred within the study period; however, was reported after database lock.

Overall, 9 (90.0%) patients in the OCA and 9 (75.0%) patients in the placebo groups experienced an adverse event of special interest (AESI).

Overall, no patients had clinically relevant abnormal electrocardiogram (ECG) findings at Week 48 or Double-Blind Extension Month 12 across treatment groups.

Several mean baseline laboratory values were out of range, consistent with patients with PBC with moderate to advanced cirrhosis. These values did not change meaningfully over time following multiple dose administration of OCA or placebo; additionally, no meaningful discernible differences over time were noted between OCA and placebo.

There were no clinically relevant changes from baseline (blood pressure, heart rate, temperature, and weight) in OCA group compared with placebo. No additional physical examination findings were observed, and no trends were detected.

747-401 – PK Summary

Six patients with hepatic impairment (CP-B) were included in the PK analysis: 6 patients received OCA 5 mg once weekly, of which 4 patients were titrated to 5 mg twice weekly and of the 4 patients, 2 patients were titrated to 10 mg twice weekly. No patients with severe hepatic impairment (CP-C) were evaluable for PK assessment.

The PK results of this study demonstrated the accuracy of the simulation to predict total OCA exposure following the OCA 5 mg once weekly dose regimen. The observed mean area under the plasma concentration time curve from 0 to 24 hours (AUC_{0-24h}) for total OCA at Week 12 (i.e., steady-state) was 2970 ng·h/mL comparable to the simulated predicted mean AUC_{0-24h} of 2633 ng·h/mL (data on file), which is comparable to the observed total OCA exposure (AUC_{0-24h} = 2762 ng·h/mL) following a 10 mg daily dose in patients without hepatic impairment. Based on these PK results, the initial dose of OCA 5 mg once weekly achieved targeted OCA exposure. Dose proportional increases in total OCA exposure were observed with dose titration from 5 mg once weekly to 5 mg twice weekly and 10 mg twice weekly.

747-401 – Efficacy Summary

Study 747-401 was not designed to detect differences in efficacy. OCA demonstrated no clear clinical benefit in this advanced PBC population (CP-B or CP-C) who is considered contraindicated per the EU SmPC. No clinically meaningful differences were noted between OCA versus placebo for the composite outcome of death, including liver-related death, liver transplant, MELD, uncontrolled ascites, and hospitalizations for decompensating events. There was also no significant difference between OCA and placebo for individual components of the composite outcome, except for variceal bleeding (unclear relevance given the small sample size).

There was a trend toward improving liver stiffness measurement (LSM) over time among OCA versus placebo, however, because of the small sample size and a large standard error of the mean (SEM) the significance of this observation is unclear. Overall, change and percent change in liver stiffness (as assessed by TE) and enhanced liver fibrosis (ELF) were not statistically different than placebo.

Overall changes in total bile acids, total endogenous bile acids, fibroblast growth factor-19 (FGF-19) and 7 α -hydroxy-4-cholesten-3-one (C4) concentrations were observed in the OCA group over time, however, were not clinically significant at any timepoint. Interpretation of these results is limited due to the small sample size and the study was not designed to detect outcome differences.

Overall Conclusions (as provided by the MAH)

- The safety profile of OCA was consistent with that expected in a PBC patient population with moderate to advanced cirrhosis.
- Despite the low patient numbers for PK assessment (N=6), total OCA exposure following OCA 5 mg once weekly was consistent with the modelled predictions of AUC_{0-24h} and maximum plasma concentration (C_{max}) demonstrating that the modified OCA dose regimen of 5 mg once weekly achieved targeted OCA exposure.
- No clinically meaningful differences were noted between OCA and placebo for efficacy endpoints, though the number of patients was small, and the study was not designed to detect differences between treatment groups.

Study 747-302: A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients with Primary Biliary Cholangitis

747-302 – Study Population

A total of 334 patients were randomized in the study and were included in the ITT Population: 168 patients in the OCA and 166 patients in the placebo groups.

Treatment groups were well balanced for each key demographic variable. The majority of patients were female (90%) and White (87%). Overall, the mean age of patients was 53.7 (range: 29 to 77 years old). A total of 84% of patients were <65 years of age.

The study population had advanced disease consistent with the study inclusion criteria of a diagnosis of PBC with bilirubin levels >ULN and $\leq 5 \times$ ULN and/or ALP >3x ULN. The majority of patients were compensated at baseline (265 [79%] patients) versus decompensated (69 [21%] patients).

747-302 - Efficacy Summary

The estimated effect of treatment from the ITT analyses, shown below, was under-powered (due to incomplete recruitment and the prespecified number of endpoints not achieved) and potentially biased (due to differential drop out and quality of follow up) resulting in difficulties in the interpretation of the tests of hypotheses for the primary, expanded primary, and key secondary endpoints.

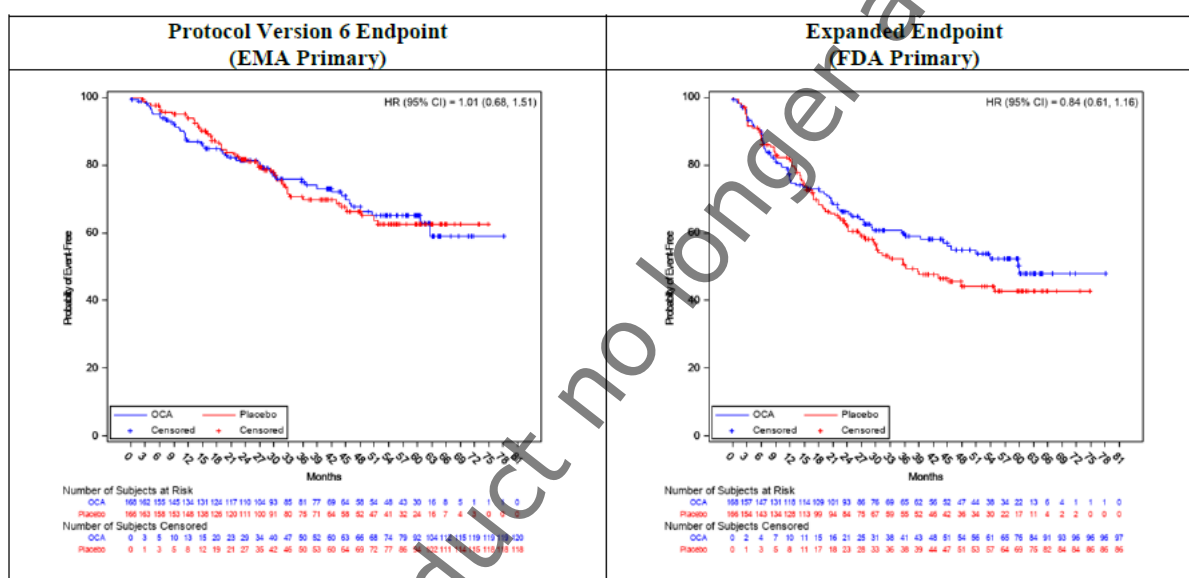
747-302: Time to First Occurrence of Primary Outcome Event (Overall Population, ITT Analyses)

	Primary Endpoint ^a		Expanded Primary Endpoint ^a	
	Placebo (N=166)	OCA (N=168)	Placebo (N=166)	OCA (N=168)
Number of Patients with Clinical Event, n (%)	48 (28.9)	48 (28.6)	80 (48.2)	71 (42.3)
Log-Rank p-value	0.954		0.304	
HR (95% CI)	1.01 (0.68, 1.51)		0.84 (0.61, 1.16)	
IPCW HR (95% CI)	0.82 (0.53, 1.27)		0.80 (0.58, 1.12)	

CI = confidence interval; HR = hazard ratio; IPCW = inverse probability of censoring weighting; ITT = Intent-to-Treat; OCA = obeticholic acid.

^a Endpoints are defined in Table 1 (primary endpoint) and Table 2 (expanded primary endpoint).

Kaplan-Meier Time to First Occurrence of Composite Primary Endpoint – (ITT Population)



CI=confidence interval; EMA=European Medicines Agency; FDA=Food and Drug Administration; HR=hazard ratio;

ITT=Intent-to-Treat; OCA=obeticholic acid

Note: Detailed definitions for the primary composite endpoints are summarized in Section 8.1, Table 1 (Protocol Version 6 Endpoint) and Table 2 (Expanded Endpoint).

Source: Figures 14.2.1.1.1, 14.2.2.2.1

The MAH argues that several factors impacted the assessment of treatment effect including:

- In alignment with the FDA and EMA and upon recommendation from the DMC, the Sponsor terminated Study 747-302 early due to feasibility challenges in the setting of commercially available Ocaliva.
- In 2021, the EU SmPC was revised to contraindicated use of OCA in patients with decompensated cirrhosis (e.g., CP Class B or C) or a prior decompensation event. A total of 21% of patients enrolled in Study 747-302 prior to this revision met the contraindication criteria at screening and thus, would have not been eligible to receive commercial Ocaliva per the updated SmPC.
- At the time of study termination by the Sponsor, the study had randomized less than 80% of planned enrolment (i.e., 334 of the targeted 428 patients) and approximately 67% of the protocol-specified number of clinical events had been observed.

Sensitivity analyses and subgroup analyses for the primary, expanded primary, and key secondary endpoints, and baseline and demographic subgroup analyses were consistent with the results observed in the Overall Population based on ITT analyses.

The table below include the results of some of the conducted sensitivity analyses of Time to First Occurrence of Primary Clinical Outcome Event (in the ITT population).

Statistics	Primary Composite Endpoint			
	Protocol Version 6 Endpoint (EMA Primary)		Expanded Endpoint (FDA Primary)	
	Placebo (N=166)	OCA (N=168)	Placebo (N=166)	OCA (N=168)
Data Excluded After 90 Days of Investigational Product Discontinuation				
Number of Subjects with Clinical Event, n (%)	30 (18.1)	27 (16.1)	66 (39.8)	60 (35.7)
Log Rank p-value ^a	0.481		0.200	
Hazard Ratio (95% CI) ^b	0.83 (0.49, 1.40)		0.79 (0.56, 1.13)	
Data Excluded After Subject Initiated Commercial Ocaliva				
Number of Subjects with Clinical Event, n (%)	42 (25.3)	47 (28.0)	71 (42.8)	70 (41.7)
Log Rank p-value ^a	0.796		0.407	
Hazard Ratio (95% CI) ^b	1.06 (0.70, 1.60)		0.87 (0.62, 1.21)	
Data Excluded Based on Commercially Available Ocaliva per Subject's Country				
Number of Subjects with Clinical Event, n (%)	25 (15.1)	29 (17.3)	48 (28.9)	45 (26.8)
Log Rank p-value ^a	0.463		0.746	
Hazard Ratio (95% CI) ^b	1.22 (0.71, 2.09)		0.93 (0.62, 1.40)	
Data Excluded After Intercurrent Events				
Number of Subjects with Clinical Event, n (%)	143 (86.1)	156 (92.9)	148 (89.2)	158 (94.0)
Log Rank p-value ^a	0.294		0.778	
Hazard Ratio (95% CI) ^b	1.13 (0.90, 1.43)		1.03 (0.82, 1.30)	

In addition, a sensitivity analysis of the Time to First Occurrence of Primary Clinical Outcome Event in the per protocol (PP) population was also provided. See table below.

Statistics	Primary Composite Endpoint			
	Protocol Version 6 Endpoint (EMA Primary)		Expanded Endpoint (FDA Primary)	
	Placebo (N=138)	OCA (N=144)	Placebo (N=138)	OCA (N=144)
Number of Subjects with Clinical Event, n (%)	35 (25.4)	37 (25.7)	62 (44.9)	57 (39.6)
Log Rank p-value ^a	0.986		0.270	
Hazard Ratio (95% CI) ^b	1.00 (0.63, 1.58)		0.82 (0.57, 1.17)	

Patients with earlier stage PBC (i.e., compensated) were less likely to experience an endpoint than advanced stage PBC at baseline (i.e., decompensated).

747-302: Time to First Occurrence of Primary Clinical Outcome Event by Baseline Disease Severity: Compensated vs Decompensated Subpopulations (ITT Analyses)

	Primary Endpoint			Expanded Primary Endpoint		
	Number of Patients with Event, n (%)	Log-Rank p-value	HR (95% CI)	Number of Patients with Event, n (%)	Log-Rank p-value	HR (95% CI)
Compensated						
Placebo (N=129)	28 (21.7)	0.932	0.98 (0.58, 1.64)	58 (45.0)	0.114	0.74 (0.50, 1.08)
OCA (N=136)	29 (21.3)			50 (36.8)		
Decompensated						
Placebo (N=37)	20 (54.1)	0.544	1.22 (0.65, 2.28)	22 (59.5)	0.521	1.22 (0.67, 2.24)
OCA (N=32)	19 (59.4)			21 (65.6)		

CI = confidence interval; HR = hazard ratio; ITT = Intent-to-Treat; OCA = obeticholic acid

Analyses for the key secondary endpoints, including time to the first occurrence of: 1) the primary endpoint; 2) severe decompensating events of the expanded primary endpoint; or 3) liver transplant or death (all-cause) were consistent with the results observed in the ITT analyses.

Analyses for death or other individual event outcomes (liver transplant, first occurrence of hospitalization event, uncontrolled or refractory ascites, MELD score ≥ 15 , development of varix/varices, or liver related death) were summarized and consistent with the results observed in the ITT primary analyses.

As prespecified in the SAP, analyses of changes in liver biochemistry at each visit through Month 24 were compared between treatment groups using a restricted MMRM. Consistent with previous PBC studies, OCA treatment was associated with greater mean (SE) reductions in total bilirubin, direct bilirubin, ALP, GGT, ALT, and AST over time, compared to placebo up to Month 24. Statistically significant least square (LS) mean (SE) differences (OCA – placebo) in change from baseline were at Month 24 based on nominal p-values for ALP (p=0.039), ALT (p=0.028), AST (p=0.026), and albumin (p=0.010).

Patients in the OCA group showed improvements in several prognostic endpoints (MELD score, MELD-Na score, CP score, and Mayo Risk Score) that are predictive of clinical outcomes for chronic liver disease. The median difference (OCA-placebo) (SE, p-value) at Month 24 and Month 36 for MELD were -0.40 (0.230, p=0.037) and -0.70 (0.357, p=0.026), respectively. The median difference (OCA-placebo) (SE) at Month 24 and Month 36 for MELD-Na were -1.0 (0.26, p=0.051) and -1.0 (0.51, p=0.028), respectively. Mean (SE) CP-score remained generally stable through Month 60. The median difference (OCA-placebo) (SE) at Month 12, Month 24, and Month 36 was 0. Mean (SE) MRS remained generally stable over time. The median difference (OCA – placebo) (SE, p-value) at Month 24 was -0.190 (0.099, p=0.032).

The median difference (OCA – placebo) (SE, p-value) for liver stiffness change from baseline was -0.80 (0.867, p=0.341), -2.00 (1.199, p=0.073), and -2.30 (1.531, p=0.153) at Month 12, Month 24, and Month 36, respectively.

The median difference (OCA – placebo) (SE, p-value) for ELF change from baseline was -0.10 (0.102, p=0.218), -0.30 (0.153, p=0.034), and -0.20 (0.179, p=0.373) at Month 12, Month 24, and Month 36, respectively.

Various responder analyses were performed to assess improvement in ALP over time (e.g., reductions of $\geq 15\%$, $\geq 40\%$, or $\leq \text{ULN}$). A higher percentage of OCA-treated patients responded to each respective endpoint at each timepoint, compared with placebo-treated patients.

A total of 21 (6.3%) of patients enrolled in Study 747-302 met the primary endpoint in the pivotal Phase 3 Study 747-301 of an ALP $< 1.67 \times \text{ULN}$ and total bilirubin $\leq \text{ULN}$ and ALP decrease from baseline of $\geq 15\%$. A numerically greater percentage of patients in the OCA group (17/168 [10.1%]) achieved this endpoint compared to placebo (4/166 [2.4%]). The observed HR (95% CI) of responders to non-

responders was 0.23 (0.07, 0.72), with a nominal p-value=0.006, indicating responders were less likely to experience a negative outcome based on the expanded primary endpoint. Further, the association between responder/non-responder status and outcomes was stronger in OCA-treated patients (observed HR [95% CI] of 0.19 [0.05, 0.78], with a nominal p-value=0.010) compared to placebo-treated patients (observed HR [95% CI] of 0.37 [0.05, 2.63], with a nominal p-value=0.297).

Similar patterns were observed with other ALP-based definitions of biochemical responder/non-responders (Table 9), with OCA-treated patients seeing a stronger association between biochemical response and outcomes compared to placebo-treated patients. A strong association between normalization of bilirubin at Month 12 and outcomes was observed in both treatment arms.

747-302: Time to Event by Biochemical Response Criteria at Month 12

Time to Event by Biochemical Response at Month 12				
Responder Definition	Placebo		OCA	
	HR (95% CI)	Nominal p-value	HR (95% CI)	Nominal p-value
ALP $\leq 2 \times$ ULN	1.39 (0.85, 2.29)	0.190	0.48 (0.28, 0.84)	0.009
ALP decrease $\geq 40\%$	0.44 (0.16, 1.19)	0.095	0.14 (0.05, 0.39)	<0.001
Bilirubin $< 1 \times$ ULN	0.17 (0.08, 0.36)	<0.001	0.17 (0.08, 0.35)	<0.001

ALP = alkaline phosphatase, HR = hazard ratio, OCA = obeticholic acid

Source: 747-302, TS15.1.2, S15.1.3, S15.2.1

Arguments provided by the MAH as to why drawing definitive efficacy conclusions from Study 747-302 in the ITT analyses was challenging include the early termination of study, randomization of less than 80% of planned enrolment, differential dropout between placebo and OCA groups, and OCA being commercially available to patients. The MAH argues that these challenges resulted in a failure to maintain equal distribution of background risk which may have influenced outcomes in a manner that favoured placebo and became more exaggerated as the study progressed.

747-302 - Overall Conclusions (as provided by the MAH)

- Despite extensive efforts and multiple interactions with regulatory authorities, the Sponsor encountered several enrolment and retention challenges. In alignment with EMA, FDA, and DMC recommendations, Study 747-302 was terminated early. The study randomized less than 80% of planned enrolment. Upon completion of adjudication, 96 adjudicated endpoints were observed resulting in 76% of the protocol-specified number of events necessary to provide 80% power to demonstrate a statistically significant difference between OCA and placebo.
- Patients in Study 747-302 reflected an advanced disease population. While baseline demographics including duration of PBC were similar to previous PBC studies, patients in Study 747-302 had higher baseline ALP, total bilirubin, MELD, and Rotterdam criteria. Of the 334 patients in Study 747-302, 21% were decompensated at enrolment.
- The estimated effect of treatment from the ITT analyses was under-powered and potentially biased resulting in difficulties in the interpretation of the tests of hypotheses for the primary and key secondary endpoints.
- No treatment difference was observed between OCA and placebo for either the primary endpoint or expanded primary endpoint, in the ITT analyses for the overall and compensated populations. Drawing definitive efficacy conclusions from Study 747-302 was challenging given the potential bias, particularly in the placebo arm.

Supportive evidence of efficacy: Real World Evidence Studies

The MAH acknowledges that the SOB studies as designed will be considered the primary evidence characterizing the safety and efficacy of OCA in patients with PBC but has provided data from RWE sources as supplementary evidence. In their view, similar to other rare diseases, real-world observational studies using claims and registry data have utility as external controls (ECs) for clinical trials (US FDA 2018, US FDA 2021c, ICMRA 2022).

A total of three RWE studies evaluating analyses of hepatic clinical outcomes (i.e., time to death, liver transplant and hepatic decompensation) were conducted to provide supplementary evidence. The MAH states that the eligibility criteria in these real-world studies reflect patients with compensated PBC with or without cirrhosis (hereafter referred to as the compensated population) indicated in the EU SmPC for Ocaliva.

747-301/301 LTSE EC

An EC analysis was conducted in patients on OCA in Study 747-301/301 LTSE compared to external-weighted controls (Global PBC and United Kingdom [UK] PBC Registries) consisting of PBC patients who had failed UDCA but had not been prescribed Ocaliva (Murillo Perez 2022). Controls included patients who met Study 747-301 inclusion/exclusion criteria who were then inverse probability of treatment weighted (IPTW) to the OCA-treated arm in Study 747-301/301 LTSE based on key demographic, clinical, and treatment variables. As UK-PBC only analyzed only death and liver transplant (and not hepatic decompensation), the efficacy results in Section 2.2.3.1 are based on Global PBC only, which evaluated the primary composite endpoint of time to death, liver transplant or hepatic decompensation.

Study 747-302 EC

An EC analysis was conducted in patients on OCA in Study 747-302 compared to external-weighted controls (Komodo Health US Claims database) consisting of PBC patients who had failed UDCA or discontinued UDCA for 3 or more months but had not been prescribed Ocaliva. While this database is exclusively from US claims, the association between OCA treatment and outcomes is expected to be replicable despite differences in care patterns with the EU.

Study 747-405

This fully RWE study compares the incidence of hepatic clinical outcomes in patients with PBC initiating Ocaliva to a standardized mortality/morbidity ratio (SMR)-weighted control group of patients with PBC who would otherwise be eligible for, but who are not prescribed, Ocaliva. Administrative US claims data linked (Komodo Health US Claims database) to additional data sources were used. The study was designed to conform with the draft guidance "Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision Making for drug and Biological Products" (US FDA 2021a).

Recognizing there are limited guidelines on conduct of RWE studies to support regulatory decision making, the Sponsor has extensive documentation regarding data sources, data storage and management, and SOPs governing data analyses. These have been submitted to FDA per draft guidance (US FDA 2021b, US FDA 2021d) and can be provided to EMA upon request.

Methods

This summary of efficacy includes supplemental evidence sources for OCA-treated groups and non-OCA-treated, but treatment eligible, comparator groups to provide a comprehensive evidence package characterizing the efficacy and safety of OCA in patients with PBC.

Two studies provide supportive efficacy analyses from Study 747-301 and 747-302 using EC comparator arms. In addition, efficacy is supported by RWE Study 747-405, which compares the incidence of hepatic clinical outcomes in patients with PBC initiating Ocaliva to a standardized morbidity weighted control group of patients with PBC who would otherwise be eligible for, but who are not prescribed, Ocaliva. Importantly, the eligibility criteria in these studies are reflective of a compensated population in alignment with the SmPC for Ocaliva.

A summary of key elements and schematics of study designs from the RWE studies are summarized in the table and figures included below, respectively.

Key Elements of Observational Data from External Databases

	747-301 EC Analyses (Murillo Perez 2022)	747-302 EC Analyses (Komodo)	747-405 RWE
Population			
Primary	Compensated (with or without cirrhosis) ^a	Compensated (with or without cirrhosis) and decompensated	Compensated (with or without cirrhosis)
Secondary	NA	Compensated	NA
Data Sources			
OCA-treated	747-301/Long-term Safety Extension (OCA arm)	747-302 (OCA arm)	Komodo Health US claims database ^c
Non-OCA-Treated	Global PBC registry ^b (EC)	Komodo Health US Claims Database ^c (EC)	
Endpoints			
Primary	Time to all cause death or liver transplant	Time to all cause death, liver transplant, uncontrolled ascites ^d or hospitalization for new onset or recurrent decompensating event ^d	Time to all cause death, liver transplant, or hospitalization for hepatic decompensation
Secondary	Time to all cause death, liver transplant or hepatic decompensation ^e	Time to expanded endpoint ^{f,g}	NA
Index Date(s)			
OCA-treated	Date of randomization	Date of randomization	Date of OCA prescription fulfillment
Non-OCA-Treated	One randomly selected from all eligible index dates	One randomly selected from all eligible index dates	All eligible index dates
Comparability of Treated and Untreated			
Step 1	Meet 747-301 eligibility criteria	Meet 747-302 eligibility criteria	Inclusion / exclusion criteria were designed to meet requirements for a clinically compensated population ^h
Step 2	Propensity score generated IPT weights (both treated and controls weighted)	Propensity scores generated SMR weights (controls are weighted)	Propensity scores generated SMR weights (controls are weighted)
Primary Analysis	Cox proportional hazards model	Cox proportional hazards model	Cox proportional hazards model

EC = external control; NA = not applicable; PBC = primary biliary cholangitis; IPT = inverse probability treatment; MELD = Model for End Stage Liver Disease; TIPS = transvenous intrahepatic portosystemic shunt(s); RWE = real world evidence; SMR = standardized morbidity/mortality ratios

^a Though the exclusion criteria included diuretic resistant and poorly controlled ascites, it did not exclude the presence of any ascites.

^b The Global PBC registry includes >5,000 patients with PBC recruited from 31 liver centers across 14 countries in Europe and North America. It utilizes the CASTOR trial platform for electronic case report form collection of medical history, clinical events, and laboratory and treatment data.

^c The Komodo Health claims database contains administrative claims from >350 US payers covering more than 325 million patient lives, including commercial (63%), Medicaid (23%), Medicare (10%), dual eligible (<1%), and other (2%). Data were de-identified and merged via Datavant tokenization to allow for patient tracking across payers.

^d Uncontrolled ascites includes SBP, transvenous intrahepatic portosystemic shunt [TIPS] procedure or paracentesis ≥ 2 x per month for ≥ 2 months; Decompensated events include gastroesophageal bleed or hepatic encephalopathy

^e The Global PBC defined ascites as the presence of ascitic fluid confirmed by abdominal imaging or in the event of prescribed diuretic treatment for clinically obvious ascites. Hepatic encephalopathy was defined as expert (physician) opinion. Variceal bleeding was defined as hematemesis or melena due to endoscopically documented haemorrhage originating from gastro-oesophageal varices. Spontaneous bacterial peritonitis was reported if confirmed by diagnostic paracentesis.

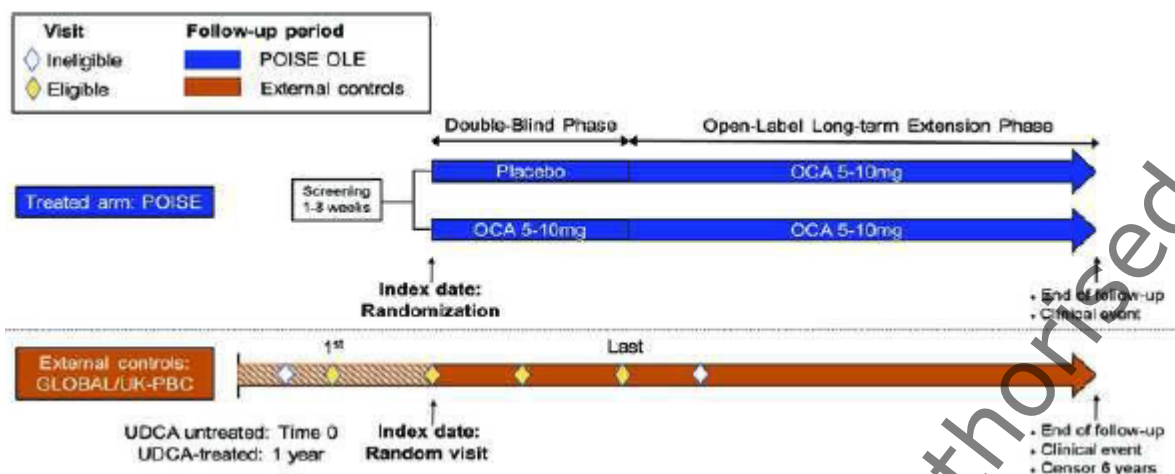
^f The second endpoint for 747-302 EC is considered an expanded endpoint which consists of the following: Death (all-cause); Liver transplant; For patients with decompensation prior to index: 1) Hospitalization for new onset or recurrence of variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis; 2) Uncontrolled or refractory ascites requiring hospitalization and/or ≥ 2 paracentesis per month for ≥ 2 months or TIPS procedure; 3) Portal hypertension syndromes (hepatorenal or hepatopulmonary syndrome); For patients without decompensation at index, progression to decompensated liver disease defined as all of the above plus: ascites requiring treatment with diuretics, hepatic encephalopathy requiring lactulose and/or rifaximin treatment, or new onset of total bilirubin >3 mg/dL; For patients without decompensation or portal hypertension at index, progression to decompensation or portal hypertension, defined as all of the above plus: new gastroesophageal varices, or requiring a banding procedure or platelets $<150 \times 10^9/L$ with a diagnosis of splenomegaly.

^g Given the nature of the Komodo claims database, not all of the endpoints in Study 747 302 could have been reasonably and reliably assessed. For example, MELD scores and TE values (used to assess for portal hypertension without decompensation) were not available in Komodo.

^h See 747-405 CSR

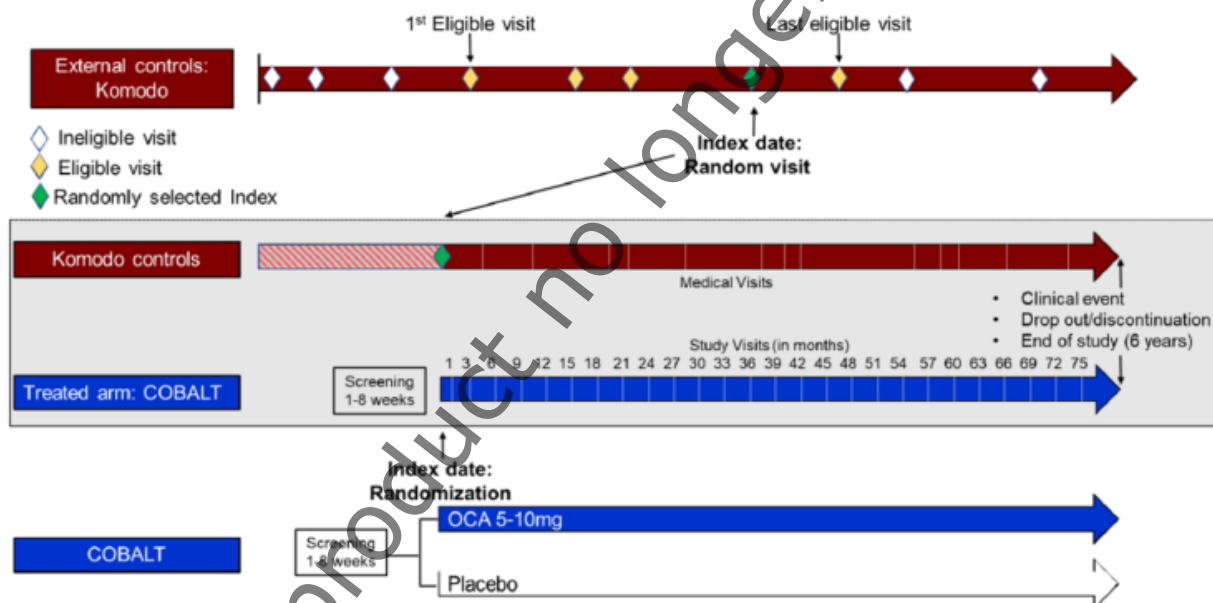
Study schematics

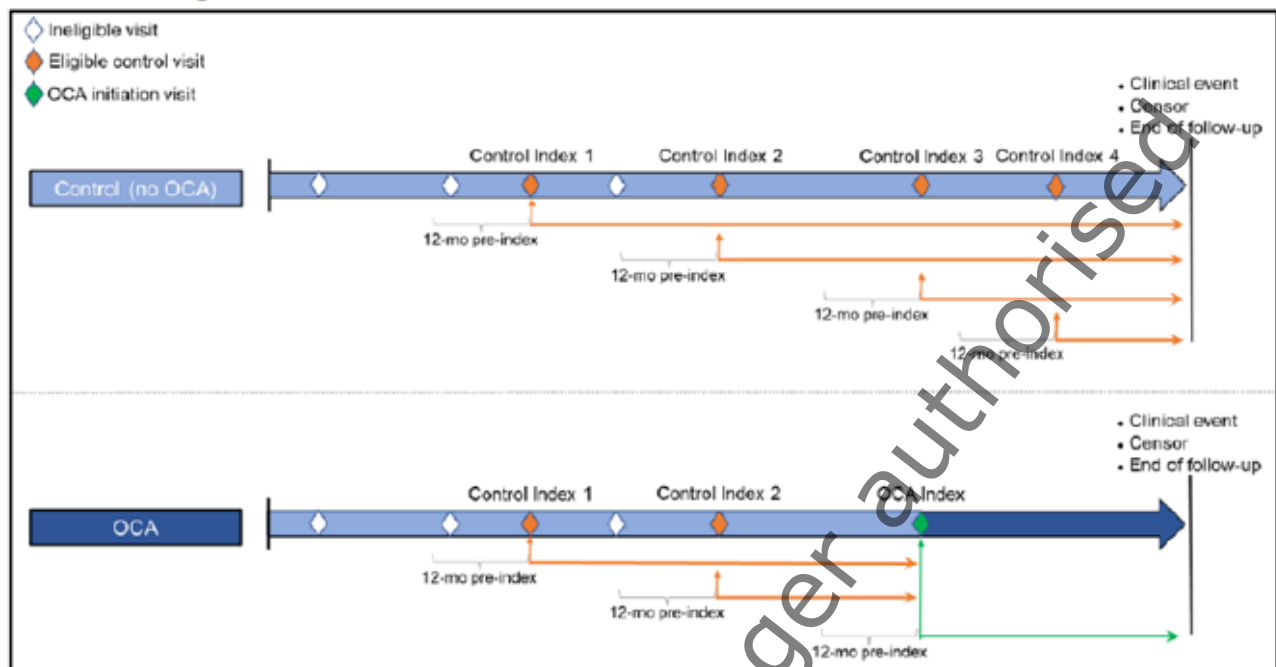
747-301/301 LTSE External Control (Global PBC and UK-PBC Registries)



UK-PBC included death and liver transplant but not hepatic decompensation. Global PBC Registry included death, liver transplant and hepatic decompensation.

747-302 External Control (Komodo Health US Claims Database)





Results

747-301/301 LTSE - External Control Study

Study 747-301/301 LTSE EC (Murillo Perez 2022): External Control Analysis of a Phase 3, Double-Blind, Placebo-Controlled Trial and Long-Term Safety Extension of Obeticholic Acid in Patients with Primary Biliary Cirrhosis POISE: Primary Biliary Cirrhosis Obeticholic Acid International Study of Efficacy

747-301/301 LTSE EC - Study Population

747-301/301 LTSE inclusion criteria were met by 1381 patients in the Global PBC registry, with 6702 qualifying visits from which 1 index was randomly selected. Of the 6543 patients in the UK PBC registry, 2135 patients met 747-301/301 LTSE inclusion criteria, with 8331 qualifying visits. The final sample for the 747-301/301 LTSE arm was 209 patients. No patients in Global PBC were treated with OCA or fibrates. In the UK PBC, 32 patients were treated with fibrates and 54 with OCA during follow up, <4% of the sample. As this was an ITT analysis, these patients were not censored. Standardized variable differences before and after weighting show that all variables were within the pre-specified ± 0.25 standardized mean difference (SMD) and the samples were comparable after weighting.

Table 10: Baseline (Unweighted) Characteristics of the 747-301/301 LTSE and Global PBC and UK-PBC Cohorts

	747-301/301 LTSE (n=209)	Global PBC (n=1381)	UK-PBC (n=2135)
Female, (%)	190 (90.9)	1253 (90.7)	1907 (89.3)
UDCA, n (%)	197 (94.3)	1265 (91.6)	1849 (86.6)
Year of diagnosis, median (IQR)	2005 (2000-2009)	1999 (1994-2003)	2004 (2000-2009)
Year of visit median (IQR)	2012 (2012-2012)	2005 (2000-2009)	2011 (2006-2015)
Age, years, mean (SD)	55.7 (10.6)	56.9 (12.3)	60.55 (11.6)
Duration of disease, years, median	7.8 (3.6-12.6)	4.5 (2.1-7.9)	4.5 (1.7-9.1)
ALP, ×ULN, median (IQR)	2.41 (2.00-3.15)	2.08 (1.75-2.81)	2.16 (1.78-3.03)
Bilirubin, ×ULN, median (IQR)	0.47 (0.34-0.67)	0.67 (0.45-1.09)	0.57 (0.40-1.00)
AST, ×ULN, median (IQR)	1.68 (1.20-2.36)	1.20 (0.88-1.78)	Not Available
ALT, ×ULN, median (IQR)	2.09 (1.44, 3.02)	Not Available	1.16 (0.74-1.84)
Cirrhosis at inclusion, n (%)	36 (17.2)	197 (14.3)	Not Available

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate aminotransferase; IQR = interquartile range; LTSE = long-term safety extension; Not Available; PBC = primary biliary cholangitis; UDCA = ursodeoxycholic acid; ULN = upper limit of normal

747-301/301 LTSE EC - Efficacy Summary

Primary Analysis

The primary outcome was time to first occurrence of liver transplant or death, also referred to as transplant-free survival. Over the 6-year follow-up period, there were 5 (2.4%) of 209 patients with composite events (2 liver transplants and 3 deaths) in Study 747-301/301 LTSE (2.4%), 135 (10.0%) of 1381 patients with events (51 liver transplants and 84 deaths) in the Global PBC EC group, and 281 events (119 liver transplants and 162 deaths) in 2135 patients in the UK PBC control group (13.2%). The pre-specified primary analysis using IPTW for the random index date yielded a HR of 0.29 (95% CI: 0.10 to 0.83, $p=0.02$) for Study 747-301/301 LTSE vs Global PBC and 0.30 (95% CI: 0.12 to 0.75, $p<0.01$) for Study 747-301/301 LTSE vs UK PBC.

Table 11: 747-301/301 LTSE Results of Cox Regression on Time to Composite Event (ITT Analysis)

Transplant Free Survival					
Parameter	N		HR	HR 95% CI ^a	p-value
	OCA	Control			
Global PBC Registry	209	1381	0.29	0.10, 0.83	<0.02
UK-PBC Registry	209	2135	0.30	0.12, 0.75	0.02

Secondary Analysis

The secondary outcome, time to first occurrence of liver transplant, death, or hepatic decompensation, was conducted only using the Global PBC EC, as hepatic decompensation was not systematically collected in the UK PBC registry.

Over the 6-year follow-up period, there were 16 (7.7%) of 209 patients with composite events of death, liver transplant, or hepatic decompensation in the Study 747-301/301 LTSE and 212 (15.4%) of 1381 patients with composite events patients in the Global PBC EC group. The IPTW HR was 0.42 (95% CI 0.21, 0.85; $p=0.02$), indicating that patients treated with OCA in a trial setting had significantly greater event-free survival than patients in the Global PBC control group.

Exploratory Analysis

As sensitivity analyses were conducted to explore potential bias, point and variance estimates were calculated but formal statistical testing with p-values was not performed. The sensitivity analyses assessed the effect of varying the index date for the control group (random index date [primary analysis], first qualifying visit date, and last qualifying visit date) on the HR estimates in the Global PBC database. The HRs were all ≤ 0.52 , and overall, slightly higher for first qualifying visit and slightly lower for last qualifying visit. The 95% CIs all overlapped.

Subgroup Analyses

The Cox regression was run separately for patients with and without cirrhosis. Using the random index date, the HR for death or liver transplant among patients with evidence of cirrhosis for OCA-treated patients in 747-301/301 LTSE versus Global PBC controls was HR=0.20 (95% CI 0.03, 1.22). For patients without cirrhosis, the HR=0.31 (95% CI 0.09, 1.04). Thus, while the effect size was somewhat larger in the patients with evidence of cirrhosis, the CIs were widely overlapping, indicating no significant difference between patients with or without cirrhosis.

747-301/301 LTSE EC - Safety Summary

This study was not designed to assess safety, and there were no pre-specified safety analyses.

747-301/301 LTSE EC - Overall Conclusions (as provided by the MAH)

- Patients treated with OCA in the trial setting demonstrated a statistically significant and clinically meaningful greater event (liver transplant or death)-free survival than comparable ECs with a relative risk reduction over a 6-year period of 70% for Global PBC and 71% for UK-PBC, respectively.
- Patients treated with OCA demonstrated a 58% relative risk reduction over a 6-year period for the composite endpoint of hepatic decompensation, liver transplant, or death compared to non-OCA treated patients in the Global PBC registry.
- Reduction in risk was independent of presence or absence of cirrhosis.
- These results support the use of long-term OCA therapy to optimize prognosis of patients with PBC inadequately responding or intolerant to UDCA.

747-302 - External Control Analysis (Komodo)

Study 747-302 EC: A Phase 4, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study Evaluating the Effect of Obeticholic Acid on Clinical Outcomes in Patients with Primary Biliary Cholangitis Compared to External Control from the Komodo Health Claims Database

747-302 EC (Komodo) – Study Population

A total of 334 patients were randomized into Study 747-302 of whom 168 patients were in the OCA group. At the time of study termination, the study randomized less than 80% of planned enrollment.

Overall, 162,587 patients in the Komodo Health claims database had at least 1 PBC claim between 01 Jan 2014 and 31 Dec 2021, of whom 109,970 patients had 1 inpatient PBC claim and/or 2 outpatient PBC claims on different days. Of the 109,970 patients with 1 inpatient PBC claim and/or 2 outpatient PBC claims on different days, laboratory values of total bilirubin, ALP, ALT, AST, and platelets were available for 58,615 patients, of whom 19,944 had evidence of at least 1 total bilirubin and/or ALP elevation ≤ 12 months before index or at the index. Of the 19,944 patients, 7693 patients had closed claims data available for at least 12 months before any total bilirubin or ALP elevation. In total, 5332 of the 7693 patients used UDCA any time before the index, of whom 2325 met the definition of UDCA failure (1021 patients with an inadequate UDCA response, 1475 patients discontinued UDCA, [171 patients had both inadequate UDCA response and UDCA discontinuation indexes]). Of the 2325 patients with UDCA failure, 2307 were at least 18 years old at index.

A total of 1233 patients met Study 747-302 eligibility criteria, of whom 944 had compensated disease at index.

During propensity score analyses, 182 of 1233 control patients were removed listwise in the logistic regression if they were missing a predictor variable, e.g., if there was not a lab value proximal to the index leaving 1051 eligible control patients. Of the 1051 eligible EC group patients, 88.3% were female compared to 89.8% of the 168 eligible OCA-treated patients from Study 747-302. The mean age of the 1051 eligible EC group patients from birth until index was 53.8 years (median 55; interquartile range [IQR] 46-63; range 18-87 years), versus 53.4 years for the eligible OCA-treated patients (median 53.5; IQR 46-60; range 29-75 years).

The mean baseline total bilirubin and albumin levels for the EC group patients was similar to that of 747-302 OCA-treated patients, and ALP, ALT, and AST levels were slightly lower for EC patients. Of the 1051 eligible EC patients, 86.8% were taking UDCA at index, versus 87.5% of the OCA-treated subjects in 747-302. Note that one non-OCA-treated patient was removed from the outcome analyses as the death date (set to the 1st of the month to maintain deidentification) occurred before the index date, leaving a total of 1232 non-OCA-treated patients.

747-302 EC (Komodo) – Efficacy Summary

The first endpoint (302 EC composite) in the 302 EC analysis excluded MELD score, as data were not available in Komodo for some of the individual biomarker components of the MELD score. The 302 EC expanded composite endpoint excluded MELD, CP-score, and bacterial empyema, as individual biomarker components of MELD and CP were not available in the Komodo database, and there is not an International Classification of Diseases (ICD)-10 code for bacterial empyema. There was not additional confirmation of hepatic encephalopathy with West Haven scores; ascites with diagnostic paracentesis; or portal hypertension with transient elastography.

The 302 EC SAP addendum specified: "Once data are unblinded and the event rate in the OCA-treated group of 747-302 is known, formal power analyses will be undertaken for each individual endpoint in each cohort, based upon an effect size of $HR=0.60$, $\alpha=0.05$, and with known numbers of OCA-treated and control patients. Any endpoint analysis with either cohort that lacks sufficient power (less than 70%) will not be undertaken."

The power analyses showed that the only analysis that met pre-specified power requirements was the 302 EC expanded composite endpoint for the overall population ($1-\beta$: 0.76). Because the power was

close to the pre-specified threshold for the 302 EC composite endpoint, this analysis was undertaken as ad-hoc despite an understanding that it was under-powered ($1-\beta$: 0.65).

302 EC Composite Endpoint

The first endpoint was a composite event of the time to all cause death, liver transplant, uncontrolled ascites, or hospitalization for hepatic decompensation.

OCA treatment was associated with a clinically meaningful 61% reduction in the relative risk (HR = 0.39: 95% CI: 0.22-0.69; $p=0.001$) for death, liver transplant, uncontrolled ascites, or hospitalization for hepatic decompensation among 747-302 OCA-treated patients (event rate = 17/168) compared to weighted non-OCA-treated patients in the EC group (event rate = 35.44/164.9).

Table 12: 747-302 EC Composite Endpoint: Cox Regression on Time to Composite Event (Death, Liver Transplant, Uncontrolled Ascites, or Hospitalization for Hepatic Decompensation) (Unweighted and Weighted)

Parameter	N		HR	HR 95% CI ^a	p-value
	OCA-treated	Non-OCA-treated			
Unweighted	168	1232	0.326	0.199, 0.534	<0.001
Weighted	168	164.9	0.387	0.216, 0.693	0.001

CI=confidence interval; HR=hazard ratio; OCA=obeticholic acid

^a The HR and 95% CI were estimated based on a weighted (using SMR weights) Cox regression model to estimate the magnitude of the effect.

^b Because the primary endpoint was the same primary endpoint for Study 747-302, and because the power was close to the pre-specified threshold, this analysis was undertaken as an ad-hoc despite an understanding that it was under-powered ($1-\beta$: 0.65).

Source: 747-302 EC CSR, Table 14.2.1.1 and Table 14.2.1.2.

Among the weighted OCA-treated patient indexes, 10.1% had an event, 38.7% discontinued OCA-treatment during the study period, 4.8% were censored for initiating commercial OCA, and 45.2% were censored at last contact. Among the weighted non-OCA-treated EC group patient indexes, 21.5% had an event, 14.8% were censored for initiating commercial OCA, 37.7% were censored for disenrollment, and 25.9% were censored for disenrollment/study end. Note that, unlike a clinical trial, the non-OCA-treated EC group patients are not enrolled and then followed for a fixed period, thus only indexes in the first month could remain uncensored for the entire follow-up period.

Similar results based on an ad hoc analysis were observed in the compensated subpopulation for the 302 EC composite endpoint (see Section 3.3).

302 EC Expanded Composite Endpoint

The second endpoint was time to an expanded composite endpoint (see Table 4), footnote f for a detailed definition).

OCA treatment was associated with a statistically significant and clinically meaningful 52% reduction in the relative risk for the expanded composite endpoint among 747-302 OCA-treated patients (event rate = 28/168) compared to weighted non-OCA-treated patients in the EC group (event rate = 45.52/164.9). For the pre-specified primary analysis in the SMR-weighted groups, the HR was 0.48 (95% CI: 0.30-0.77; $p=0.002$).

Table 13: 747-302 EC Expanded Composite Endpoint: Cox Regression on Time to Expanded Composite Event (Unweighted and Weighted)

Parameter	N		HR	HR 95% CI ^a	p-value
	OCA-treated	Non-OCA-treated			
Unweighted	168	1232	0.427	0.290, 0.630	<0.001
Weighted	168	164.9	0.479	0.298, 0.770	0.002

CI=confidence interval; HR=hazard ratio; OCA=obeticholic acid

^a The HR and 95% CI were estimated based on a weighted (using SMR weights) Cox regression model to estimate the magnitude of the effect.

Source: 747-302 EC CSR, Table 14.2.1.5 and Table 14.2.1.6

OCA-treated Patients in the Komodo Health Database

Based on descriptive analysis, the event rates for the following groups using same censoring rules and as-treated approach for the primary EC analysis were assessed:

- 747-302 OCA-treated group
- 747-302 placebo group
- Komodo OCA-treated group
- Komodo non-OCA-treated EC

For both 747-302 OCA-treated and Komodo OCA-treated patients, the event rates were similar for both OCA-treated groups for the 302 EC composite endpoint analyses (9.3% for the Komodo OCA-treated and 10.1% for the 747-302 OCA-treated), and for the 302 EC expanded composite endpoint analyses (16.7% for both OCA-treated groups). The concordance between event rates between the study and real-world data increases confidence in the reliability of these event rates. The event rates and survival curves for the 747-302 placebo group and Komodo non-OCA-treated EC differed significantly. The steady accumulation of events in the Komodo EC group is more consistent with the natural history of a population with advanced PBC disease failing first line therapy without second line treatment.

747-302 EC (Komodo) – Safety Summary

This study was not designed to assess safety, and there were no pre-specified safety analyses.

747-302 EC (Komodo) – Overall Conclusions (as provided by the MAH)

- The only analysis that met the pre-specified power requirements was the 302 EC expanded composite endpoint for the overall population ($1-\beta$: 0.76). OCA treatment was associated with a statistically significant and clinically meaningful 52% reduction in the relative risk (HR = 0.48: 95% CI: 0.30-0.77; $p=0.002$) for this endpoint among 747-302 OCA-treated patients compared to weighted non-OCA-treated patients in the EC group.
- Analyses for the 302 EC composite endpoint for the overall population, compensated, and USPI subgroups and the 302 EC expanded composite endpoint for the compensated subgroup were underpowered and were undertaken as ad-hoc analyses. – For the overall population (302 EC composite endpoint), OCA treatment was associated with a clinically meaningful 61% reduction in the relative risk (HR = 0.39: 95% CI: 0.22-0.69; $p=0.001$) for death, liver transplant, uncontrolled ascites, and hospitalization for hepatic decompensation among 747-302 OCA-treated patients compared to weighted non-OCA-treated patients in the EC group.

- In the subgroup of patients compensated at baseline, the reduction in relative risk for the 302 EC composite endpoint was 64% (HR=0.36; CI 0.17-0.76; p=0.008); and for the 302 EC expanded composite endpoint was 57% (HR=0.43; 95% CI 0.25-0.75; p=0.003).
- While event rates were not similar for the 747-302 placebo-treated patients compared to the non-OCA-treated patients in the Komodo database, the event rates in the 747-302 OCA-treated group were very similar to the events rates in the OCA-treated patients in the Komodo Health database.

747-405 - Fully Real-World Evidence Study

Study 747-405: A Study to Evaluate the Effectiveness of Obeticholic Acid on Hepatic Real-World Outcomes in Patients with Primary Biliary Cholangitis (HEROES PBC): US Komodo Health Claims Database

This observational, retrospective cohort study employed a nested trial emulation design using Komodo Health claims data linked to laboratory, death, and transplant registry data to evaluate the effect of OCA treatment on time to occurrence of all-cause death, liver transplant, or hospitalization for hepatic decompensation in PBC patients.

747-405 - Study Population

Patients were selected to represent a compensated population (with or without cirrhosis) in order to align with real-world practices. A total of 4,535 eligible patients contributed approximately 12,400 control indexes (mean 2.7; median 2; range 1 to 41) and 432 eligible patients contributed an OCA index (only one allowed; 218 patients also contributed at least 1 control index before initiating OCA). Note that 361 control and 29 OCA-treated patients were missing variables temporal to index and were excluded list-wise from the logistic regression, producing a final weighted sample of 403 OCA-treated and 4174 non-OCA-treated controls for outcomes analysis. Person-time of follow-up was 498 patient-years for the OCA-treated group and 17,167 patient-years for non-OCA-treated controls. After SMR weighting and the application of SMR weights, all SMRs for key demographic and baseline characteristics were below the pre-specified ± 0.1 SMD threshold, indicating the samples were balanced and comparable.

747-405 - Efficacy Summary

Primary Analysis

Before weighting, there were 8 composite events among the 432 OCA-treated patients (1.9%), and 260 composite events among the 4,535 non-OCA-treated control patients (5.7%). There were 741 events among the 12,399 control indexes (6.0%). After SMR weighting, there were 8 composite events among the 403 OCA-treated patients (2.0%), and 31.8 events among the 405.4 weighted control indexes (7.9%).

The unweighted HR for the composite outcome of death, liver transplant or hospitalization for hepatic decompensations for OCA-treated versus non-OCA-treated patients was 0.41 (95% CI: 0.15-0.74; p-value <0.001). The SMR-adjusted HR was 0.37 (95% CI: 0.14-0.75; p-value <0.001).

Table 14: 747-405: Results Unweighted and Weighted Cox Regression on Time to Composite Event (As-Treated Analysis)

Time to Death, Liver Transplant or Hospitalization for Hepatic Decompensation					
Parameter	N		HR	HR 95% CI ^a	p-value
	OCA	Control			
Unweighted	432	4535	0.407	0.148, 0.736	<0.001
Weighted	403	405.4	0.370	0.143, 0.752	<0.001

CI = confidence interval; HR = hazard ratio.

^a The CI is the 95% CI computed using 2.5th and 97.5th percentile from bootstrap samples.

OCA treatment was associated with a statistically significant and clinically meaningful 63% reduction in the relative risk for death, liver transplant, and hospitalization for hepatic decompensation compared to OCA-eligible but non-OCA-treated controls. These results closely mirror the previously reported HR of 0.42 (58% reduction observed) in the Study 747-301/301 LTSE study (Murillo Perez 2022) with ECs, which utilized similar eligibility criteria and endpoints, as well as similar to the 747-302 EC analyses despite 747-302 representing a more advanced population with PBC.

Exploratory Analyses

The exploratory analyses evaluated the effect of OCA on each of the components of the composite endpoints in the SMR-weighted cohorts: death, liver transplant, and hospitalization for hepatic decompensation using competing risk models. The results for death (HR=0.38; 95% CI: 0.00-1.26; p-value=0.118) and for hepatic decompensation (HR=0.37; 95% CI: 0.09-0.85; p-value=0.012) were similar in effect size to the composite endpoint. The HR for liver transplant could not be estimated as no liver transplants occurred in the OCA-treated group.

Table 15: 747-405: Individual Composite Endpoint Analyses Using Competing Risk Models

Individual Composite Endpoint Analyses Using Competing Risk Models	
Composite Endpoint Component (SMR-weighted)	HR; 95% CI
Death	0.375; 0.00-1.26; p-value = 0.118
Hepatic Decompensation	0.368; 0.09-0.85; p-value = 0.012
Liver Transplant	N/A (no liver transplants occurred for OCA-treated group)

CI = confidence interval; HR = hazard ratio; N/A = not applicable; SMR = standardized mortality/morbidity ratio.

Subgroup Analyses

Apart from male gender, all subgroup analyses results were directionally the same. The subgroup analyses showed a largely consistent benefit of OCA treatment on the risk of the composite endpoint.

Table 16: 747-405: Time to Death, Liver Transplant or Hospitalization for Hepatic Decompensation by Subgroup

Time to Death, Liver Transplant or Hospitalization for Hepatic Decompensation by Subgroup			
Subgroup	N		HR; 95% CI
	OCA	Controls	
Age <55 years	167	1200	0.44; 0.09-1.31
Age ≥55 years	236	3061	0.35; 0.07-0.81
No Cirrhosis	200	2597	0.26; 0.00-0.81
Cirrhosis	203	1756	0.41; 0.12-1.09
Before COVID	276	2616	0.37; 0.13-0.80
After COVID	127	2345	0.34; 0.00-1.33
South region	186	1870	0.12; 0.00-0.38
Northeast/West/Midwest regions	217	2309	0.55; 0.16-1.34
No portal hypertension	308	3252	0.17; 0.00-0.55
Portal hypertension	95	1034	0.72; 0.21-1.56
Female	369	3763	0.29; 0.08-0.66
Male	34	411	1.00; 0.00-4.28

CI = confidence interval; COVID = coronavirus disease; HR = hazard ratio. N: distinct patient count

The quantitative bias assessment demonstrated that the observed OCA treatment benefit would continue to be observed even in the presence of significant confounding, i.e., a confounder present in 50% of the population and highly associated with both probability of treatment and occurrence of outcomes. This was also true if the HR was at the upper end of the 95% CI (HR=0.752) and the confounder was prevalent in 5% of the population. Even when a hypothetical confounder is prevalent in 50% of the population with a HR=0.752, only when its association with the outcome is very strong (HR<0.50) does the HR stop reflecting treatment benefit. Thus, the observed benefit is highly robust in the face of unmeasured confounding.

747-405 - Safety Summary

This study was not designed to assess safety, and there were no pre-specified safety analyses.

747-405 - Overall Conclusions (as provided by the MAH)

- The results of this study demonstrate that OCA treatment is associated with a statistically significant and clinically meaningful benefit, a HR of 0.37 equivalent to a 63% reduction in relative risk for hospitalization for hepatic decompensation, liver transplant or death compared to OCA-eligible but non-OCA-treated controls.
- The exploratory efficacy endpoint analyses showed similar reductions separately for death (62%) and for hepatic decompensation (63%). As no liver transplants occurred in the OCA-treated group, a HR could not be calculated.
- The effect of OCA treatment on the risk of the composite endpoint was directionally consistent across subgroups, and largely consistent in terms of effect size, with the exception of male gender where HR=1.0 (limited by small sample size n=34).
- The quantitative bias assessment demonstrated that the observed OCA treatment benefit would continue to be observed even in the presence of significant confounding.

Discussion

OCA was granted CMA in the EU in December 2016, for its administration in combination with UDCA for

the treatment of adult patients with PBC who have an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. This initial approval was based on results from the phase 3, randomized, double blind, placebo-controlled Study 747-301, which demonstrated a clinically and statistically significant, sustained reduction in ALP.

At the time of the CMA granted for Ocaliva, benefit had only been shown in terms of ALP reductions, with rare cases of normalization. Thus, the main efficacy uncertainty was to what extent those changes in laboratory parameters correlate with a risk reduction in relevant clinical liver outcomes in PBC patients, and thus, on the actual clinical benefit of OCA treatment. Other important uncertainties were the lack of efficacy/safety data in patients with a more advanced stage of the disease, and concerns on long-term (liver and CV) safety data. Given the lack of treatment options in patients unresponsive or unable to tolerate UDCA and the debilitating nature of PBC, a CMA was granted based on incomplete data with the condition to address these limitations, and provide comprehensive data, within two PAES requested as specific obligations (SOBs). Full approval of OCA was contingent on a post-approval requirement to confirm benefit by assessing the effect of OCA on clinical outcomes such as hepatic decompensation, liver transplant, and death and across the spectrum of liver disease severity.

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the effect of obeticholic acid on clinical outcomes in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the lack of data in a population with more advanced liver disease	Final report: 2023

The MAH has now submitted results of these two SOBs, which are the primary evidence of efficacy and safety, aimed to confirm the benefits and risks of Ocaliva across the spectrum of PBC patients after failure or intolerance to UDCA. Unfortunately, none of these two studies have been completed given that both were prematurely terminated.

Study 747-401 was a double-blind, randomized, placebo-controlled study evaluating the PK and safety of OCA in patients with PBC and moderate to severe hepatic impairment followed for 48 weeks. The Sponsor terminated prematurely this study given that the whole study population (n=22, 10 in OCA and 12 in placebo) had decompensated liver disease, in whom a contraindication was included in the SmPC while the study was ongoing (variation submitted Jul 2021-EC decision June 2022). The majority of patients had CP Class B (100.0% [OCA] and 91.7% [placebo]) whereas 0.0% (OCA) and 8.3% (placebo) patients had CP Class C.

Study 747-302 was a double-blind, randomized, placebo-controlled, multicenter study designed to prospectively obtain evidence to confirm the clinical benefit in terms of liver clinical outcomes and to

further evaluate the benefit-risk profile of OCA treatment in patients with PBC. The primary analysis was a log rank test comparing the OCA-treated arm to the placebo arm on time to first occurrence of an adjudicated event in the composite endpoint (all cause death, liver transplant, MELD score ≥ 15 , hospitalization for new onset or recurrence of: variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥ 2 , confirmed spontaneous bacterial peritonitis, uncontrolled ascites requiring paracentesis at least twice in a month). The study was event driven and total duration was determined on the time required to accrue approximately 127 adjudicated primary endpoint events (based on the assumed HR of 0.6 and to provide 80% power), estimated to be approximately 10 years. Patients were expected to have a minimum follow-up time of approximately 6 years.

As supplementary information, the following data are provided:

- results of the long-term safety extension (LTSE) of Study 747-301, initially submitted as pivotal Phase 3 trial, plus
- results of 3 RWE studies (2 were indeed external controlled analyses of OCA-treated patients from Studies 747-301 and 747-302).

Based on this evidence, the MAH is seeking to revert the CMA to a regular MA for Ocaliva.

Results

- Study 747-401 (top line PK and safety data)

At the time of granting of the CMA for Ocaliva, the CHMP imposed the MAH (SOB) to submit the results of Study 747-401, aimed to assess the PK and safety profile of OCA in patients with more advanced liver disease. The study was prematurely terminated upon the EU SmPC update in 2021, following a contraindication for the use of OCA in patients with advanced liver disease.

PK data were only available for 6 patients with moderate hepatic impairment; according to the MAH 5 mg once weekly OCA achieved OCA exposure like the general PBC population without hepatic impairment. No clinically meaningful differences were noted between OCA and placebo for efficacy endpoints, though the number of patients was small, and the study was not designed to detect differences between treatment groups.

Of note, safety data of this study, not unexpectedly, are concerning. The study only included 22 out of the planned 50 subjects. Results of this study show a significant toxicity and the possible contribution of OCA treatment cannot be ruled out. Despite testing a reduced dose of OCA (5mg once a week, titrated to 5mg twice a week), treatment was poorly tolerated in both treatment arms. All 22 (100.0%) subjects reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were ascites, oesophageal varices haemorrhage, pneumonia, all of them reported most frequently in OCA treated arm. Treatment-related TEAEs occurred in 4 (40.0%) subjects in the OCA group and 6 (50.0%) subjects in the placebo group. Nine (90.0%) subjects in the OCA group and 9 (75.0%) subjects in the placebo group experienced TEAEs of special interest. Six (60.0%) subjects in the OCA group and 7 (58.3%) subjects in the placebo group experienced severe (Grade 3) TEAEs. Related Grade 3 TEAEs included upper gastrointestinal haemorrhage, hepatic failure, pyrexia, and hepatic function abnormal. Of the Grade 3 TEAEs, 4 subjects experienced a TEAE (multiple organ dysfunction syndrome, cardiac arrest, hepatic encephalopathy, and aortic aneurysm rupture, respectively) that resulted in a fatal outcome, which were all not related or unlikely related to the study treatment. Overall, study treatment discontinuations occurred in 5 (50.0%) subjects in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) subjects in the OCA and 4 (33.3%) subjects in the placebo groups. Four subjects (3 OCA-treated and 1 placebo-treated) experienced a TEAE of upper gastrointestinal haemorrhage, cardiac arrest secondary to bleeding from oesophageal varices, hepatobiliary disorder, and ascites, respectively) that led to both study drug interruption and study discontinuation. A total of

7 (70.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced serious adverse events (SAEs). Six out of the 7 subjects in OCA reported SAEs of bleeding of oesophageal varices/upper GI haemorrhage (4 cases) or cardiac arrest/MI (2) vs no subjects in placebo. Five subjects died during the study (3 in placebo-treated subjects: hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal cell carcinoma; and 2 in OCA-treated subjects: multiple organ dysfunction syndrome and cardiac arrest).

Overall, no relevant differences were observed between treatment arms in the incidences of TEAEs, G3 TEAEs, SAEs TEAEs, and those noted can be explained by the low number of subjects in each treatment arm. Indeed, the low number of subjects included and premature study interruption, do not allow reaching sound conclusions on the actual safety profile of OCA in PBC with an advanced liver disease. Nevertheless, a numerical difference between treatment arms, disavouring OCA treatment, is systematically observed for hepatic AESI (9 patients (14 events) OCA vs 8 patients (11 events) placebo), cardiac AESIs (3 patients 5 events in OCA vs 1 subject/event placebo), pruritus (3 OCA vs 1 placebo), and bleeding GI events (both G3 and SAEs were reported in OCA patients while no such cases were reported in placebo (4 in OCA: 3 events of bleeding of oesophageal varices +1 upper GI haemorrhage OCA treated groups), which should be noted and support the current contraindication in the SmPC.

Cumulative post-marketing evidence has led to contraindicate the use of OCA in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event due to increased reporting of hepatic failure events, sometimes fatal or resulting in liver transplant. Further, precautionary wording has been included in section 4.4 of the SmPC and section 4.8 ('Undesirable effects') was also updated to include hepatobiliary disorders in the tabulated list of adverse reactions. It is agreed with the MAH that the data from this study 401 are of limited value to prescribers for Ocaliva in PBC, the use of OCA is contraindicated in this subset of the PBC population. However, the increased incidence of liver events and AESI seen in patients with a more advanced liver disease treated with OCA raises important questions on whether the problem is truly restricted to this subset of patients, or by contrary, if similar findings can be expected in the general population with PBC. The results of the following study may add some clarity in this regard.

The above said, the SOB is considered fulfilled given that the main uncertainty driving the requirement, i.e. lack of evidence in patients with more advanced liver disease to establish B/R, is now adequately addressed.

Study 747-302

This SOB was imposed at the time of approval to confirm the clinical benefit, in clinical relevant outcomes/endpoints, associated with OCA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment.

A total of 334 patients were randomized in the study and were included in the ITT Population: 168 patients in the OCA and 166 patients in the placebo groups.

Although the protocol did originally plan for 2 interim analyses, one at ~50% (64 events) and the other at ~75% (96 events) information fraction, the first interim analysis was postponed to after regulatory authority review of the interim SAP. As a result, the first interim analysis occurred after the accrual of approximately 65% (83 events) of the required total clinical outcome events. It was agreed that the second interim analysis would be omitted. O'Brien-Fleming Boundaries were used for superiority in the interim analysis.

According to the MAH the study has faced enrolment and retention difficulties and a transition to an open label design versus historic control was proposed. This plan was discussed several times with the CHMP and deemed not acceptable. The MAH also proposed a revision of the composite primary endpoint, to

extend the list of components adding some less robust components to increase the power of the study, which was not agreed by the CHMP either. The study was prematurely terminated by the Sponsor, at the time when the study had randomized nearly 80% of planned enrolment (i.e., 334 of the targeted 428 patients) and approximately 67% of the protocol-specified number of clinical events had been observed (last patient last visit Dec 2021), based on the recommendations of the data monitoring committee due to "feasibility challenges". However, it is noted that with 67% of the planned events, which is not a negligible portion, the study failed to show any differences between treatments for the primary composite endpoint of death, liver transplant, or hepatic decompensation for the ITT population: HR 1.01 (95%CI 0.68, 1.51), p value 0.954.

Notably, the results for the primary endpoint according to the liver disease status compensated vs decompensated show a numerical increment in the risk of event outcomes in decompensated patients treated with OCA (59.4% OCA vs 54.1% in placebo, HR 1.22 (0.65, 2.28)), though not statistically significant. By contrary, results were nearly identical in both treatment arms in the subgroup of compensated PBC patients (21.3% vs 21.7% OCA and placebo, respectively, HR 0.98 (0.58, 1.64)). Thus, the study has failed to demonstrate any clinical benefit of OCA treatment in relevant clinical outcomes and across the spectrum of PBC patients.

Secondary endpoint analyses show that only a total of 21 (6.3%) patients enrolled in Study 747-302 met the primary endpoint as defined in the initial pivotal phase 3 Study 747-301 of an ALP $<1.67\times$ ULN and total bilirubin $\leq$ ULN and ALP decrease from baseline of $\geq 15\%$. Indeed, the rate of responders was substantially lower compared to that previously reported and this was the case in both treatment arms, but rather noticeable in the OCA treated group (OCA 10.1% vs 2.4% placebo in Study 747-302 vs OCA 34.0% vs 7% placebo in Study 747-301). No statistically significant differences were reported, adding even further uncertainties to the actual efficacy of OCA in the treatment of PBC. The MAH was requested to explain the observed differences, considering that Study 302 included a more advanced liver disease population likely representative of the actual target population in clinical practice. The MAH argues that the actual target population in clinical practice is more like that included in Study 747-301, based on comparison of baseline disease characteristics of European registries, and much less severe than that included in Study 747-302. It is also argued that subjects with higher values at baseline might unlikely reach normal (or near normal) biochemical ALP/BR values, and that similar absolute changes in ALP values are expected (and thus similar benefits from treatment). However, the actual meaning of the observed quantitative reductions of ALP/BR values, in the absence of concurrent changes in histological progression, is highly uncertain and of doubtful clinical relevance. Indeed, the predictive value of the changes in biochemical parameters with respect to relevant clinical outcomes in PBC has not been established yet. In fact, it is argued by the expert's community that isolated changes in ALP/BR, without changes in histological progression, are of doubtful relevance to patients.

In line with previous minor changes in relevant biochemical parameters, changes in prognostic endpoints (MELD score, MELD-Na score, CP score, and Mayo Risk Score) that are predictive of clinical outcomes for chronic liver disease did not show significant differences between groups in a consistent way. Indeed, isolated statistically significant differences at some time points and limited to MELD and MELD-Na scores, accounting mostly for biochemical changes and of doubtful clinical relevance, were noted. CP score and MRS remained stable over time.

In conclusion, the two PAES required as SOBs of the OCA CMA have been prematurely terminated one due to the negative safety profile of OCA in PBC patients with moderate to severe liver impairment or decompensation, that led to a treatment contraindication in this subset of patients, and the other due "recruitment challenges", but indeed showing treatment futility regardless of the severity of liver impairment. Thus, the confirmatory study 302 has failed to demonstrate the efficacy of OCA in reducing

the risk of relevant clinical outcomes in patients with PBC, regardless of the liver disease severity. Consequently, the benefit of OCA in the treatment of PBC is not demonstrated.

The MAH argues that results of the confirmatory Study 302 cannot be interpreted due to lack of power and to the risk of bias, and this justifies the need for “supportive” external controls. Surprisingly, the HR does not even show a trend for a favourable effect in the primary composite endpoint (despite the significant portion of events) or in any of the individual or composite event outcomes analysed as secondary endpoints. The plan to conduct a post-hoc external control analyses using RWE to overcome the “risk of bias” of a well-designed randomised, double-blind, placebo-controlled trial, even recognising challenges in the study conduct, does not seem a convincing approach bearing in mind the inherent bias of this type of comparisons and the huge difficulties to adequately control them. Several relevant problems are identified, which preclude relying on these analyses to reach any conclusions on the efficacy of OCA in preventing relevant liver outcomes and, definitively, to use these results to counterbalance or even overcome failed results of a RCT. Further discussion in this regard is included below.

The MAH justifies the need for the EC group by stating that the validity of ITT analyses depends on successfully balancing randomisation and maintaining treatment and placebo allocation throughout the trial. Additional arguments are based on the claim that the reported results in Study 747-302 were underpowered and potentially biased for a list of reasons discussed below.

Firstly, according to the MAH, an unblinded analysis, with a weighting procedure to balance the groups on the post-hoc observed between-group differences, would be better than a fully blinded randomisation procedure. Notably, this would guarantee asymptotically similarity only on the observed variables and, from a regulatory perspective a weighting (or even a matching) procedure will never be considered better or even equivalent to randomisation.

Secondly, while it is agreed that the availability of commercial OCA might be considered as an intercurrent event that might potentially interfere the results of the trial, the sensitivity analyses provided by the MAH on the trial results do not support their hypothesis. Sensitivity analyses on the per protocol (PP) population and several data exclusion analyses on the ITT population (after 90 days of investigational product discontinuation, after commercial Ocaliva initiation, commercial availability of Ocaliva per subject’s country and other intercurrent events) were consistent with the results observed in the ITT population.

Thirdly, the MAH states that differential discontinuation of the study drug was observed, resulting in lower exposure in the placebo group, and this was considered by the MAH to be a source of bias. However, time on-treatment should not be a major issue to gather the endpoints if patient follow-up after discontinuation is ensured, and the potential effect of the concomitant Ocaliva off-study was addressed in the sensitivity analyses discussed above with no change in the interpretation of the trial results.

Fourthly, while it is agreed that the fact that the trial was stopped prematurely theoretically reduced the chances of a positive outcome, post-hoc power is meaningless once the trial is finished. In fact, the post-hoc power was calculated on the assumption that the size of the treatment effect was true, which is not clear at all according to the primary trial results. In any case, it could ultimately be a problem of lack of sample size, but never a problem of bias.

Overall, the observed differences in the estimation of the treatment effect for the primary endpoint using the primary randomisation and the IPCW, demonstrate the high risk of bias associated to the reported analyses based on the weighting procedure, as compared to the results of Study 747-302. All results based on the EC are considered to have the same problem of bias. Furthermore, in addition to all the issues discussed above, the analyses resulting from the comparisons with EC should be understood in

the context of a pivotal trial in which the primary analysis failed, leaving no alpha for confirmatory testing. As a result, any further analyses should be considered exploratory only.

8. Clinical Safety aspects

Methods – analysis of data submitted

The safety summary presented as part of the Clinical Overview focuses only on the results from the following:

- PMR Study 747-302 in patients with PBC using the Safety population, which comprised of 334 patients (265 patients with compensated liver disease (with or without cirrhosis) at baseline, which is the indicated population per SmPC), and in the subset of compensated liver disease.
- Post-marketing experience in over 28000 cumulative estimated patient-years defined as all patients who received at least 1 dose of investigational product through the data cut off of 26 May 2022

Safety data from Study 747-301 LTSE and Study 747-401 have been briefly summarized in the previous Section.

Results

Patients exposure

The clinical safety information is based on approximately 4518 patients who received at least one dose of OCA in clinical trials sponsored by Intercept and Sumitomo Dainippon Pharma Co., Ltd. (Intercept's former development partner in China, Korea, and Japan). Estimated cumulative patient exposure in Intercept- and Sumitomo-sponsored clinical trials since the beginning of the OCA development program is summarized in Table 12.

Table 12: Estimated Cumulative Patient Exposure from Clinical Trials

Treatment	Number of Patients ^a
Obeticholic Acid:	4518
Renal Impairment	28
Healthy Adult Patients	1006
Primary biliary cholangitis	634
Nonalcoholic steatohepatitis with fibrosis	2069
Nonalcoholic steatohepatitis with cirrhosis	629
Diabetes mellitus/nonalcoholic fatty liver disease	41
Alcoholic cirrhosis/portal hypertension	33
Biliary atresia	6
Primary sclerosing cholangitis	72
Active Comparator:	63
Bezafibrate:^c	31
Placebo:	1899
Total:	6308^b

Note: Data cutoff date 26 May 2022. Studies include 747-101, 747-102, 747-103, 747-104, 747-105, 747-107, 747-108, 747-109, 747-110, 747-111, 747-112, 747-113, 747-114, 747-115, 747-116, 747-117, 747-118, 747-120, 747-121, 747-123, 747-201 DB, 747-201 LTSE, 747-202 DB, 747-201 LTSE, 747-203, 747-204, 747-205 PTP, 747-205 LTSE, 747-206, 747-207 DB, 747-207 LTSE, 747-209 DB, 747-209 LTSE, 747-213, 747-301 DB, 747-301 LTSE, 747-302, 747-303, 747-304, 747-401, D8602001, D8602021, D8601002, and FLINT.

Note: Patients receiving obeticholic acid and another drug are counted under the obeticholic acid group only. The FLINT study (FXR Ligand Obeticholic Acid in NASH Treatment) was conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the study's investigational new drug (IND) application was transferred from NIDDK to Intercept in December 2014.

OCA Exposure in Post-marketing Requirement Study 747-302

Duration of investigational product exposure 334 patients in enrolled in Study 747-302 is presented in Figure 7 and Table 13. The mean durations of exposure for the OCA and placebo groups were 876 days and 745 days, respectively. The OCA group had more patients than the placebo group who received investigational product >721 days (91 patients in the OCA group and 71 patients in the placebo group).

Patients with compensated disease (with or without cirrhosis), which is the indicated population per the EU SmPC, received investigational product for a longer duration than patients with more advanced stage PBC (i.e., decompensated). The mean durations of exposure for patients with compensated disease were: 951 days for the OCA group and 814 days for the placebo group. The mean durations of exposure for patients with decompensated disease were: 561 days for the OCA group and 505 days for the placebo group.

Figure 7: Duration of Investigational Product Exposure in 747-302 (Safety Population, N=334)

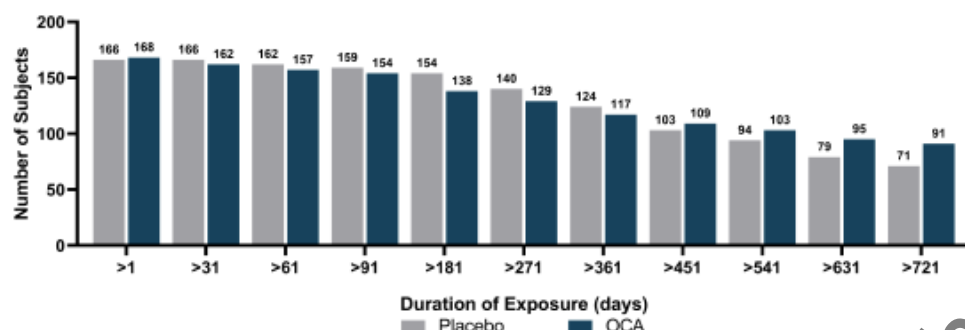


Table 13: Summary of Investigational Product Exposure by Baseline Disease Stage in 747-302 (Safety Population, N=334)

	All Patients		Compensated		Decompensated	
	Placebo (N=166)	OCA (N=168)	Placebo (N=129)	OCA (N=136)	Placebo (N=37)	OCA (N=32)
Duration of Exposure to IP (days)*						
n	166	168	129	136	37	32
Mean (SD)	745.1 (511.30)	876.3 (641.80)	813.8 (526.95)	950.5 (644.55)	505.3 (367.26)	560.8 (531.91)
Median (Q1, Q3)	609.0 (360.0, 1094.0)	812.0 (298.0, 1461.5)	699.0 (391.0, 1236.0)	887.5 (381.0, 1592.0)	408.0 (217.0, 642.0)	340.5 (148.0, 818.0)
Min, Max	34, 2181	3, 2181	34, 2181	3, 2181	41, 1517	49, 1754

OCA=obeticholic acid

* Duration of exposure to IP (days)=(last treatment date – first treatment date + 1) – Duration of temporary IP discontinuation.

Source: 747-302 CSR, [Table 14.3.1](#) and [Table 14.3.1.1.2](#)

Cumulative and Interval Patient Exposure from Post-marketing Experience

As of 26 May 2022, the estimated cumulative patient exposure from marketing experience is more than 28000 patient-years. Estimates of post-marketing exposure are based on sales distribution data that are provided by the Sponsor's commercial organization (Table 14). The data reflect sales of the Sponsor's products and contain information on the number of units shipped each month. Each unit (bottle) of Ocaliva contains 30 tablets and is assumed to be prescribed at 1 tablet per day. Sales distribution data are converted into an estimate of exposure in patient-years by total units*30 days per unit/365.25 days per year. Where product volume sales information is not yet available, post-marketing exposure is estimated by prorating the trailing 3-month mean exposure.

It should be noted that the use of sales data for patient exposure calculations overestimate or underestimate exposure depending on the accumulation of stock in the distribution channels, and the reduced dosing schedule in patients with hepatic impairment and for the management of tolerability.

Table 14: Postmarketing Patient Exposure Summary

Country	Estimated Patient-Years Cumulative
USA	14428.70
Italy	2473.59
Spain	2323.12
UK #	2273.35
Germany	2242.35
Canada	1883.94
France #	1399.10
Norway	245.08
Austria	240.00
Portugal #	206.98
RoW	641.36
Total	28,358

RoW=Rest of World; UK=United Kingdom; USA=United States of America

Product was available through an early access program

Source: Module 5.3.6, PBRER-08, Section 5.2, Table 4

OCA Exposure in Long-Term Safety Extension Study 747-301

A total of 193 patients received at least 1 dose of OCA during the LTSE (Table 15). The median number of days on OCA was 1944.0 days (5.3 years) from initiation of OCA regardless of initiation in the double-blind or LTSE phase. The median weighted average daily OCA dose was 8.3 mg. Forty-two (of the 193 patients (22%)) received OCA >10 mg daily at some point during the study.

Table 15: OCA Exposure: Safety Population (N=193)

	Total OCA (N=193)
Number of Days on OCA	
Mean (SD)	1689.8 (584.87)
Median	1944.0
Min, Max	7, 2301
Weighted Average Daily OCA Dose (mg)	
Mean (SD)	8.5 (3.42)
Median	8.3
Min, Max	2, 19
≤5 mg	30 (16%)
>5 to ≤10 mg	121 (63%)
>10 mg	42 (22%)

OCA=obeticholic acid; SD=standard deviation

Source: 747-301 LTSE CSR, Table 14.3.5.1

Baseline Characteristics Study 302 (vs Study 301)

The demographic characteristics of the patients with compensated liver disease (with or without cirrhosis) at baseline in Study 747-302, which is the indicated population in the EU SmPC, and in Study

747-301 were representative of that expected in clinical practice (Table 16). Patients were predominantly women presenting with PBC after the age of 50 years.

Overall, patients in Study 747-302 reflected an advanced disease population compared to previous PBC studies (i.e., 747-301): 69 (21%) patients had decompensated disease at baseline and are considered contraindicated per the CCDS and SmPC revision that occurred while the study was ongoing (32 patients in the OCA group and 37 patients in the placebo group). Patients with compensated disease in Study 747-302 were predominantly women presenting with PBC after the age of 50 years, had higher baseline ALP, total bilirubin, Model for End-Stage Liver Disease (MELD), and Rotterdam criteria compared to patients in Study 747-301 (Table 17).

Table 16: Demographics Comparison: Studies 747-301 and 747-302

	747-301 Overall			747-302 Compensated	
	Placebo (N=73)	OCA Titration (N=70)	OCA 10 mg (N=73)	Placebo (N=129)	OCA (N=136)
Age, Mean (SD)	55.5 (10.0)	55.8 (10.5)	56.2 (11.0)	53.5 (10.6)	52.9 (9.9)
Age subgroup, <65 years, n (%)	60 (82)	60 (86)	56 (77)	109 (85)	115 (85)
Female, n (%)	68 (93)	65 (93)	63 (86)	117 (91)	121 (89)
White, n (%)	66 (90)	67 (96)	70 (96)	109 (85)	118 (87)
UDCA Current Use at Baseline, n (%)	68 (93)	65 (93)	67 (92)	112 (87)	116 (85)
Duration of PBC years, Mean (SD)	8.3 (5.4)	8.3 (5.8)	9.2 (6.9)	7.7 (6.5)	7.5 (5.5)

Note: Results from 747-301 was from the Safety Population and 747-302 was from the ITT Population.

Source: 747-301 CSR, Section 10.3.1, Table 13 and Section 10.3.2 Table 14; 747-302 CSR Table 14.1.3.1.1.2 and Table 14.1.3.2.1.2

Table 17: Baseline Disease Severity Comparison: Studies 747-301 and 747-302

	747-301 Overall			747-302 Compensated	
	Placebo (N=73)	OCA Titration (N=70)	OCA 10 mg (N=73)	Placebo (N=136)	OCA (N=129)
ALP (U/L), Mean (SD)	327.5 (115.0)	325.9 (116.2)	316.3 (103.9)	526.8 (299.37)	499.9 (276.42)
Total Bilirubin (mg/dL), Mean (SD)	0.69 (0.42)	0.60 (0.33)	0.66 (0.39)	1.37 (0.585)	1.38 (0.618)
Total Bilirubin >ULN, n (%)	7 (10)	4 (6)	7 (10)	80 (62.0)	87 (64.0)
MELD, Mean (SD)	6.9 (0.8)	7.4 (2.9)	7.2 (1.9)	8.09 (1.499)	8.02 (1.452)
Baseline Rotterdam Criteria, n (%)					
Early	56 (77)	58 (83)	60 (82)	51 (39.5)	53 (39.0)
Moderate	13 (18)	12 (17)	11 (15)	74 (57.4)	80 (58.8)
Advanced	4 (5)	2 (3)	2 (3)	4 (3.1)	3 (2.2)

Note: Results from 747-301 was from the Safety Population, 747-302 was from the ITT Population.

Source: 747-301 CSR, Section 10.3.3, Table 15; 747-302 CSR Table 14.1.3.2.1.2

Safety Results

Study 747-302

The Safety population included 334 subjects with PBC, who received at least 1 dose of investigational product (166 subjects received placebo and 168 subjects received OCA). Separate safety results are presented for the subset of 265 patients with compensated liver disease (with or without cirrhosis) included in Study 747-302, 129 patients in placebo and 136 patients treated with OCA.

Table 55: Summary of Investigational Product Exposure (Safety Population)

	Placebo (N=166)	OCA (N=168)
Duration of Exposure to IP (days)^a		
n	166	168
Mean (SD)	745.1 (511.30)	876.3 (641.80)
Median (Q1, Q3)	609.0 (360.0, 1094.0)	812.0 (298.0, 1461.5)
Min, Max	34, 2181	3, 2181
Total IP Exposed (mg)		
n	166	168
Mean (SD)	5531.2 (4633.55)	5688.5 (5879.06)
Median (Q1, Q3)	4102.5 (2145.0, 7500.0)	3500.0 (1012.5, 8690.0)
Min, Max	135, 20195	15, 20840
Dose Frequency at Day 1		
Daily	161 (97.0)	163 (97.0)
Weekly	5 (3.0)	5 (3.0)
Number of Subjects with Increased Dose at Least Once, n (%)	130 (78.3)	114 (67.9)
Number of Subjects with Decreased Dose at Least Once, n (%)	68 (41.0)	86 (51.2)
Number of CP-B or CP-C Subjects with Dose Adjustment at Least Once, n (%) ^b	69 (41.6)	61 (36.3)
Number of CP-B or CP-C Subjects with Dose Interruption/Discontinuation at Least Once, n (%)	46 (27.7)	42 (25.0)
Number of CP-B or CP-C Subjects with Frequency Modification at Least Once, n (%)	46 (27.7)	42 (25.0)
Percent Compliance (%)^c		
n	166	168
Mean (SD)	69.190 (17.503)	62.340 (23.977)
Median (Q1, Q3)	72.750 (59.000, 83.500)	66.150 (45.700, 84.150)
Min, Max	13.50, 94.00	4.00, 98.00
Percent Compliance Categories, n (%)		
<80%	112 (67.5)	111 (66.1)
80-100%	54 (32.5)	57 (33.9)
100-120%	0	0
>120%	0	0

CP-B=Child-Pugh B; CP-C=Child-Pugh C; IP=investigational product; Max=maximum; Min=minimum; OCA=obeticholic acid; SD=standard deviation; SE=standard error

Note: Percentages are based on number of subjects in the Safety Population within each treatment group.

Note: Data after initiation of commercial OCA are excluded.

Note: CP-B or CP-C subjects are those who are classified as CP-B or CP-C at any time during the study, including baseline.

^a Duration of exposure to IP (days)=(last treatment date – first treatment date + 1) – Duration of temporary IP discontinuation.

^b If the subject has multiple dose adjustments caused by the same reason, the subject is only counted once per reason category.

^c Percent compliance=(number of tablets consumed during study / number of tablets expected to be consumed during study) *100

Source: Table 14.3.1

Adverse events

For the **Safety population**, higher rates of events were reported for OCA compared to placebo, including any TEAE (96.4% OCA vs 95.2% placebo), any TEAE leading to discontinuation (36.9% OCA vs 27.1% placebo), any TEAE leading to study discontinuation (17.3% Oca vs 11.4%placebo), treatment related TEAE (79.2% OCA vs 66.9% placebo), treatment related TEAE leading to discontinuation (20.8% OCA vs 12.7% placebo), treatment-emergent SAE (31.5% OCA vs 31.9% placebo), Severe TEAE (51.2% OCA vs 39.2% placebo), and TEAEs leading to death (3.0% OCA vs 1.2% placebo), which is very concerning. Overall, 162 (96.4%) subjects in the OCA group had a total of 2349 TEAEs and 158 (95.2%) in the placebo group had a total of 1815 TEAEs. Consistent with earlier studies, pruritus was the most frequently reported treatment-related TEAE and the most common TEAE leading to discontinuation of investigational product.

Overall, 162 (96.4%) subjects in the OCA group had a total of 2349 TEAEs and 158 (95.2%) in the placebo group had a total of 1815 TEAEs.

Table 56: Overview of Treatment-Emergent Adverse Events (Safety Population)

Number of Subjects With, n (%)	Placebo (N=166)	OCA (N=168)
Any TEAE	158 (95.2)	162 (96.4)
Leading to Discontinuation of IP	45 (27.1)	62 (36.9)
Leading to Study Discontinuation	19 (11.4)	29 (17.3)
Leading to IP Interruption	43 (25.9)	48 (28.6)
Leading to Dose Reduction	23 (13.9)	45 (26.8)
Treatment-Related TEAE	111 (66.9)	133 (79.2)
Leading to Discontinuation of IP	21 (12.7)	35 (20.8)
Leading to Study Discontinuation	10 (6.0)	18 (10.7)
Leading to IP Interruption	14 (8.4)	35 (20.8)
Leading to Dose Reduction	19 (11.4)	41 (24.4)
Treatment-emergent SAE	53 (31.9)	53 (31.5)
Severe TEAE	65 (39.2)	86 (51.2)
TEAEs Leading to Death	2 (1.2)	5 (3.0)

IP=investigational product; OCA=obeticholic acid; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Note: TEAEs with missing severity are considered severe. TEAEs with a missing relationship are considered related.

Source: [Table 14.3.1.2.1](#)

In the **compensated group**, the incidence of patients who reported a treatment-emergent adverse event (TEAE) was similar across treatment groups: 95.6% patients in the OCA group and 94.6% in the placebo group. The majority of TEAEs were mild and moderate in severity. The incidence of severe TEAEs was higher in the OCA group (47.1%) than the placebo group (36.4%), which was driven by the occurrence of severe pruritus. Treatment-related TEAEs were reported by 78.7% patients in the OCA group and 62.0% patients in the placebo group. The incidence of TEAEs leading to discontinuation of investigational product was higher in the OCA group (33.1%) than the placebo group (27.9%). Consistent with earlier studies, pruritus was the most frequently reported treatment-related TEAE and the most common TEAE leading to discontinuation of investigational product. In the compensated group, the incidence of TEAEs leading to death was similar across treatment groups (2 patients each in the OCA and placebo group). All TEAEs leading to death were assessed by the Investigator as not related or unlikely related to investigational product.

The incidence of SAEs in the compensated group was numerically lower in OCA-treated patients (24.3%) than the placebo group (31.0%).

In the overall Safety population (both patients with compensated and decompensated disease) in Study 747-302, the safety profile was similar to that in the compensated group. The most frequently reported TEAE was pruritus, which had a higher incidence in the OCA group (78.6%) than in the placebo group (51.2%). In addition to pruritus, other TEAEs in $\geq 10\%$ of OCA-treated subjects and were reported more frequently in the OCA group compared with placebo included peripheral edema (18.5% in the OCA group and 10.8% in the placebo group); abdominal pain which includes the following preferred terms: Abdominal Pain Upper PT (14.9% in the OCA group and 7.2% in the placebo group), Abdominal Pain PT (12.5% in the OCA group and 10.8% in the placebo group) and Abdominal Pain Lower PT (4.8% in the OCA group and 1.2% in the placebo group); nausea (14.9% in the OCA group and 12.7% in the placebo group); headache (13.7% in the OCA group and 12.7% in the placebo group); constipation (11.3% in the OCA group and 6.0% in the placebo group); and nasopharyngitis (10.7% in the OCA group and 8.4% in the placebo group). (Table 18).

Table 18: Treatment-Emergent Adverse Events in $\geq 10\%$ of OCA-treated Patients by System Organ Class and Preferred Term in Descending Frequency in Overall and in Patients with Compensated Disease at Baseline in 747-302 (Safety Population, N=334)

System Organ Class Preferred Term	Overall		Compensated	
	Placebo (N=166) n (%)	OCA (N=168) n (%)	Placebo (N=129) n (%)	OCA (N=136) n (%)
Patients with Any TEAE	158 (95.2)	162 (96.4)	122 (94.6)	130 (95.6)
Skin and subcutaneous tissue disorders	101 (60.8)	138 (82.1)	79 (61.2)	111 (81.6)
Pruritus	85 (51.2)	132 (78.6)	66 (51.2)	108 (79.4)
Gastrointestinal disorders	106 (63.9)	117 (69.6)	81 (62.8)	95 (69.9)
Abdominal pain upper	12 (7.2)	25 (14.9)	8 (6.2)	21 (15.4)
Nausea	21 (12.7)	25 (14.9)	16 (12.4)	17 (12.5)
Abdominal pain	18 (10.8)	21 (12.5)	14 (10.9)	16 (11.8)
Diarrhoea	26 (15.7)	21 (12.5)	21 (16.3)	17 (12.5)
Varices oesophageal	28 (16.9)	20 (11.9)	23 (17.8)	16 (11.8)
Constipation	10 (6.0)	19 (11.3)	7 (5.4)	13 (9.6)
Ascites	21 (12.7)	18 (10.7)	18 (10.1)	9 (6.6)
Infections and infestations	90 (54.2)	91 (54.2)	71 (55.0)	74 (54.4)
Urinary tract infection	30 (18.1)	20 (11.9)	23 (17.8)	17 (12.5)
Nasopharyngitis	14 (8.4)	18 (10.7)	12 (9.3)	16 (11.8)
General disorders and administration site conditions	68 (41.0)	78 (46.4)	50 (38.8)	55 (40.4)
Oedema peripheral	18 (10.8)	31 (18.5)	9 (7.0)	18 (13.2)
Fatigue	25 (15.1)	18 (10.7)	15 (11.6)	14 (10.3)

System Organ Class Preferred Term	Overall		Compensated	
	Placebo (N=166) n (%)	OCA (N=168) n (%)	Placebo (N=129) n (%)	OCA (N=136) n (%)
Musculoskeletal and connective tissue disorders	71 (42.8)	66 (39.3)	58 (45.0)	57 (41.9)
Arthralgia	29 (17.5)	23 (13.7)	25 (19.4)	19 (14.0)
Investigations	68 (41.0)	61 (36.3)	51 (39.5)	46 (33.8)
Blood bilirubin increased	25 (15.1)	20 (11.9)	18 (14.0)	14 (10.3)
Nervous system disorders	59 (35.5)	51 (30.4)	44 (34.1)	39 (28.7)
Headache	21 (12.7)	23 (13.7)	16 (12.4)	19 (14.0)

Source: 747-302 CSR Table 14.3.1.2.2 and Table 14.3.1.2.2.2

A total of 133 (79.2%) subjects in the OCA group and 111 (66.9%) subjects in the placebo group experienced at least 1 TEAE assessed by the Investigator as related to investigational product (OCA or placebo) (Table 58). The most frequently reported treatment-related TEAE was pruritus (70.2% in the OCA group and 43.4% in the placebo group). Other more frequently reported treatment-related TEAEs ($\geq 5\%$ in OCA-treated subjects) were nausea (6.5% in the OCA group and 4.8% in the placebo group) and blood bilirubin increased (7.7 % in the OCA group and 9.6% in the placebo group).

Table 58: Treatment-related Treatment-Emergent Adverse Events in ≥ 2 OCA-treated Subjects by System Organ Class and Preferred Term (Safety Population, N=334)

System Organ Class Preferred Term	Placebo (N=166) n (%)	OCA (N=168) n (%)
Subjects with at Any Treatment-related TEAE	111 (66.9)	133 (79.2)
Skin and subcutaneous tissue disorders	77 (46.4)	120 (71.4)
Pruritus	72 (43.4)	118 (70.2)
Rash	0	5 (3.0)
Skin lesion	0	3 (1.8)
Eczema	0	2 (1.2)
Papule	0	2 (1.2)
Urticaria	1 (0.6)	2 (1.2)
Gastrointestinal disorders	32 (19.3)	37 (22.0)
Nausea	8 (4.8)	11 (6.5)
Abdominal pain	3 (1.8)	8 (4.8)
Ascites	6 (3.6)	6 (3.6)
Abdominal distension	1 (0.6)	5 (3.0)
Abdominal pain upper	6 (3.6)	5 (3.0)
Diarrhoea	7 (4.2)	4 (2.4)
Vomiting	5 (3.0)	3 (1.8)
Abdominal discomfort	0	2 (1.2)
Abdominal pain lower	2 (1.2)	2 (1.2)
Constipation	0	2 (1.2)
Faeces pale	0	2 (1.2)
Portal hypertensive gastropathy	0	2 (1.2)
Investigations	32 (19.3)	28 (16.7)
Blood bilirubin increased	16 (9.6)	13 (7.7)
Alanine aminotransferase increased	1 (0.6)	2 (1.2)
Aspartate aminotransferase increased	1 (0.6)	2 (1.2)
Hepatic enzyme increased	3 (1.8)	2 (1.2)
General disorders and administration site conditions	26 (15.7)	21 (12.5)
Fatigue	10 (6.0)	8 (4.8)
Oedema peripheral	6 (3.6)	8 (4.8)

System Organ Class Preferred Term	Placebo (N=166) n (%)	OCA (N=168) n (%)
Asthenia	2 (1.2)	2 (1.2)
Pyrexia	0	2 (1.2)
Nervous system disorders	7 (4.2)	14 (8.3)
Headache	3 (1.8)	5 (3.0)
Burning sensation	0	2 (1.2)
Hepatic encephalopathy	1 (0.6)	2 (1.2)
Hepatobiliary disorders	17 (10.2)	13 (7.7)
Jaundice	6 (3.6)	5 (3.0)
Drug-induced liver injury	0	2 (1.2)
Hepatic failure	1 (0.6)	2 (1.2)
Hyperbilirubinaemia	7 (4.2)	2 (1.2)
Psychiatric disorders	5 (3.0)	10 (6.0)
Insomnia	3 (1.8)	6 (3.6)
Blood and lymphatic system disorders	1 (0.6)	6 (3.6)
Increased tendency to bruise	0	3 (1.8)
Leukopenia	0	2 (1.2)
Respiratory, thoracic and mediastinal disorders	6 (3.6)	4 (2.4)
Dyspnoea	1 (0.6)	2 (1.2)
Injury, poisoning and procedural complications	2 (1.2)	3 (1.8)
Skin abrasion	0	2 (1.2)

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.6.1

A total of 86 (51.2%) subjects in the OCA group and 65 (39.2%) subjects in the placebo group had at least 1 severe TEAE (Table 59). The difference in incidence of severe TEAEs across treatment groups was driven by the occurrence of severe pruritus (30.4% in the OCA group and 9.0% in the placebo group). With the exception of pruritus and esophageal varices hemorrhage, severe TEAEs by PT occurred in less than 2% subjects.

Table 59: Summary of Severe Treatment-Emergent Adverse Events in ≥ 2 OCA-treated Subjects by Preferred Term (Safety Population)

System Organ Class Preferred Term	Placebo (N=166) n (%)	OCA (N=168) n (%)
Subjects with Any Severe TEAE	65 (39.2)	86 (51.2)
Skin and subcutaneous tissue disorders	16 (9.6)	51 (30.4)
Pruritus	15 (9.0)	51 (30.4)
Gastrointestinal disorders	15 (9.0)	23 (13.7)
Oesophageal varices haemorrhage	3 (1.8)	4 (2.4)
Abdominal pain upper	1 (0.6)	3 (1.8)
Ascites	1 (0.6)	3 (1.8)
Abdominal pain	2 (1.2)	2 (1.2)
Diarrhoea	1 (0.6)	2 (1.2)
Melaena	0	2 (1.2)
Vomiting	0	2 (1.2)
Infections and infestations	5 (3.0)	11 (6.5)
Urinary tract infection	0	3 (1.8)
Peritonitis bacterial	0	2 (1.2)
Sepsis	0	2 (1.2)
Hepatobiliary disorders	4 (2.4)	10 (6.0)
Hepatic cirrhosis	1 (0.6)	2 (1.2)
Hepatic failure	1 (0.6)	2 (1.2)
Nervous system disorders	12 (7.2)	9 (5.4)
Cerebrovascular accident	0	2 (1.2)
General disorders and administration site conditions	4 (2.4)	7 (4.2)
Fatigue	3 (1.8)	2 (1.2)
Injury, poisoning and procedural complications	7 (4.2)	6 (3.6)
Fall	0	2 (1.2)
Respiratory, thoracic and mediastinal disorders	4 (2.4)	6 (3.6)
Acute respiratory failure	0	2 (1.2)
Blood and lymphatic system disorders	3 (1.8)	5 (3.0)
Anaemia	1 (0.6)	3 (1.8)
Thrombotic thrombocytopenic purpura	0	2 (1.2)
Musculoskeletal and connective tissue disorders	1 (0.6)	3 (1.8)
Back pain	0	2 (1.2)

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: [Table 14.1.1.4.1](#)

Adverse Events of Special Interest

TEAEs that were prespecified as adverse events of special interest (AESIs) in Study 747-302 included Cardiovascular, Cholecystitis/cholelithiasis, Dyslipidemia, Hepatic, Pruritus, and Renal TEAEs.

The majority of treatment-emergent AESIs were mild or moderate, with a similar incidence across treatment groups. Severe treatment emergent AESIs were more common in the OCA group (38.7%) than the placebo group (22.9%).

Table 66: Summary of Treatment-Emergent AESIs (Safety Population [N=334])

AESI, n (%)	Placebo (N=166)	OCA (N=168)
Subjects with ≥1 TEAE of Special Interest	137 (82.5)	152 (90.5)
Mild	42 (25.3)	20 (11.9)
Moderate	57 (34.3)	67 (39.9)
Severe	38 (22.9)	65 (38.7)
Cardiovascular	7 (4.2)	16 (9.5)
Cholecystitis/Cholelithiasis	9 (5.4)	9 (5.4)
Dyslipidemia	9 (5.4)	6 (3.6)
Hepatic	97 (58.4)	80 (47.6)
Pruritus	86 (51.8)	133 (79.2)
Renal	13 (7.8)	17 (10.1)

AESI=adverse event of special interest; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: [Table 14.3.1.10.1](#), [Table 14.3.1.10.2](#)

In the compensated group, the incidence of treatment emergent AESIs was 88.2 in the OCA group and 79.8% in placebo (Table 19). Similarly, a higher incidence of cardiovascular AEs, pruritus and renal AEs were reported in this subgroup of patients. The higher incidences of CVs and renal AESIs is concerning.

Table 19: Treatment-Emergent Adverse Events of Special Interest in Patients with Compensated Disease in Study 747-302 (Safety Population)

System Organ Class Preferred Term	Placebo (N=129) n (%)	OCA (N=136) n (%)
Patients with Any TEAE of Special Interest	103 (79.8)	120 (88.2)
Cardiovascular	5 (3.9)	11 (8.1)
Cholecystitis/Cholelithiasis	8 (6.2)	7 (5.1)
Dyslipidemia	6 (4.7)	5 (3.7)
Hepatic	73 (56.6)	58 (42.6)
Pruritis	67 (51.9)	109 (80.1)
Renal	8 (6.2)	12 (8.8)

Pruritus

Pruritus was identified as an adverse drug reaction (ADR) in the labeling of Ocaliva for PBC and was removed as an important identified risk (as it is considered well characterized in the product labels, there are no outstanding pharmacovigilance activities, and the measures to avoid the risk are adequately described in the product information) in EU RMP V.1.3, approved on 11 June 2021. The exact pathogenesis of the pruritic effect of OCA is unknown, although it is currently hypothesized to be associated with an on-target FXR effect.

In Study 747-302, mild to moderate pruritus was the most commonly reported TEAE. In patients with compensated disease, 80.1% patients in the OCA group and 51.9% patients in the placebo group reported pruritus. Of these, eye pruritus and pruritus allergic occurred only in the OCA group in 1.5% patients. The majority of TEAEs reported in patients with compensated disease was pruritus: 79.4% in the OCA group and 51.2% in the placebo group. The incidence of pruritus SAEs was low in the compensated group: 2 patients in the OCA group and none in the placebo group. The majority of pruritus events, regardless of severity, were experienced within the first few months of treatment. In the

compensated group, pruritus events led to permanent discontinuation of the investigational product in 12.5% patients in the OCA group and 1.6% in the placebo group.

Among those patients experiencing any pruritus, most were able to continue treatment with OCA. Of those patients able to tolerate pruritus and remain on investigational product, the majority (approximately 70%) had used some form of management strategy for their pruritus, with treatment interruption appearing to be the most effective approach. Management and dosage adjustment for intolerable pruritus are addressed in the SmPC.

Table 72: Pruritus Treatment-Emergent AESIs by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with ≥ 1 Pruritus TEAE of Special Interest	86 (51.8)	133 (79.2)
Pruritus	85 (51.2)	132 (78.6)
Eye pruritus	0	2 (1.2)
Pruritus allergic	0	2 (1.2)
Rash pruritic	1 (0.6)	1 (0.6)
Vulvovaginal pruritus	1 (0.6)	1 (0.6)
Cholestatic pruritus	1 (0.6)	0

AESI=adverse event of special interest; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.10.1

Cardiovascular adverse events

In the overall safety population, 16 (9.5%) subjects in the OCA and 7 (4.2%) subjects in the placebo groups reported a cardiovascular treatment-emergent AESI (Table 67). The following cardiovascular treatment-emergent AESIs were reported in 2 (1.2%) subjects each in the OCA group: angina pectoris, cerebrovascular accident, coronary artery disease, myocardial infarction, subarachnoid hemorrhage, and thrombotic thrombocytopenic purpura.

A total of 9 subjects in the OCA group reported cardiovascular SAEs of special interest. Of these, the majority were considered not related or unlikely related to investigational product. Two subjects in the OCA group reported cardiovascular SAEs of special interest that were considered possibly related to investigational product.

Table 67: Cardiovascular Treatment-Emergent AESIs by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with ≥ 1 Cardiovascular TEAE of Special Interest	7 (4.2)	16 (9.5)
Angina pectoris	1 (0.6)	2 (1.2)
Cerebrovascular accident	1 (0.6)	2 (1.2)
Coronary artery disease	0	2 (1.2)
Myocardial infarction	0	2 (1.2)
Subarachnoid haemorrhage	0	2 (1.2)
Thrombotic thrombocytopenic purpura	0	2 (1.2)
Portal vein thrombosis	0	1 (0.6)
Pulmonary embolism	1 (0.6)	1 (0.6)
Reversible cerebral vasoconstriction syndrome	0	1 (0.6)
Thrombophlebitis	0	1 (0.6)
Thrombosis	0	1 (0.6)
Venous recanalisation	0	1 (0.6)
Venous thrombosis	0	1 (0.6)
Carotid artery stenosis	1 (0.6)	0
Mesenteric vein thrombosis	1 (0.6)	0
Paraplegia	1 (0.6)	0
Splenic infarction	1 (0.6)	0

AESI=adverse event of special interest; OCA=obetichonic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.10.1

Adjudicated Major Adverse Cardiovascular Events

All suspected MACE, including cardiovascular death, myocardial infarction, and stroke were independently adjudicated in a blinded fashion. In the Safety population, 4 (2.4%) subjects in the OCA group reported a MACE. The median time to first occurrence of MACE in the OCA group was 394.5 days (p-value=0.045). None of the subjects in the placebo group had a MACE. Overall, 2 subjects in the OCA group (173003 and 263002) experienced a MACE (cerebrovascular accident and myocardial infarction, respectively) that were considered possibly related by the Investigator. Two subjects (297001 and 164005) had SAEs of subarachnoid hemorrhage and cerebrovascular accident that were considered not related or unlikely related by the Investigator (Table 68).

Table 68: Listing of Treatment-Emergent MACE (Safety Population)

IP	Preferred Term	Cardiovascular Event	SAE	Onset Day/ Treatment Duration	Relatedness	Outcome
OCA	Cerebrovascular accident	Non-fatal Stroke	Yes	631/628	Possible	Last dose of OCA was 3 days prior event; resolved
OCA	Myocardial infarction	Non-fatal MI	Yes	177/177	Possible	Drug withdrawn; resolved
OCA	Subarachnoid haemorrhage	Cardiovascular Death	Yes	342/342	Not related	Drug withdrawn; subject died
OCA	Cerebrovascular accident	Non-fatal Stroke	Yes	441/441	Unlikely	Drug withdrawn; resolved

IP=investigational product; MI=myocardial infarction; SAE=serious adverse event

Note: Relatedness was reported by the Investigator.

Source: Listing 16.2.6.8.3.1, Listing 16.2.6.8.3.2 and Listing 16.2.7.1

In patients with compensated disease, the incidence rate for adjudicated events for Core major adverse cardiovascular events (MACE) was low (2 patients in the OCA group and none in the placebo group). Of these, 1 patient in the OCA group experienced a cerebrovascular accident which was considered possibly related by the Investigator and resolved.

Dyslipidaemias

Overall, 6 (3.6%) subjects in the OCA and 9 (5.4%) subjects in the placebo groups reported a dyslipidaemia treatment-emergent AESI (Table 70). The incidence of low-density lipoprotein increased only occurred in the OCA group (2 [1.2%] subjects). None of the reported dyslipidaemia treatment-emergent AESIs were considered SAEs.

Table 70: Dyslipidemia Treatment-Emergent AESIs by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with ≥ 1 Dyslipidemia TEAE of Special Interest	9 (5.4)	6 (3.6)
Low density lipoprotein increased	0	2 (1.2)
Blood cholesterol increased	1 (0.6)	1 (0.6)
Dyslipidemia	3 (1.8)	1 (0.6)
Hypercholesterolaemia	4 (2.4)	1 (0.6)
Hypertinglyceridaemia	1 (0.6)	1 (0.6)
Hyperlipidaemia	1 (0.6)	0

AESI=adverse event of special interest; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.10.1

Cholecystitis/cholelithiasis

There is a biological plausibility for an association between OCA exposure and the development or exacerbation of gallstones: increased lithogenicity of bile secondary to chronic FXR activation due to

higher cholesterol supersaturation resulting from decreased bile acid concentration in gallbladder bile (Al-Dury 2019).

In the overall safety population, 9 (5.4%) subjects in the OCA and 9 (5.4%) subjects in the placebo groups reported a cholecystitis/cholelithiasis treatment-emergent AESI (Table 69). The incidence of cholelithiasis was higher in the OCA group (7 [4.2%] subjects) than the placebo group (4 [2.4%] subjects). A total of 5 subjects reported cholecystitis/cholelithiasis SAEs of special interest. Of these, 3 subjects in the OCA group reported cholelithiasis, bile duct stone, and cholecystitis acute and 2 subjects in the placebo group reported an SAE of cholecystitis.

In patients with compensated disease, 5.1% OCA-treated and 6.2% placebo-treated patients experienced a cholecystitis/cholelithiasis TEAEs. Of these, 4 patients reported cholecystitis/cholelithiasis SAEs (3 patients in the OCA group: 2 patients with cholelithiasis and 1 patient with bile duct stone; 1 patient in the placebo group with cholecystitis). Of the 4 SAEs reported in the compensated group, 1 patient in the OCA group reported an SAE (bile duct stone) that was considered possibly related to investigational product. The total number of treatment-emergent cholecystitis/cholelithiasis AESIs was too small to make definitive conclusions.

Table 69: Cholecystitis/Cholelithiasis Treatment-Emergent AESIs in by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with ≥ 1 Cholecystitis/Cholelithiasis TEAE of Special Interest	9 (5.4)	9 (5.4)
Cholelithiasis	4 (2.4)	7 (4.2)
Hyperplastic cholecystopathy	0	2 (1.2)
Bile duct stone	0	1 (0.6)
Cholecystitis acute	0	1 (0.6)
Biliary colic	1 (0.6)	0
Cholecystitis	3 (1.8)	0
Cholecystitis chronic	1 (0.6)	0

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.10.1

Liver injury

Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with OCA treatment in patients with PBC with decompensated or compensated disease. Accordingly, per the CCDS v.2.0 dated 01Jun2021 and v.3.0 dated 03Aug2021, Ocaliva is contraindicated in patients with decompensated cirrhosis (e.g., CP-B or -C) or a prior decompensation event and in patients with complete biliary obstruction. In the EU, Ocaliva is also contraindicated in patients with decompensated cirrhosis or a prior decompensation event (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy) per the SmPC.

In the **overall safety population**, 80 (47.6%) subjects in the OCA and 97 (58.4%) subjects in the placebo groups reported a hepatic treatment-emergent AESI (Table 71). The majority of hepatic AESIs ($\geq 10\%$ of OCA-treated subjects) were blood bilirubin increased (including blood bilirubin increased PT and hyperbilirubinemia PT), varices oesophageal, and ascites. The incidence of hepatic AESIs of portal hypertensive gastropathy and DILI was higher in the OCA group (14 [8.3%] subjects and 4 [2.4%] subjects, respectively) than the placebo group (7 [4.2%] subjects and 0 subjects, respectively). The

majority of the hepatic AESIs in the OCA group were considered not related and did not lead to discontinuation of investigational product.

Table 71: Hepatic Treatment-Emergent AESIs in ≥ 4 OCA-treated Subjects by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with Any Hepatic TEAE of Special Interest	97 (58.4)	80 (47.6)
Blood bilirubin increased	25 (15.1)	20 (11.9)
Varices oesophageal	28 (16.9)	20 (11.9)
Ascites	21 (12.7)	18 (10.7)
Portal hypertensive gastropathy	7 (4.2)	14 (8.3)
Hepatic cirrhosis	8 (4.8)	10 (6.0)
Hepatic encephalopathy	11 (6.6)	8 (4.8)
Jaundice	10 (6.0)	8 (4.8)
Blood alkaline phosphatase increased	5 (3.0)	5 (3.0)
Oesophageal varices haemorrhage	5 (3.0)	5 (3.0)
ALT increased	5 (3.0)	4 (2.4)
AST increased	4 (2.4)	4 (2.4)
Drug-induced liver injury	0	4 (2.4)
Hyperbilirubinaemia	11 (6.6)	4 (2.4)
Hypoalbuminaemia	1 (0.6)	4 (2.4)
INR increased	2 (1.2)	4 (2.4)

AESI=adverse event of special interest; ALT=alanine aminotransferase; AST=aspartate aminotransferase increased; INR=international normalized ratio; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Note: Hyperbilirubinaemia is presented in table to show all subjects

Source: Table 14.3.1.10.1

In **patients with compensated disease in Study 747-302**, 42.6% patients in the OCA and 56.6% patients in the placebo groups reported a hepatic TEAEs. The incidence of hepatic AESIs of portal hypertensive gastropathy and drug-induced liver injury (DILI) was higher in the OCA group (14 [8.3%] subjects and 4 [2.4%] subjects, respectively) than the placebo group (7 [4.2%] subjects and 0 subjects, respectively). The majority of the hepatic AESIs in the OCA group were considered not related and did not lead to discontinuation of investigational product.

Liver Transplants and Deaths

In the Safety Population, a total of 7 (4.2%) subjects in the OCA group and 2 (1.2%) subjects in the placebo group experienced a liver transplant or death during treatment or within 30 days of the reporting period. All liver transplants and deaths were independently adjudicated in a blinded manner by a Hepatic Safety Adjudication Committee (HSAC), also referred to as the Hepatic Outcomes Committee.

In the ITT Population, 32 subjects in the OCA group and 28 subjects in the placebo group experienced a liver transplant or death (Table 35). Overall, 4 (12.5%) subjects in the OCA group and 1 (3.6%) subject in the placebo group experienced a liver transplant or death event that was assessed as possibly related by the HSAC. A total of 9 subjects in the OCA group and 4 subjects in the placebo group experienced a liver transplant or death event within 90 days of last dose of investigational product. Of these, 1 (11.1%) subject in the OCA group and 1 (25%) subject in the placebo group experienced a liver transplant or death event that was assessed as possibly related to investigational product by the HSAC. A total of 11 subjects in the OCA group and 2 subjects in the placebo group who were on-label per USPI experienced

a liver transplant or death event during the study. Of these, 3 subjects in the OCA group experienced a liver transplant or death event within 90 days of last dose of investigational product, which were all assessed as unlikely related by the HSAC. A total of 20 subjects in the OCA group and 14 subjects in the placebo group with compensated disease experienced a liver transplant or death event during the study. Of these, 1 (16.7%) subject in the OCA group experienced a liver transplant or death event within 90 days of last dose of investigational product, which was assessed as possibly related to investigational product by the HSAC. All liver transplant or death events experienced by subjects with compensated cirrhosis in the placebo group were assessed as unlikely related to investigational product.

Table 35: Exposure-Adjusted Incidence Rate of Liver Transplant or Death Events (ITT Population)

	Placebo (N=166)	OCA (N=168)
Liver Transplant or Death	28 (16.9)	32 (19.0)
Subject-Years	526.24	535.56
Number of subjects with event per 100 subject years	5.321	5.975

OCA=obeticholic acid

Note: Subject-years=sum of individual subject-years for event. Each individual's subject-years will be derived as the first onset date of an event or last contact date if no event minus the first dose date plus 1 divided by 365.25 days/year.

Source: Table 14.2.2.3.3

A total of 60 liver transplants and deaths in patients overall were retrospectively adjudicated in a blinded manner by an independent Hepatic Safety Adjudication Committee (HSAC). Of these, slightly less than half (26 patients) occurred in patients with decompensated liver disease at baseline. Of the remaining 34 patients with compensated liver disease, 14 occurred in the placebo group and 20 occurred in the OCA group. All liver transplants and deaths in the placebo group were assessed as unlikely related to investigational product by the HSAC. Of the 20 patients with compensated disease in the OCA group, 17 were assessed as unlikely related to investigational product, and 3 as possibly related by the HSAC. Upon patient level review, 1 of the 3 patients had ascites on ultrasound imaging prior to baseline and the patient would be considered contraindicated by the SmPC due to decompensated cirrhosis.

Renal

Overall, 17 (10.1%) subjects in the OCA and 13 (7.8%) subjects in the placebo groups reported a renal treatment-emergent AESI (Table 73). The distribution of renal AESIs was similar across treatment groups, with none of the TEAEs occurring in >3% of subjects by PT. The incidence of acute kidney injury, hypoalbuminemia, hyponatremia, proteinuria, and thrombotic thrombocytopenic purpura was slightly higher in the OCA group than the placebo group.

Table 73: Renal Treatment-Emergent AESIs in ≥ 1 OCA-treated Subject by Preferred Term (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subject with ≥ 1 Renal TEAE of Special Interest	13 (7.8)	17 (10.1)
Acute kidney injury	2 (1.2)	5 (3.0)
Hypoalbuminemia	1 (0.6)	4 (2.4)
Hyponatraemia	1 (0.6)	2 (1.2)
Proteinuria	0	2 (1.2)
Thrombotic thrombocytopenic purpura	0	2 (1.2)
Diabetic nephropathy	0	1 (0.6)
Haematuria	2 (1.2)	1 (0.6)
Hyperkalaemia	1 (0.6)	1 (0.6)
Leukocyturia	0	1 (0.6)

AESI=adverse event of special interest; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Source: Table 14.3.1.10.1

While nonclinical evidence indicates that FXR activation, including by OCA, may have anti-fibrotic and renoprotective effects (Jiang 2007, Wang 2009, Levi 2011, Hu 2012, Bae 2014, Gai 2016), it has been reported that exposure to OCA was associated with a small reduction in estimated glomerular filtration rate (eGFR) in a NASH clinical study (Corey 2016). Similar to the results in the general safety population, in patients with compensated disease at Baseline, 8.8% OCA-treated and 6.2% placebo-treated patients experienced a renal AESI. The incidence of acute kidney injury (AKI) was low across treatment groups, but numerically higher in OCA treated groups (2.2% in the OCA group and 1.6% in the placebo group). A total of 3 patients in the OCA group and 1 patient in the placebo group experienced an AKI, which were all considered not related to investigational product by the Investigator. With the exception of AKI, frequency of any individual renal AESI was 2 or less (maximum 1.5%).

Overall, the distribution of renal TEAEs was similar across treatment groups, with none of the individual TEAEs occurring in $>3\%$ of patients. The majority of patients overall had normal albumin and creatinine values at Baseline and no clinically meaningful changes were observed overtime.

Adverse Drug Reactions

No new significant safety signals have been identified from Study 747-302.

The most common ADRs ($\geq 5\%$ in any OCA group and at a rate that was at least 3% greater than that observed in the placebo group) were pruritus/skin eruptions, fatigue/tiredness, abdominal pain and discomfort, oropharyngeal pain, arthralgia, procedural pain, oedema peripheral, palpitations, eczema, and pyrexia.

Serious adverse events and deaths, other significant events

Deaths

A total of 7 subjects had a TEAE leading to death (5 in OCA-treated subjects: acute respiratory failure, respiratory failure, subarachnoid hemorrhage, sepsis, and lower respiratory tract infection; and 2 in placebo-treated subjects: sarcopenia and hepatocellular carcinoma). All TEAEs leading to death were considered not related or unlikely related to the investigational product (Table 61). Subjects who died in the compensated and on-label per USPI subgroups are briefly discussed below. All other deaths occurred in the contraindicated per USPI and/or decompensated subgroups. Deaths that occurred post 30 days

after discontinuation of investigational product were not included in the safety analyses and are discussed in more detail in Section 11.1.3.2.

A female subject with PBC in the on-label per USPI and compensated subgroup died of acute respiratory failure on 05 Sep 2016, approximately 10 months after the initiation of OCA. Investigational product was withdrawn in response to the events of lymphoma and acute kidney injury with the last dose administered on 20 Aug 2016. The death was considered not related to investigational product by the Investigator.

A male subject with PBC in the contraindicated per USPI and compensated subgroup died of lower respiratory tract infection on 09 Feb 2017, approximately 6 months after the initiation of OCA. The subject's last dose of investigational product was on 15 Dec 2016. The death was considered unlikely related to investigational product by the Investigator.

Table 61: Listing of Treatment-Emergent Adverse Events Leading to Death Safety Population)

Subject ID	IP	Baseline Disease Severity 1	Baseline Disease Severity 2	Preferred Term	Relatedness	Onset Day / Day of Death ^a
207007	OCA	On-label per USPI	Compensated	Acute respiratory failure	Not related	312 / 317
219005	OCA	Contraindicated per USPI	Decompensated	Respiratory failure	Not related	1370 / 1370
297001	OCA	Contraindicated per USPI	Decompensated	Subarachnoid haemorrhage	Not related	342 / 348
301005	OCA	Contraindicated per USPI	Decompensated	Sepsis	Not related	Unknown / 187
313002	OCA	Contraindicated per USPI	Compensated	Lower respiratory tract infection	Unlikely	128 / 183
210001	Placebo	Contraindicated per USPI	Compensated	Sarcopenia	Unlikely	1311 / 1373
219010	Placebo	Contraindicated per USPI	Compensated	Hepatocellular carcinoma	Not related	718 / 843

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.

Note: Adverse events are coded using MedDRA Version 24.0.

^a Time to onset/death from first dose of investigational product.

Source: Table 14.3.1.9.5, Table 14.3.1.9.5.1, Table 14.3.1.9.5.2, Table 14.3.1.12.6

Table 61: Listing of Treatment-Emergent Adverse Events Leading to Death Safety Population)

IP	Baseline Disease Severity 1	Baseline Disease Severity 2	Preferred Term	Relatedness	Onset Day / Day of Death ^a
OCA	On-label per USPI	Compensated	Acute respiratory failure	Not related	312 / 317
OCA	Contraindicated per USPI	Decompensated	Respiratory failure	Not related	1370 / 1370
OCA	Contraindicated per USPI	Decompensated	Subarachnoid haemorrhage	Not related	342 / 348
OCA	Contraindicated per USPI	Decompensated	Sepsis	Not related	Unknown / 187
OCA	Contraindicated per USPI	Compensated	Lower respiratory tract infection	Unlikely	128 / 183
Placebo	Contraindicated per USPI	Compensated	Sarcopenia	Unlikely	1311 / 1373
Placebo	Contraindicated per USPI	Compensated	Hepatocellular carcinoma	Not related	718 / 843

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.

Note: Adverse events are coded using MedDRA Version 24.0.

^a Time to onset/death from first dose of investigational product.

Source: Table 14.3.1.9.5, Table 14.3.1.9.5.1, Table 14.3.1.9.5.2, Table 14.3.1.12.6

Other Serious Adverse Events

In the **overall safety population**, the incidence of treatment-emergent SAEs was generally similar across treatment groups: 31.5% in the OCA group and 31.9% in the placebo group (Table 62). The most frequently reported SAEs (≥ 3 [1.8%] subjects) among OCA-treated subjects included esophageal varices hemorrhage (4 subjects [2.4%]), hepatic encephalopathy (3 [1.8%] subjects), and urinary tract infection (3 [1.8%] subjects).

There was similar exposure-adjusted incidence of esophageal varices hemorrhage, urinary tract infection, ascites, hepatic failure, and edema peripheral across treatment groups. The exposure-adjusted incidence of hepatic encephalopathy was higher in the placebo group (5 [3.0%] subjects) than the OCA group (3 [1.8%] subjects).

Other reported treatment-emergent SAEs (2 [1.2%] subjects) among OCA-treated subjects were acute kidney injury, acute respiratory failure, ascites, cerebrovascular accident, coronary artery disease, disease progression, hepatic cirrhosis, hepatic failure, edema peripheral, pruritus, sepsis, and thrombotic thrombocytopenic purpura.

Table 62: Serious Treatment-Emergent Adverse Events in ≥ 2 Subjects by Preferred Term in Descending Frequency (Safety Population, N=334)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subjects with Any Serious TEAE	53 (31.9)	53 (31.5)
Oesophageal varices haemorrhage	5 (3.0)	4 (2.4)
Hepatic encephalopathy	5 (3.0)	3 (1.8)
Urinary tract infection	1 (0.6)	3 (1.8)
Acute kidney injury	0	2 (1.2)
Acute respiratory failure	0	2 (1.2)
Ascites	4 (2.4)	2 (1.2)
Cerebrovascular accident	0	2 (1.2)
Coronary artery disease	0	2 (1.2)
Disease progression	1 (0.6)	2 (1.2)
Hepatic cirrhosis	0	2 (1.2)
Hepatic failure	2 (1.2)	2 (1.2)
Oedema peripheral	1 (0.6)	2 (1.2)
Pruritus	0	2 (1.2)
Sepsis	0	2 (1.2)
Thrombotic thrombocytopenic purpura	0	2 (1.2)
Pleural effusion	2 (1.2)	1 (0.6)
Breast cancer	2 (1.2)	0
Cholecystitis	1 (0.6)	0
Urosepsis	3 (1.8)	0
Gastrointestinal haemorrhage	3 (1.8)	0
Hepatocellular carcinoma	2 (1.2)	0
Hip fracture	2 (1.2)	0

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0.

Note: Summaries are presented as n (%): number of subjects (percentage).

Source: Table 14.3.1.8.2

In patients with **compensated disease** at baseline in Study 747-302, more patients in the placebo group (31.0%) experienced an SAE than the OCA group (24.3%) (Table 20). These events predominantly occurred in 1 patient each for any given PT. With the exception of esophageal varices hemorrhage SAEs, which were experienced by 3 patients in the OCA group and 4 patients in the placebo group, each SAE was reported by ≤ 2 patients suggesting no particular pattern or trend for SAEs in the compensated group.

Table 20: Serious Treatment-Emergent Adverse Events in ≥ 2 Patients with Compensated Disease at Baseline by System Organ Class and Preferred Term in 747-302 (Safety Population)

System Organ Class Preferred Term	Placebo (N=129) n (%)	OCA (N=136) n (%)
Patients with Any SAE	40 (31.0)	33 (24.3)
Gastrointestinal disorders	11 (8.5)	8 (5.9)
Oesophageal varices haemorrhage	4 (3.1)	3 (2.2)
Gastrointestinal haemorrhage	3 (2.3)	0
Infections and infestations	5 (3.9)	8 (5.9)
Urinary tract infection	1 (0.8)	2 (1.5)
Urosepsis	2 (1.6)	0
Hepatobiliary disorders	2 (1.6)	5 (3.7)
Hepatic cirrhosis	0	2 (1.5)
Nervous system disorders	8 (6.2)	4 (2.9)
Hepatic encephalopathy	3 (2.3)	1 (0.7)
Cerebrovascular accident	0	2 (1.5)
Respiratory, thoracic and mediastinal disorders	5 (3.9)	5 (3.7)
Pleural effusion	2 (1.6)	1 (0.7)
Blood and lymphatic system disorders	0	3 (2.2)
Thrombotic thrombocytopenic purpura	0	2 (1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (3.9)	2 (1.5)
Breast cancer	2 (1.6)	0
Renal and urinary disorders	0	2 (1.5)
Acute kidney injury	0	2 (1.5)
Skin and subcutaneous tissue disorders	0	2 (1.5)
Pruritus	0	2 (1.5)

Source: Data on File

Discontinuation due to adverse events

Adverse Events Leading to Discontinuation of Investigational Product

Overall, 62 (36.9%) subjects in the OCA group and 45 (27.1%) subjects in the placebo group had a TEAE leading to permanent discontinuation of investigational product (Table 64). With the exception of pruritus, the incidence of all TEAEs leading to discontinuation of investigational product was $\leq 5.4\%$ of subjects in any treatment group.

Table 64: Treatment-Emergent Adverse Events Leading to Discontinuation of Investigational Product in ≥ 2 Subjects by Preferred Term in Descending Frequency (Safety Population)

Preferred Term, n (%)	Placebo (N=166)	OCA (N=168)
Subjects with Any TEAE Leading to Discontinuation of IP	45 (27.1)	62 (36.9)
Pruritus	3 (1.8)	19 (11.3)
Blood bilirubin increased	9 (5.4)	6 (3.6)
Ascites	1 (0.6)	4 (2.4)
Disease progression	4 (2.4)	3 (1.8)
Drug-induced liver injury	0	3 (1.8)
Hepatic cirrhosis	2 (1.2)	2 (1.2)
Hepatic enzyme increased	2 (1.2)	2 (1.2)
Hyperbilirubinaemia	2 (1.2)	2 (1.2)
Jaundice	1 (0.6)	2 (1.2)
Thrombotic thrombocytopenic purpura	0	2 (1.2)
Hepatic encephalopathy	1 (0.6)	1 (0.6)
Bilirubin conjugated increased	2 (1.2)	0
GGT increased	2 (1.2)	0

GGT=gamma-glutamyl transferase; IP=investigational product; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0

Source: Table 14.3.1.9.1

Pruritus led to discontinuation of investigational product in 19 (11.3%) subjects in the OCA group and 3 (1.8%) subjects in the placebo group. The incidence of ascites leading to discontinuation of investigational product was higher in the OCA group (4 [2.4%] subjects) than the placebo group (1 [0.6%] subject). All cases of ascites leading to discontinuation of investigational product were observed in subjects in the contraindicated per USPI subgroup (4 [4.6%] subjects in the OCA group and 1 [1.0%] subject in the placebo group) (Table 14.3.1.9.1.1). Two subjects in the decompensated subgroup (1 [3.1%] OCA-treated subject and 1 [2.7%] placebo) experienced ascites leading to discontinuation of investigational product; all cases in the compensated subgroup (3 [2.2%] subjects) were OCA-treated subjects (Table 14.3.1.9.1.2).

Of the TEAEs leading to discontinuation of investigational product occurring in ≥ 2 subjects, DILI and thrombotic thrombocytopenic purpura (TTP) were reported only in the OCA group (3 [1.8%] subjects and 2 [1.2%] subjects, respectively). Two out of 3 cases of DILI were considered probably or definitely related to investigational product. The two cases of TTP were considered not related/unlikely related to investigational product.

Adverse Events Leading to Study Discontinuation

Overall, 29 (17.3%) subjects in the OCA group and 19 (11.4%) subjects in the placebo group had a TEAE leading to study discontinuation (Table 65). With the exception of pruritus, which had an incidence of 6.5% in the OCA group and 0.6% in the placebo group, the incidence of all TEAEs leading to study discontinuation was $\leq 2.4\%$ for any treatment group.

Table 65: Treatment-Emergent Adverse Events Leading to Study Discontinuation by Preferred Term in Descending Frequency (Safety Population [N=334])

Preferred Term, n (%)	Placebo (N=168)	OCA (N=166)
Subjects with Any TEAE Leading to Study Discontinuation	19 (11.4)	29 (17.3)
Pruritus	1 (0.6)	11 (6.5)
Blood bilirubin increased	2 (1.2)	4 (2.4)
Ascites	0	2 (1.2)
Disease progression	3 (1.8)	2 (1.2)
Jaundice	0	2 (1.2)
Anal incontinence	0	1 (0.6)
Arthralgia	1 (0.6)	1 (0.6)
Cerebrovascular accident	0	1 (0.6)
Drug-induced liver injury	0	1 (0.6)
Dry mouth	0	1 (0.6)
Hepatic cirrhosis	1 (0.6)	1 (0.6)
Hypertransaminasaemia	0	1 (0.6)
Subarachnoid haemorrhage	0	1 (0.6)
Thrombotic thrombocytopenic purpura	0	1 (0.6)
Urticaria	0	1 (0.6)

OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: Adverse events are coded using MedDRA Version 24.0

Source: Table 14.3.1.9.2

Laboratory findings

- Hematology and Coagulation*

No clinically significant changes over time or across groups were observed with respect to hematology and coagulation parameters. Across treatment groups, the majority of subjects were in the normal range for platelets. No meaningful differences in shifts from Normal to High or Normal to Low were observed for any hematology parameter between treatment groups.

- Serum Chemistry*

Already discussed in the efficacy section.

Vital Signs, Physical Findings, and Other Observations Related to Safety

No clinically meaningful changes over time or across groups were observed with respect to vital signs.

There were no clinically meaningful changes in ECG parameters across the treatment groups. There were no apparent differences in the number of subjects in the OCA and placebo groups with new onset clinically significant (CS) abnormal ECG results.

No clinically meaningful changes over time or across groups were observed with respect to physical examination

Safety in special populations

Elderly population

No safety concerns specific to elderly patients have been identified based on the safety profile from Study 747-302. As PBC is a chronic disease usually diagnosed in the fourth and fifth decades of life, it is

anticipated that a substantial number of patients in the ≥ 65 -year age group will have long-term treatment with OCA.

Hepatic impairment

Per the EU SmPC, Ocaliva is contraindicated in patients with:

- Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event
- Complete biliary obstruction

Exposure to OCA and its active conjugates increases significantly in patients with moderate to severe hepatic impairment (CP-B and -C), and these patients may be at higher risk of liver injury.

Renal impairment

OCA is primarily eliminated through the feces and only minimally eliminated by the kidneys, and therefore renal impairment was not expected to meaningfully influence the PK of OCA. No specific clinical studies have been conducted in patients with PBC who had renal impairment. In a Phase 1 clinical study conducted in healthy patients using radiolabeled OCA, less than 3% of the dose was eliminated in urine (Study 747-113). These results are consistent with the lack of measurable OCA and its conjugates in urine in other previously conducted Phase 1 clinical studies (747-101 and 747-102).

Per the EU SmPC, in a dedicated single-dose pharmacokinetic study using 25 mg of obeticholic acid, plasma exposures to obeticholic acid and its conjugates were increased by approximately 1.4- to 1.6-fold in patients with mild (modification of diet in renal disease [MDRD] $\text{eGFR} \geq 60$ and < 90 mL/min/1.73 m²), moderate (MDRD $\text{eGFR} \geq 30$ and < 60 mL/min/1.73 m²) and severe (MDRD $\text{eGFR} \geq 15$ and < 30 mL/min/1.73 m²) renal impairment compared to patients with normal renal function. This modest increase is not considered to be clinically meaningful.

Based on these data, it is highly unlikely that renal impairment will affect the PK or safety profile of OCA and therefore no dose adjustment of OCA is required for renal impairment.

Study 747-401

Methods – analysis of data submitted

Number of Subjects (planned and analyzed):

Planned for inclusion: 50 subjects (25 subjects in the OCA group and 25 subjects in the placebo group). Enrolled and randomized: 22 subjects (10 subjects in the OCA group and 12 subjects in the placebo group).

Analyzed: 22 subjects in the Randomized Population, 22 subjects in the Intent-to-Treat (ITT) Population; 22 subjects in the Safety Population; 6 subjects in the Pharmacokinetic Population, and 12 subjects in the Non-Covid-19 Impacted Population.

Safety analyses (adverse events [AEs], exposure to study treatment, clinical labs, electrocardiograms, vital signs, and physical examinations) were performed using the Safety Population including by treatment groups and pooled across all active dose levels. No inferential comparison of safety endpoints was performed. AEs were mapped to preferred terms and system organ classes using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0. Categories of AEs of special interest (AESIs) included hepatic (decompensation/disorder), cardiovascular, renal, pruritus, fatigue, dyslipidemia, and cholecystitis/cholelithiasis.

Results

In the Double-Blind Phase and Double-Blind Extension Phase, the overall mean duration of exposure to study treatment was 296.5 days in the OCA and 233.4 days in the placebo groups. In the Safety Population, all subjects in the OCA and placebo groups reported at least 1 treatment-emergent adverse event (TEAE) during the Double-Blind Phase and Double-Blind Extension Phase of the study.

The most frequently reported TEAEs ($\geq 30\%$) were ascites, esophageal varices hemorrhage, pneumonia, urinary tract infection, pruritus, and anemia. The majority of TEAEs in both treatment groups were reported to be mild (Grade 1) or moderate (Grade 2) in severity.

Study treatment or study discontinuations occurred in 5 (50.0%) subjects in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) subjects in the OCA and 4 (33.3%) subjects in the placebo group. The most common TEAE leading to study treatment interruption was ascites (2 [20.0%] subjects in OCA and 1 [8.3%] in placebo groups).

A total of 7 (70.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced serious adverse events (SAEs). In general, the nature of SAEs is consistent with the underlying advanced liver disease in this patient population.

A total of 5 deaths were reported (3 subjects in the placebo group [hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal carcinoma] and 2 subjects in the OCA group [multiple organ dysfunction syndrome and cardiac arrest]), which were all considered by the Investigator as not related or unlikely related to the study treatment. The case of death from clear cell renal cell carcinoma occurred within the study period; however, was reported after database lock.

Overall, 9 (90.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced an AESI.

Overall, no subjects had clinically relevant abnormal electrocardiogram (ECG) findings at Week 48 or Double-Blind Extension Month 12 across treatment groups.

Several mean baseline laboratory values were out of range, consistent with patients with PBC with moderate to advanced cirrhosis. These values did not change meaningfully over time following multiple dose administration of OCA or placebo; additionally, no meaningful discernible differences over time were noted between OCA and placebo.

There were no clinically relevant changes from baseline (blood pressure, heart rate, temperature, and weight) in OCA group compared with placebo. No additional physical examination findings were observed, and no trends were detected.

Post-marketing safety experience

The most recent PSUR/PBRER for OCA (Ocaliva; PBC) summarizes available safety data received by the Sponsor from worldwide sources during the reporting interval from 27 May 2021 to 26 May 2022 (Module 5.3.6, PBRER-08). The estimated cumulative patient exposure from marketing experience is over 28000 patient years.

The currently approved EU Risk Management Plan (RMP; Version 1.3 revised in June 2021) describes the important potential risks of liver injury and atherosclerotic cardiovascular events secondary to changes in lipids. However, the risk of liver injury was recategorized as an important identified risk during the reporting period (CCDS v.3.0). The RMP will be updated to reflect this change at the next regulatory opportunity. Additionally, in postmarketing safety reports, liver disorder events have been reported in patients taking OCA. Although information for postmarketing reports is often incomplete, out of an abundance of caution and in the interest of public health, four ADRs related to liver injury were added to the SmPC. The ADRs included: Hepatic failure, Bilirubin increase, Jaundice, and Cirrhosis (Module 5.3.6, PBRER-08).

The prevention of liver injury in patients with PBC receiving OCA requires a careful assessment of the status of the liver disease before OCA therapy starts. Continued monitoring during the course of treatment with appropriate dose adjustments is recommended. Updated labeling contraindicating the use of OCA in patients with hepatic decompensation, or a prior decompensation event will reduce the incidence and severity of the identified risk of liver injury. Therefore, the impact on public health is estimated to be low.

The lipid abnormalities may be managed in patients with PBC receiving OCA, by monitoring and managing lipid levels and other CVD risk factors.

The important identified and potential risks may be mitigated through careful patient monitoring, provider education, and patient outreach.

OCA remains the only approved treatment to meet the medical need of appropriate PBC patients who do not respond or are intolerant to UDCA. The benefit conferred by OCA exceeds the important identified and potential risks associated with OCA.

Discussion on safety

The main source of safety evidence is derived from Study 747-302. In addition, supportive evidence from Study 747-301 (LTSE) has been submitted.

Post-marketing experience is also provided from approximately 4518 patients who received at least one dose of OCA in clinical trials, including 634 patients with primary biliary cholangitis.

OCA Exposure in Study 747-302

The mean durations of exposure for the OCA and placebo groups in the Safety population (334 subjects with PBC, 166 in placebo and 168 in OCA) were 876 days and 745 days, respectively. The mean durations of exposure for the subset of patients with compensated disease (265 subjects, 129 in placebo and 136 in OCA) were: 951 days for the OCA group (129 subjects) and 814 days for the placebo group (136 subjects). The mean durations of exposure for patients with decompensated disease were: 561 days for the OCA group and 505 days for the placebo group.

Overall, patients in Study 747-302 reflected an advanced disease population compared to previous PBC studies (i.e., 747-301): 69 (21%) patients had decompensated disease at baseline and are considered contraindicated per the CCDS and SmPC revision that occurred while the study was ongoing (32 patients in the OCA group and 37 patients in the placebo group). The MAH provided the baseline characteristics of the patients excluded from the overall safety analysis, confirming that these patients fulfil criteria for contraindication for OCA treatment according to the EU SmPC. Patients with compensated disease in Study 747-302 had higher baseline ALP, total bilirubin, Model for End-Stage Liver Disease (MELD), and Rotterdam criteria compared to patients in Study 747-301, but a shorter duration of PBC (mean 7.7 years placebo - 7.5 years OCA in Study 302 vs 8.3 years placebo - 8.3 years OCA titration - 9.2 years OCA 10 in Study 301) and less patients were on current UDCA use at baseline (87-85% placebo and OCA, respectively, in Study 302, vs 92-93% across treatment arms in Study 301).

The safety population included 334 subjects with PBC, who received at least 1 dose of investigational product (166 subjects received placebo and 168 subjects received OCA). Ninety-seven percent (97%) of patients in each treatment group received daily dose of OCA, while 3% received weekly doses. Treatment compliance was not particularly high, with most patients both in placebo (67.5%) and OCA (66.1%) less than 80% compliance, which does not speak in favour of a particularly good tolerability. In addition, the number of subjects who required decreased dose at least once was higher in OCA treated group: 41.0 % in placebo and 51.2% in OCA. A high proportion of subjects in both treatment groups

required dose adjustments at least once, dose interruptions/discontinuations, but this information is only presented for CP-B or CP-C patients at any time during the study. The MAH has presented information for the overall population and for both the subset of compensated and decompensated patients at baseline and raises no concerns. The high proportion of patients that required dose changes can be explained by the implementation of the approved SmPC posology at the time of MA in the ongoing clinical trial 747-302. These changes affected both subjects non-cirrhotic/CPA and subjects with CP B/C, which explains the high and comparable results across subpopulations. No relevant differences were observed in the proportion of patients requiring any drug holidays, but the actual number of drug holidays required in each treatment group has not been provided, what would be an interesting piece of information to know about the actual tolerability of treatment. This should be provided (OC). The only exception, where a higher proportion of any drug-holiday was noted, was in OCA-treated subjects with hepatic decompensation (56.3% OCA vs 32.4% placebo). These subjects are now contraindicated in the SmPC.

Overall, 62 (36.9%) subjects in the OCA group and 45 (27.1%) subjects in the placebo group had a TEAE leading to permanent discontinuation of investigational product. With the exception of pruritus (11.3% OCA vs 1.8% placebo), the incidence of all TEAEs leading to discontinuation of investigational product was $\leq 5.4\%$ of subjects in any treatment group. Other AEs leading to treatment discontinuation more frequently in OCA vs placebo were: ascites, DILI, and TTP. Similarly, more subjects discontinued study due to AEs in OCA treated group: 17.3% vs 11.4% in placebo, mostly driven by pruritus, blood bilirubin increased, ascites, jaundice, DILI, cerebrovascular accident, TTP, subarachnoid haemorrhage, hypertransaminasemia.

In the **total safety population**, higher rates of events were reported for OCA compared to placebo, including any TEAE (96.4% OCA vs 95.2% placebo), any TEAE leading to discontinuation (36.9% OCA vs 27.1% placebo), any TEAE leading to study discontinuation (17.3% OCA vs 11.4% placebo), treatment related TEAE (79.2% OCA vs 66.9% placebo), treatment related TEAE leading to discontinuation (20.8% OCA vs 12.7% placebo), severe TEAE (51.2% OCA vs 39.2% placebo) and TEAEs leading to death (3.0% OCA vs 1.2% placebo), which is very concerning. Similar rates of treatment-emergent SAE were reported 31.5% OCA vs 31.9% placebo. Overall, 162 (96.4%) subjects in the OCA group had a total of 2349 TEAEs and 158 (95.2%) in the placebo group had a total of 1815 TEAEs. Consistent with earlier studies, pruritus was the most frequently reported treatment-related TEAE and the most common TEAE leading to discontinuation of investigational product.

When considering only the subset of **compensated patients**, the incidence of patients who reported a treatment-emergent adverse event (TEAE) was similar across treatment groups: 95.6% patients in the OCA group and 94.6% in the placebo group. The majority of TEAEs were mild and moderate in severity. The incidence of severe TEAEs was higher in the OCA group (47.1%) than the placebo group (36.4%). Treatment-related TEAEs were reported by 78.7% patients in the OCA group and 62.0% patients in the placebo group. The incidence of TEAEs leading to discontinuation of investigational product was higher in the OCA group (33.1%) than the placebo group (27.9%). Consistent with earlier studies, pruritus was the most frequently reported treatment related TEAE and the most common TEAE leading to discontinuation of investigational product. In the compensated group, the incidence of TEAEs leading to death was similar across treatment groups (2 patients each in the OCA and placebo group). All TEAEs leading to death were assessed by the investigator as not related or unlikely related to investigational product. The incidence of SAEs in the compensated group was numerically lower in OCA-treated patients (24.3%) than the placebo group (31.0%).

No major differences in the general safety profile observed in the overall safety population and the subset of patients with compensated disease, not totally unexpected considering that this subgroup accounts for approximately 80% of the overall population. Indeed, even in the compensated subset of patients, a higher incidence of TEAE, severe TEAE (nearly half of patients), treatment related TEAE, and TEAE

leading to treatment discontinuation were seen in the OCA treated group. The high rate of TEAE, including severe TEAEs and discontinuations due to TEAE speaks against the acceptable tolerability for OCA claimed by the MAH.

The high rate of **severe TEAEs** both in the general safety population (51.2% OCA vs 39.2% placebo) and in the subset of compensated patients (47.1% vs 36.4%) is noted. This is mainly driven by pruritus TEAEs, but also by a higher rate of severe gastrointestinal disorders (oesophageal varices haemorrhage, abdominal pain, vomiting, melaena, and ascites), infections, hepatobiliary disorders (hepatic cirrhosis, hepatic failure), acute respiratory failure, back pain, and cerebrovascular accident are reported in OCA treated patients, which is concerning.

In the overall safety population, like the safety profile in the compensated group, the most frequently reported TEAE was pruritus, which had a higher incidence in the OCA group (78.6%) than in the placebo group (51.2%). In addition to pruritus, other TEAEs in $\geq 10\%$ of OCA-treated subjects and were reported more frequently in the OCA group compared with placebo included peripheral oedema (18.5% in the OCA group and 10.8% in the placebo group); abdominal pain which includes the following preferred terms: Abdominal Pain Upper PT (14.9% in the OCA group and 7.2% in the placebo group), Abdominal Pain PT (12.5% in the OCA group and 10.8% in the placebo group) and Abdominal Pain Lower PT (4.8% in the OCA group and 1.2% in the placebo group); nausea (14.9% in the OCA group and 12.7% in the placebo group); headache (13.7% in the OCA group and 12.7% in the placebo group); constipation (11.3% in the OCA group and 6.0% in the placebo group); and nasopharyngitis (10.7% in the OCA group and 8.4% in the placebo group). Overall, higher incidences of AEs by SOCs were reported in OCA treated subjects for the following: skin and subcutaneous tissue disorders, gastrointestinal disorders, investigations (BR, ALT, AST increments), nervous system disorders, blood and lymphatic disorders, and psychiatric disorders.

Also a numerical imbalance was seen in the **incidence of deaths** across treatment groups. A total of 7 subjects had a TEAE leading to death (5 in OCA-treated subjects: acute respiratory failure, respiratory failure, subarachnoid haemorrhage, sepsis, and lower respiratory tract infection; and 2 in placebo-treated subjects: sarcopenia and hepatocellular carcinoma). Deaths occurred in both compensated (4 cases, 2 placebo vs 2 OCA) and decompensated patients (3 cases, all in OCA), were considered in most cases not-related (vs 2 unlikely related in the compensated group).

In patients overall, incidence of **treatment-emergent SAEs** was generally similar across treatment groups (31.5% in the OCA group and 31.9% in the placebo group). The most frequently reported SAEs (≥ 3 [1.8%] subjects) among OCA-treated subjects included oesophageal varices haemorrhage (4 subjects [2.4%]), hepatic encephalopathy (3 [1.8%] subjects), and urinary tract infection (3 [1.8%] subjects). Treatment-emergent SAEs reported more frequently in OCA were acute kidney injury (2 [1.2%] subjects), acute respiratory failure (2 [1.2%] subjects), cerebrovascular accident (2 [1.2%] subjects), coronary artery disease (2 [1.2%] subjects), disease progression (2 [1.2%] subjects), hepatic cirrhosis (2 [1.2%] subjects), pruritus (2 [1.2%] subjects), sepsis (2 [1.2%] subjects), and thrombotic thrombocytopenic purpura (2 [1.2%] subjects).

In patients with compensated disease at baseline in Study 747-302, more patients in the placebo group (31.0%) experienced an SAE than the OCA group (24.3%). These events predominantly occurred in 1 patient each for any given PT. With the exception of oesophageal varices haemorrhage SAEs, which were experienced by 3 patients in the OCA group and 4 patients in the placebo group, each SAE was reported by ≤ 2 patients suggesting no particular pattern or trend for SAEs in the compensated group. However, the higher incidence of SAEs of hepatobiliary disorders (3.7% OCA vs 1.6% placebo) is worrisome, as it is the higher incidences of infections SAEs (5.9% OCA vs 3.9% placebo), and SAEs of cerebrovascular accidents (2(1.5%) vs 0 in OCA and placebo, respectively), thrombotic thrombocytopenic purpura

(2(1.5%) vs 0 in OCA and placebo, respectively), acute kidney injury (2(1.5%) vs 0 in OCA and placebo, respectively) and pruritus (2(1.5%) vs 0 in OCA and placebo, respectively).

TEAEs that were prespecified as **adverse events of special interest (AESIs)** in Study 747-302 included Cardiovascular, Cholecystitis/cholelithiasis, Dyslipidemia, Hepatic, Pruritus, and Renal TEAEs. The overall incidence of TEAEs of special interest was 82.5% patients in placebo vs 90.5% subjects in OCA treated groups. The majority reported treatment emergent AESIs were mild or moderate in severity (60.8% subjects in OCA treated group vs 59.6% subjects in placebo reported M-M AESIs), with a numerical imbalance in the incidence of moderate AESIs disfavoring OCA treatment (29.9% OCA vs 34.3%). Notably, severe treatment emergent AESIs were reported by a high portion of the study population in both treatment groups, but the rate in OCA treated group is almost double than that reported in placebo (38.7% OCA vs 22.99% placebo). In particular, a higher incidence of cardiovascular (9.5% OCA vs 4.2% placebo), pruritus (79.2% vs 51.8%) and renal AESI (10.1% OCA vs 7.8% placebo) were reported for OCA treated patients. When excluding patients with decompensated disease, a similar pattern is seen: the incidence of treatment emergent AESIs was 88.2% in the OCA treated group and 79.8% in placebo, with cardiovascular AESIs (8.1% in OCA vs 3.9% placebo), pruritus (80.1% OCA vs 51.9% placebo), and renal AEs (8.8% OCA vs 6.2% placebo), more commonly reported in OCA treated patients.

-The incidence of **CV AESI** in the overall safety population was 9.5% vs 4.2% in placebo. For the compensated subset, a similar pattern of higher rates of AEs was seen for OCA 8.1% vs placebo treated patients (3.9%). The following cardiovascular treatment-emergent AESIs were reported in 2 (1.2%) subjects each in the OCA group: angina pectoris, cerebrovascular accident, coronary artery disease, myocardial infarction, subarachnoid haemorrhage, and thrombotic thrombocytopenic purpura, and venous thrombotic events. All suspected MACE, including cardiovascular death, myocardial infarction, and stroke were independently adjudicated in a blinded fashion. In the Safety population, 4 (2.4%) subjects in the OCA group reported a MACE vs none patients in placebo. The median time to first occurrence of MACE in the OCA group was 394.5 days (p-value=0.045). In patients with compensated disease, the incidence rate for adjudicated events for Core major adverse cardiovascular events (MACE) was low (2 patients in the OCA group and none in the placebo group). Although most CV AEs were considered not related to OCA by investigators, the higher rate of CV adverse events in OCA treated patients, including higher rates of adjudicated MACE, both in the overall safety population and in the compensated subset, is worrisome. Contrary to previous findings, dyslipidaemia was less frequently reported in OCA treated patients in this study. However, no information is presented for changes in HDL cholesterol. The increased incidence of CV events, including MACE, in patients treated with OCA is a major concern.

-The incidence of **cholecystitis/cholelithiasis TEAEs** was 5.4% in both treated groups, but a higher incidence of cholelithiasis-related events was seen in the OCA treated group. For the compensated subset, a similar pattern was seen: 5.1% OCA-treated and 6.2% placebo-treated patients experienced a cholecystitis/cholelithiasis TEAEs. Of these, 4 patients reported cholecystitis/cholelithiasis SAEs (3 patients in the OCA group: 2 patients with cholelithiasis and 1 patient with bile duct stone; 1 patient in the placebo group with cholecystitis). The MAH was invited to present comparative tabulated results of these cholelithiasis-related TEAE for the overall safety population vs decompensated and compensated patients and discuss if a higher incidence should be expected in patients with a more advance disease. Based on the information provided by the MAH, a potential association between treatment with OCA and this TEAE appears at least a reasonable possibility and therefore it should be included in the SmPC (**OC**).

-The incidence of **hepatic AESI** was higher in placebo 58.4% vs OCA (47.6%), but a higher incidence of blood bilirubin increased, varices oesophageal and ascites are reported for OCA treated patients, including a higher incidence of DILI (8.3% vs 2.4%). For the compensated subset, a similar pattern is

seen: 42.6% liver AESIs in OCA vs 56.6% in placebo, also with a higher incidence of portal hypertensive gastropathy (8.3% OCA vs 4.2% placebo) and DILI (2.4% OCA vs 0 placebo), which is of concern as these events appear not to be restricted to patients with severe liver disease.

When discussing the incidence of liver transplant and deaths events (adjudicated by an Hepatic Outcome Committee, HSAC), the information provided is quite confusing given the number of analyses conducted and lack of tabulated results, but all point into the same direction: a total of 60 liver transplants and deaths in the overall safety population were retrospectively adjudicated in a blinded manner by the HSAC (32 [19.0%] subjects OCA vs 28 [16.9%] placebo, considered possibly treatment related in 12.5% OCA vs 3.6% placebo). Less than half occurred in patients with decompensated liver disease (26), and the remaining 34 occurred in patients with compensated disease (20 in OCA vs 14 in placebo). This is considered a matter of major concern, given that the aim of OCA treatment is just the opposite, to prevent these clinical outcomes. The MAH was invited to provide these results, tabulated, for the overall study population, for the subset of patients with compensated disease and also for patients with decompensated conditions, and discuss on the clinical relevance of these findings in the compensated population bearing in mind that the demonstrated benefit of OCA treatment is limited to ALP reductions. However, an increased incidence of liver transplant and death events in OCA vs placebo treated subjects is observed across the spectrum of PBC populations analysed and therefore the existing concern remains.

-**Pruritus** was significantly higher in OCA (79.2%) vs placebo 51.8% in the overall safety population. For the compensated subset, mild to moderate pruritus was the most commonly reported TEAE. In patients with compensated disease, 80.1% patients in the OCA group and 51.9% patients in the placebo group reported pruritus. The incidence of pruritus SAEs was low in the compensated group: 2 patients in the OCA group and none in the placebo group. The majority of pruritus events, regardless of severity, were experienced within the first few months of treatment. In the compensated group, pruritus events led to permanent discontinuation of the investigational product in 12.5% patients in the OCA group and 1.6% in the placebo group. Among those patients experiencing any pruritus, most were able to continue treatment with OCA. Of those patients able to tolerate pruritus and remain on investigational product, the majority (approximately 70%) had used some form of management strategy for their pruritus, with treatment interruption appearing to be the most effective approach. Management and dosage adjustment for intolerable pruritus are addressed in the SmPC.

-**Renal AESI** were also reported more frequently in patients treated with OCA, both for the overall safety population (17 (10.1%) subjects in the OCA and 13 (7.8%) subjects in the placebo groups, with acute kidney injury reported by 3.0 % in OCA vs 1.2% in placebo treated patients), and for the subset of patients with compensated disease (8.8% OCA-treated and 6.2% placebo-treated patients experienced a renal AESI, with acute kidney injury reported by 2.2% in OCA and 1.6% in placebo treated patients). In addition, it has been reported that exposure to OCA was associated with a small reduction in estimated glomerular filtration rate (eGFR) in a NASH clinical study. The higher incidence of renal events in patients treated with OCA regardless of the severity of the underlying liver disease is worrisome.

The safety of OCA in special populations deserved further discussion, particularly, safety data in the elderly population should be provided and any relevant differences with previous observations will need to be discussed. Same would apply for patients with renal impairment, bearing in mind the increased risk for renal events during OCA treatment. The overall incidence of TEAEs, serious & severe TEAEs, AE leading to discontinuation and leading to death (tabulated for the different populations analysed) should be presented, including a discussion on whether a more toxic and/or less tolerated safety profile would be expected in ≥ 65 years subjects or in subjects with CKD Stage 2/3. A proposal to reflect this information in the SmPC Section 4.8 is also awaited. (OC)

The MAH recognizes there is some potential safety risk given the imbalance observed in the overall safety population of Study 747-302 and cannot exclude a contributory role of OCA. Therefore, the MAH

has proposed to further restrict the SmPC indicated population to patients with PBC without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or a prior decompensation event. This analysis was not pre-specified and the newly proposed target population for OCA is data driven by an otherwise limited subset of early stage PBC subjects of Study 747-302 (68 OCA vs 61 placebo). Thus, it is uncertain if the observed results in this subset of the study population represent an accurate estimation of their safety profile and thus if a “more benign” safety profile can be firmly concluded in them.

A reduction in the overall incidence of serious TEAEs (in newly proposed indication 18.5% OCA vs 25% placebo compared to the overall safety population 31.5% OCA vs 31.9% placebo) and TEAE leading to death (1.2% OCA vs 0 placebo in the restricted indication vs 3.0% OCA and 1.2% in the overall safety population) in the restricted PBC population is observed, with lower rates of serious TEAEs in OCA treated patients. The incidence of TEAEs leading to death remains slightly higher in OCA: 3.0% OCA vs 1.2% placebo in the overall population vs 1.2% OCA vs 0 placebo, but the number of events is too limited to firmly conclude. The lower incidence of serious TEAEs in the restricted PBC population is not totally unexpected considering that most serious TEAEs are related to the severity and progression of the underlying disease. By contrary, the incidence of severe TEAEs (45.7% OCA vs 32.4% placebo), treatment related TEAEs (75.3% OCA vs 55.9% placebo), TEAE leading to IP withdrawal (33.3% OCA vs 26.5% placebo), to dose reductions (24.7% OCA vs 10.3% placebo), dose interruptions (25.9% OCA vs 25.0% placebo) or to treatment discontinuation (14.8% OCA vs 19.1% placebo) do not show relevant changes compared to those reported for the overall safety population. Indeed, most of them remain higher for OCA treated subjects, which is not reassuring. Incidence of thrombotic and cardiovascular disorders (6.2% OCA vs 2.9% placebo), renal AESI (9.9% OCA vs 5.9% placebo), including events of AKI and renal failure, cholelithiasis (3.7% OCA vs 1.5% placebo), portal hypertensive gastropathy (3.7% OCA vs 0 placebo), DILI (2.5% OCA vs 0 placebo), liver transplant (1 case each in the early stage PBC population) or all-cause deaths (8 events in OCA vs 2 in placebo) are still observed more frequently in OCA treated subjects compared to placebo treated patients even in the newly proposed subset of early stage PBC patients. The number of events is sometimes too limited to firmly conclude, but the imbalance observed in the overall safety population remains in this restricted early stage PBC subset, which is concerning. Moreover, treatment is associated with significantly high incidences of pruritus (81.5% in OCA vs 47.1% placebo, which lead to treatment interruption in 23.5% OCA subjects and pharmacological treatment was required by 54.3% subjects in OCA (vs 7.4% and 27.9%, respectively, in placebo). OCA treatment in the newly proposed restricted population was also associated with higher gastrointestinal disorders (63% OCA vs 50% placebo), including higher rates of severe cases, and fatigue (9.9% OCA vs 7.4% placebo). All of them may have a significant negative impact in patient's health condition. It is also noted that the similar rates of hepatic TEAEs observed in OCA and placebo treated subjects in the newly proposed early stage PBC population raise doubts on the actual benefit of treatment since lower rates might have been expected by a treatment aimed to modify the disease progression.

The incidence of renal TEASIs remains rather consistent across OCA-treated subjects in the overall study population (10.1%), and in subjects with earlier stage PBC both compensated (per current SmPC) (8.8%) and proposed SmPC indicated (9.9%), but it is lower than in decompensated subjects currently contraindicated per SmPC (15.6%). It is also noted that systematically, the incidence of renal TEASIs, including renal events that manifest as renal impairment, is numerically higher in OCA treated group vs placebo-groups regardless of the PBC population analysed, i.e., the overall study population or any of the restricted subsets of milder PBC subjects. The possible contribution of OCA in the occurrence of renal TEASI events, including severe, serious, and fatal events, cannot be ruled out. Incidence rates adjusted by exposure time for the relevant renal TEASI events should be provided (**OC**).

There is a need to improve information in the SmPC concerning all these risks in Section 4.4 and 4.8. The current proposal is insufficient and the justification of the lower rates in the restricted indication is

not accepted(OC).

Conclusion

Study 747-302 show a more concerning overall safety profile as compared to that reported in the initial submission, given the higher incidence rates of all types of TEAEs overall and as compared to placebo treated patients. OCA treated patients showed a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death, both in the general safety population and the subset of patients with compensated liver disease, which does not speak in favour of a favourable and well tolerated safety profile. In addition, the higher rates observed in OCA treated patients for some relevant AESI like cardiovascular events (including adjudicated MACE), renal events (including AKI), DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events, both in the overall safety population and for the subset of patients with compensated disease are a matter of major concern. Even if an apparent less toxic safety profile is seen in the proposed restricted subset of PBC patients, taking these results with caution due to lack of pre-specification and potential loss of precision in the estimation, still an increased toxicity and poor tolerability of OCA treatment is noted in the subset of patients with an early stage, mostly asymptomatic and slow progressive condition. The anticipated long-term exposure in clinical practice and difficulties to identify and exclude patients at risk of relevant events, add further concerns. The acceptability of the identified risks, and remaining safety uncertainties, in an otherwise asymptomatic or mildly symptomatic early stage PBC population, deserves further discussion considering the demonstrated benefits.

9. PRAC advice

N/A

10. Changes to the Product Information

N/A

11. 1st Request for supplementary information

Major objections

Clinical aspects

Benefit/risk

1. The positive B/R of Ocaliva, originally demonstrated on a biochemical (intermediate) marker, is not confirmed by the updated results on relevant clinical outcomes submitted within the current procedure. The confirmatory study (747-302) has failed to demonstrate a **clinical benefit** of OCA treatment in reducing the risk of relevant clinical outcomes in patients with PBC, regardless of liver disease severity (results consistent for the primary composite endpoint and its components as well as for the secondary outcomes and further confirmed by sensitivity analyses). Moreover, external control analyses using RWE cannot counterbalance or even overcome failed results of a confirmatory RCT. Consequently, the benefit of OCA in the treatment of PBC is deemed not demonstrated.

A more concerning **overall safety profile** as compared to that reported in the initial submission is shown in both the general safety population and the subset of patients with compensated liver

disease. OCA treated patients had a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death; higher rates for relevant AESIs like cardiovascular events, including adjudicated MACE, renal events including AKI, DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events. The hepatic and CV AE profile appears particularly worrisome.

Therefore, the **benefit/risk of OCA in the current indication is considered negative.**

Safety

2. The hepatic and CV AE profile appears particularly concerning. In addition to the broad discussion requested above, the MAH should specifically discuss the following:
 - a) The observed higher incidence of DILI and other hepatic AEs (e.g. blood bilirubin increased, varices oesophageal, ascites, portal hypertensive gastropathy) in OCA treated patients, including those with compensated liver disease, is of concern. Please comment, including the possibility to implement any risk minimisation measures.
 - b) The higher rate of CV AEs in OCA treated patients, including higher rates of adjudicated MACE, both in the overall safety population and in the compensated subset, is worrisome, even if most events were considered not related to OCA by the investigators. Contrary to previous findings, dyslipidaemia was less frequently reported in OCA treated patients in this study. However, no information is presented for changes in HDL cholesterol. The increased incidence of CV events, including MACE, in patients treated with OCA is a major concern and deserves further discussion on possible associated factors, including changes in lipid parameters among others.

Other concerns

Clinical aspects (efficacy and safety)

Study 747-301 (LTSE)

3. Patients randomized to placebo in Study 747-301 crossed over to OCA treatment and all patients were followed for up to an additional 5 years (747-301 LTSE). A more comprehensive presentation of the relevant efficacy and safety results (focusing of SAEs and AESIs) of this study should be provided.

Study 747-401

4. The MAH is invited to present the safety results for this study in more detail and tabulated, including details of the nature of severe, serious TEAEs and AESIs, those leading to discontinuation and to death.
5. OCA treatment is contraindicated in "*Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see section 4.4)*", due to the increased risk of hepatic failure/decompensation events, including fatal cases. Measures have been put in place to minimise this risk, i.e. a contraindication in section 4.3 and precautionary wording in section 4.4 of the SmPC to include new information about hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, occurring with obeticholic acid treatment in patients with PBC with cirrhosis, either compensated or decompensated. Section 4.8 ('Undesirable effects') was also updated to include hepatobiliary disorders in the tabulated list of adverse reactions. It is uncertain if these measures are currently (effectively) in place in clinical practice and sufficient to minimise these risks, but probably it is too early to know. The MAH is invited to comment, and should commit to monitor the

actual effectiveness of this RMM in clinical practice.

Study 747-302

6. The MAH should provide the baseline characteristics of the patients excluded from the overall safety analysis of Study 747-302, and confirm that these patients fulfil criteria for contraindication for OCA treatment according to the EU SmPC.
7. Secondary endpoint analyses show that only a total of 21 (6.3%) of patients enrolled in Study 747-302 met the primary endpoint as defined in the pivotal Phase 3 Study 747-301 of an ALP $<1.67 \times$ ULN and total bilirubin $\leq$ ULN and ALP decrease from baseline of $\geq 15\%$. Indeed, the rate of responders was substantially lower compared to that previously reported and this was the case in both treatment arms, but rather noticeable in the OCA treated group (OCA 10.1% vs 2.4% placebo in Study 747-302 vs OCA 34.0% vs 7% placebo in Study 747-301). No statistically significant differences were reported, adding even further uncertainties to the actual efficacy of OCA in the treatment of PBC. The MAH should present a detailed description of changes in relevant liver biochemical parameters and explain the observed differences, considering that Study 747-302 included a more advanced liver disease population likely representative of the actual target in clinical practice.
8. The MAH justifies the need for the EC group by stating that the validity of ITT analyses depends on successfully balancing randomisation and maintaining treatment and placebo allocation throughout the trial. Additional arguments are based on the claim that the reported results in Study 747-302 were underpowered and potentially biased for a list of reasons discussed below. These arguments cannot be accepted. Overall, the observed differences in the estimation of the treatment effect for the primary endpoint using the primary randomisation and the IPCW, demonstrate the high risk of bias associated to the reported analyses based on the weighting procedure, as compared to the results of Study 747-302. All results based on the EC are considered to have the same problem of bias. Furthermore, in addition to all the issues discussed above, the analyses resulting from the comparisons with EC should be understood in the context of a pivotal trial in which the primary analysis failed, leaving no alpha for confirmatory testing. As a result, any further analyses should be considered exploratory only. The MAH is invited to further justify the validity of these analyses considering the CHMP arguments.
9. A high proportion of subjects in both treatment groups required dose adjustments at least once, dose interruptions/discontinuations, but this information is only presented for CP-B or CP-C patients at any time during the study. The MAH is invited to provide this information of the overall safety population, and for both the subset of compensated vs decompensated patients at baseline.
10. The MAH is invited to provide tabulated results of the overall safety profile of OCA in the total safety population and in the two subsets of patients compensated and decompensated, to better illustrate any existing differences in the safety profile of these patients.
11. The high rate of severe TEAEs both in the general safety population (51.2% OCA vs 39.2% placebo) and in the subset of compensated patients (47.1% vs 36.4%) is noted. This is mainly driven by pruritus TEAEs, but also by a higher rate of severe gastrointestinal disorders (oesophageal varices haemorrhage, abdominal pain, vomiting, melaena, and ascites), infections, hepatobiliary disorders (hepatic cirrhosis, hepatic failure), acute respiratory failure, back pain, and cerebrovascular accident are reported in OCA treated patients, which is concerning. The MAH is invited to present the safety profile of severe TEAEs for the two subsets of patients with compensated and decompensated disease and discuss to what extent any differences at all would be expected.

12. Renal AESIs were also reported more frequently in patients treated with OCA, both for the overall safety population (17 (10.1%) subjects in the OCA and 13 (7.8%) subjects in the placebo groups, with acute kidney injury reported by 3.0 % in OCA vs 1.2% in placebo treated patients), and for the subset of patients with compensated disease (8.8% OCA-treated and 6.2% placebo-treated patients experienced a renal AESI, with acute kidney injury reported by 2.2% in OCA and 1.6% in placebo treated patients). In addition, it has been reported that exposure to OCA was associated with a small reduction in estimated glomerular filtration rate (eGFR) in a NASH clinical study. The higher incidence of renal events in patients treated with OCA regardless of the severity of the underlying liver disease is worrisome. Please discuss.
13. When discussing the incidence of liver transplant and deaths events (adjudicated by an Hepatic Outcome Committee, HSAC), the information provided is quite confusing given the number of analyses conducted and lack of tabulated results, but all point into the same direction: a total of 60 liver transplants and deaths in patients overall were retrospectively adjudicated in a blinded manner by the HSAC (ITT population=32 (19.0%) subjects OCA vs 28 (16.9%) placebo, considered possibly treatment related in 12.5% OCA vs 3.6% placebo), less than half occurred in patients with decompensated liver disease (26), and the remaining 34 occurred in patients with compensated disease (20 in OCA vs 14 in placebo). This is considered a matter of major concern, given that the aim of OCA treatment is just the opposite, to prevent these clinical outcomes. The MAH is invited to provide these results, tabulated, for the overall study population, for the subset of patients with compensated disease and also for patients with decompensated conditions, and discuss on the clinical relevance of these findings in the compensated population bearing in mind that the demonstrated benefit of OCA treatment is limited to ALP reductions. The appropriateness of the current risk minimization measures deserves further discussion in view of these results. Further, the MAH should explain the differences observed in the incidence of liver transplant and deaths adjudicated events between the safety population and the ITT population.
14. The incidence of cholecystitis/cholelithiasis TEAEs was 5.4% in both treated groups, but a higher incidence of cholelithiasis-related events was seen in the OCA treated group. For the compensated subset, a similar pattern was seen: 5.1% OCA-treated and 6.2% placebo-treated patients experienced a cholecystitis/cholelithiasis TEAEs. Of these, 4 patients reported cholecystitis/cholelithiasis SAEs (3 patients in the OCA group: 2 patients with cholelithiasis and 1 patient with bile duct stone; 1 patient in the placebo group with cholecystitis). The MAH is invited to present comparative tabulated results of these cholelithiasis-related TEAE for the overall safety population vs decompensated vs compensated patients and discuss if a higher incidence should be expected in patients with a more advance disease.
15. The safety of OCA in special populations deserved further discussion, particularly, safety data in the elderly population should be provided and any relevant differences with previous observations will need to be discussed. The same would apply for patients with renal impairment, bearing in mind the increased risk for renal events during OCA treatment.

RWE

16. The external comparator analyses cannot serve as a replacement of the negative results from the placebo controlled study and are considered purely exploratory. Despite this, the MAH is requested to discuss why such remarkable differences are observed between the placebo controlled study and the RWE in order to better elucidate the value of these data.

12. Assessment of the responses to the request for supplementary information

Major objections

Clinical aspects

Question on Benefit/risk

Question 1

The positive B/R of Ocaliva, originally demonstrated on a biochemical (intermediate) marker, is not confirmed by the updated results on relevant clinical outcomes submitted within the current procedure. The confirmatory study (747-302) has failed to demonstrate a clinical benefit of OCA treatment in reducing the risk of relevant clinical outcomes in patients with PBC, regardless of liver disease severity (results consistent for the primary composite endpoint and its components as well as for the secondary outcomes and further confirmed by sensitivity analyses). Moreover, external control analyses using RWE cannot counterbalance or even overcome failed results of a confirmatory RCT. Consequently, the benefit of OCA in the treatment of PBC is deemed not demonstrated.

A more concerning overall safety profile as compared to that reported in the initial submission is shown in both the general safety population and the subset of patients with compensated liver disease. OCA treated patients had a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death; higher rates for relevant AESIs like cardiovascular events, including adjudicated MACE, renal events including AKI, DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events. The hepatic and CV AE profile appears particularly worrisome.

Therefore, the benefit/risk of OCA in the current indication is considered negative.

Summary of the MAH's response

Ocaliva (obeticholic acid; OCA) received conditional marketing authorisation (CMA) in the European Union (EU) in December 2016 and accelerated approval in the United States (US) in June 2016 for the treatment of adult patients with primary biliary cholangitis (PBC) who have an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. The initial CMA indication included PBC patients with advanced disease (e.g., hepatic decompensation).

Approval was based on a pivotal Phase 3 study (747-301), which recruited PBC subjects with early liver disease and excluded subjects with Child Pugh (CP)-B or CP-C cirrhosis or decompensated cirrhosis. Study 747-301 demonstrated a clinically and statistically significant sustained reduction in alkaline phosphatase (ALP), a surrogate endpoint which has been shown to significantly predict death, liver transplant and hepatic decompensation (Carbone 2013, Lammers 2014).

Conditional marketing authorisation included two Specific Obligations:

- Study 747-302, a randomized, double-blind, placebo-controlled study to confirm benefit based on clinical outcomes such as hepatic decompensation, liver transplant, and death.
- Study 747-401, a randomized, double-blind, placebo-controlled study evaluating the efficacy, safety,

and pharmacokinetics of OCA in subjects with PBC and moderate-to-severe hepatic impairment.

Both Obligations evaluated a notably more advanced liver disease population than Study 747-301, as demonstrated by key inclusion criteria for the three studies:

- 747-301: ALP >1.67x ULN and/or total bilirubin >ULN but <2x ULN with MELD <15
- 747-302: ALP >3x ULN and/or total bilirubin >ULN and ≤ 5x ULN with MELD ≤12
- 747-401: CP-B or CP-C with MELD between 6 and 24

The rationale to include a more advanced liver disease population in Study 747-302 was two-fold:

- To enhance accrual of clinical events by enrolling a population with later-stage PBC who were more likely to experience liver-related clinical complications during the anticipated 10-year study, and
- To evaluate the safety and efficacy of OCA in a more severe population than Study 747-301, one more consistent with the initial CMA indication.

In May 2021 and June 2022, the USPI and SmPC, respectively, were amended given the availability of new data on the use of OCA in patients with PBC with decompensated cirrhosis or that had a prior history of decompensation, specifically addressing the difficulty in differentiation of progression of liver disease to decompensation from potential drug induced liver injury (DILI). Patients with prior history of decompensation were contraindicated from OCA. Given all subjects in Study 747-401 had hepatic decompensation, the study was no longer informative for the current approved patient population and as such was terminated.

The revised contraindication also applied to 21% of subjects in Study 747-302, limiting its applicability to the current indicated population (i.e., without cirrhosis or with compensated cirrhosis). In December 2020, the Data Safety and Monitoring Board (DSMB) recommended terminating Study 747-302 for lack of feasibility. The MAH liaised with the EMA and the FDA and, with their concurrence, terminated Study 747-302 in December 2021. The study ended at 76% of anticipated enrollment, with 96 of the targeted 127 adjudicated endpoints observed, leaving the study underpowered to detect the proposed treatment effect.

In an attempt to use the data from Study 747-302 collected prior to study termination and to account for the feedback from health authorities, the MAH has provided a range of additional exploratory analyses on the efficacy and safety of OCA. While the MAH acknowledges the limitations of those analyses to fully determine the benefit and risk of OCA, the MAH does believe the analyses provides compelling evidence that OCA may offer an important treatment benefit and, importantly, remains safe for the intended use in the proposed SmPC indicated population. Further, the totality of evidence beyond Study 747-302 provides a compelling package of evidence that supports the conclusions drawn by the MAH.

1.1.2. Bias in Study 747-302

The MAH committed to conducting a robust clinical outcomes study as part of the CMA to confirm clinical benefit of OCA in subjects with PBC. It became apparent during the conduct of the study that feasibility issues and bias were present; throughout the conduct of the study the MAH worked collaboratively with global health authorities to rectify these issues. Despite these attempts, the Data Monitoring Committee (DMC) advised the MAH that Study 747-302 was unlikely to be able to fulfill its intended objectives and recommended that the MAH consult with the relevant regulatory agencies ahead of terminating the

study. The key issues were as follows:

- From Month 6 through Month 36, 52% (87/166) of subjects in the placebo group discontinued investigational product prior to an endpoint event, compared to 32% (53/168) of subjects in the OCA group. ALPs values at the time of discontinuation of investigational product in placebo subjects were substantially higher than the ALP for those placebo subjects who remained on placebo. This pattern was not observed in the OCA group during the same period (Figure 1).
- Subjects in the placebo group were more likely to initiate commercially-available PBC treatments than those in the OCA group (i.e., Ocaliva, fibrates, or UDCA if not on UDCA at baseline) (Figure 2).
- Subjects in the placebo group who initiated commercial PBC treatments showed large and sustained decreases in ALP within 3 months of initiating second line therapy, as would be expected for subjects initiating an active treatment but not expected in subjects on placebo (Figure 3).
- Placebo subjects who discontinued investigational product and who initiated commercial therapies continued to be followed and were included in the ITT analyses confounding the randomized controlled comparison of two treatment groups.
- More outcome and safety events were detected in the OCA group in part due to longer and better quality of follow up compared to the placebo group, confounding the interpretation of the efficacy and safety results.

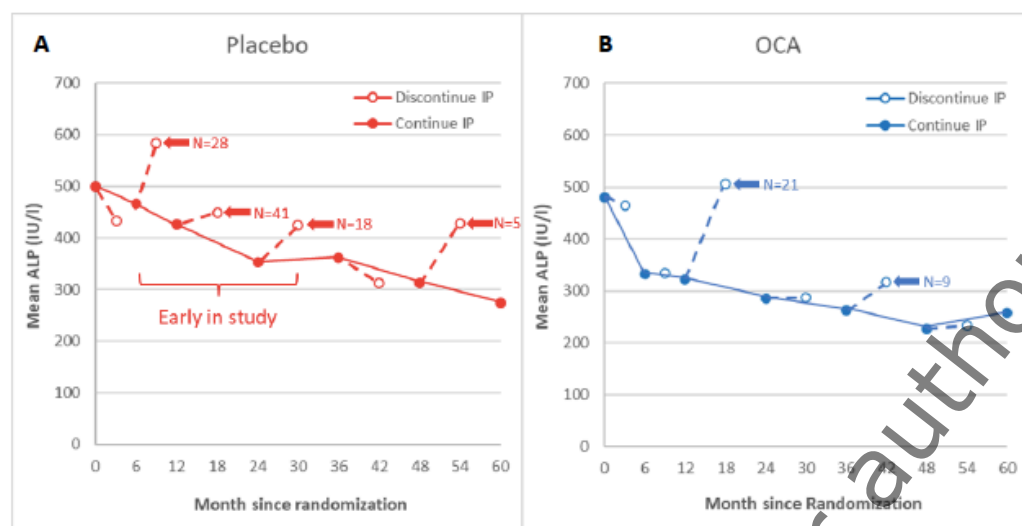
Informative Discontinuation of Investigational Product

The steady decrease in mean ALP in placebo subjects is inconsistent with the natural history of disease and was not observed in Study 747-301 or other clinical trials in PBC (Hirshfield 2015, Jones 2017, Corpechot 2018, Kowdley 2018). The mean ALP decrease in the placebo group is explained by the placebo subjects who discontinued investigational product. During the first 36 months after randomization, 60% (99/166) of subjects from the placebo group discontinued investigational product prior to an endpoint event compared to 46% (78/168) of OCA subjects. For these subjects, the mean ALP prior to discontinuation of investigational product was 481 U/L for the placebo group and 414 U/L for the OCA group.

As shown in the red open circles and dashed lines (Figure 1a), the subjects who discontinued placebo had substantially higher ALP levels than placebo subjects who remained on investigational product.

As shown in the blue open circles and dashed lines (Figure 1b), ALP levels of subjects who discontinued OCA were generally similar to those who stayed on investigational product. Only 21 subjects who discontinued OCA in the first 36 months were in a group with substantially higher mean ALP.

Figure 1: Study 747-302 - ALP Levels in Subjects Continuing and Discontinuing Investigational Product on Placebo (A) and OCA-treated (B) Groups



Note: Mean serum ALP levels in subjects remaining on investigational product (solid dots and line; red for placebo and blue for OCA) and the mean ALP levels in subjects before investigational product discontinuation prior to an endpoint event (open dots and dashed lines; red for placebo and blue for OCA).

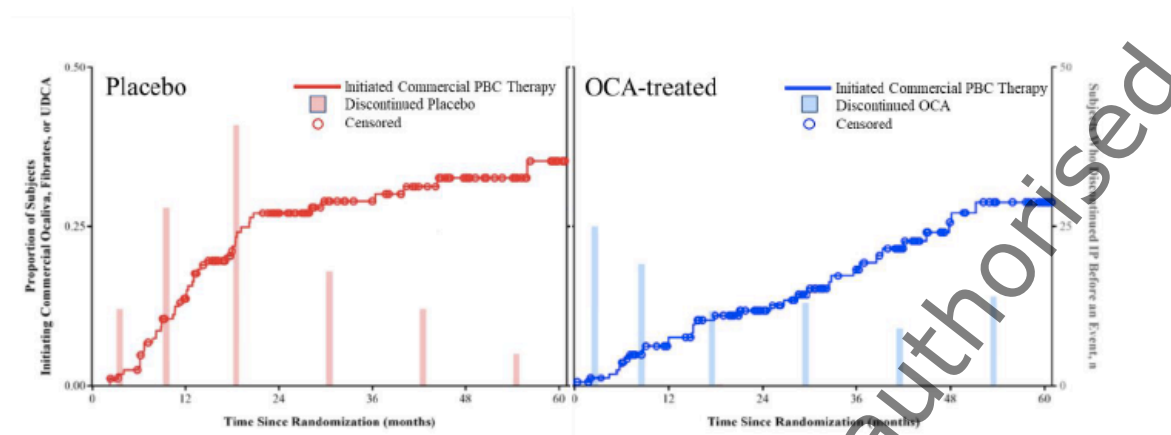
Imbalanced Initiation of Commercial PBC Treatments

Figure 2 examined investigational product discontinuation in the context of initiating commercial PBC therapies. The solid lines show the proportion of subjects initiating commercial PBC treatments (open-label OCA, fibrates, or UDCA if not taking UDCA at baseline) in the placebo group (red line) and OCA group (blue line). This is overlaid on a bar graph showing the absolute number of subjects in the placebo (pink bars) and OCA (light blue bars) groups who discontinued investigational product.

In the OCA group, peak investigational product discontinuation occurred in the first 6 months ($n=25$, 14.8%), and was primarily attributed to pruritus (10 of 25, 40%) versus none in placebo. There was minimal initiation of non-investigational product therapies in the first 6 months for either group. For OCA-treated subjects, initiation of commercial treatments is generally linear from baseline to Month 60.

In the placebo group, discontinuation increased from baseline and peaked between Month 12 and Month 24. The rise in subjects initiating commercial treatment closely mirrors the rise in investigational product discontinuations; thus, as placebo subjects dropped investigational product, they initiated commercially available PBC therapies. As discussed above, the placebo-randomized subjects discontinuing blinded investigational product had higher ALP levels than the placebo-randomized subjects who remained on blinded product. Over the entire study period, subjects in the placebo group were almost 60% more likely to initiate commercially available PBC therapy compared to subjects in the OCA group (HR [95% CI] 1.59 (1.02 to 2.50, $p<0.05$).

Figure 2: Study 747-302 - Initiation of Commercial PBC Treatments (Ocaliva, Fibrates or UDCA if Not Taking UDCA at Baseline) and Discontinuation of Investigational Product by Treatment Group over Time



IP=investigational product; OCA=obeticholic acid; UDCA=ursodeoxycholic acid

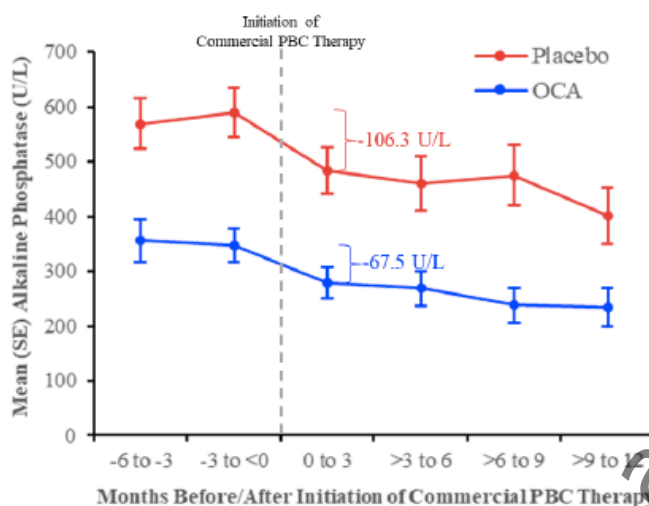
Note: Kaplan-Meier plot of initiation of PBC rescue therapy and a bar graph of the proportion of subjects discontinuing study treatment before experiencing a clinical endpoint event (red for placebo; blue for OCA).

Effect of Initiating Commercial PBC Treatment(s) on ALP

Figure 3 shows the impact of initiation of commercially available PBC therapies on mean ALP. The two cohorts of subjects had similar mean baseline ALP values (493 U/L, placebo; 481 U/L OCA). However, before initiating commercial therapies, the mean ALP in the placebo group was 590 U/L (red line) versus 347 U/L in the OCA-treated group (blue line). These substantial differences strongly suggest functional unblinding in the placebo group. Significant subject and provider education regarding the strong correlation of persistent high levels of ALP with increased risk of negative clinical outcomes, including progression to liver transplant and death, made conduct of a fully blinded clinical study unfeasible. Investigators were not prevented from reviewing real-time ALP values for their subjects, nor from sharing those values and the implications for disease progression with their patients. Anecdotal reports of decisions made between healthcare providers and study participants to discontinue blinded therapy and initiate commercially available PBC therapy were shared with MAH and regulators.

In the first 3 months after initiating commercial treatments, placebo subjects had a mean ALP of 484 U/L compared to a mean ALP of 590 U/L in the 3 months prior to initiating commercial treatment, a difference of 106.3 U/L. Subjects in the OCA-treated group who initiated commercial therapies had a mean ALP of 280 U/L in the 3 months after initiating commercial treatment compared to a mean ALP of 347 U/L in the 3 months prior to initiating commercial treatment, a difference of 67.5 U/L. Commercial PBC therapies were effective in reducing ALP in both groups during the first 36 months following randomization. Given the known association between ALP reduction and improved outcomes (Carbone 2013, Lammers 2014), the crossover to commercial therapy could be expected to significantly reduce the number of clinical outcome events in the placebo group.

Figure 3: Study 747-302 - Change in ALP Before and After Initiation of Commercial PBC Therapy by Treatment Group Over Time



OCA=obeticholic acid; PBC=primary biliary cholangitis

Imbalanced Quality of Event Capture

In an attempt to maximize data collection from enrolled subjects, the FDA guided the MAH to follow subjects after discontinuation of investigational product, and to include data from these subjects in the ITT analyses. Accordingly, the MAH initiated biannual phone follow-up with subjects who discontinued investigational product but who remained in the study.

These requests presented the following challenges:

- ITT analyses do not account for subjects switching treatment. Rather, these analyses maintain subjects in the group to which they were randomized, not allowing for reassignment based upon actual treatment received.
- When there is significant treatment crossover, ITT analyses will underestimate the treatment effect.

In-person clinic visits with a healthcare professional every 3 months will have a higher sensitivity for clinical outcome and safety events, particularly decompensation events, and will introduce less recall bias compared to assessments based on phone calls every 6 months. The MAH believes that accommodating the FDA request to retain subjects resulted in a disproportionate detection of events in the OCA group compared to the placebo group:

- A substantial and disproportionate number of subjects from the placebo group discontinued investigational product.
- More subjects in the OCA group continued 3-month clinic visits assessed by a healthcare professional, while more subjects from the placebo group were followed with the less sensitive self-reported biannual phone visits.

1.1.3. Clinical Benefit

Obeticholic acid therapy has demonstrated improvements in biochemical markers known to be associated with progression of cholestatic disease.

1.1.3.1. Biochemical Response Benefit

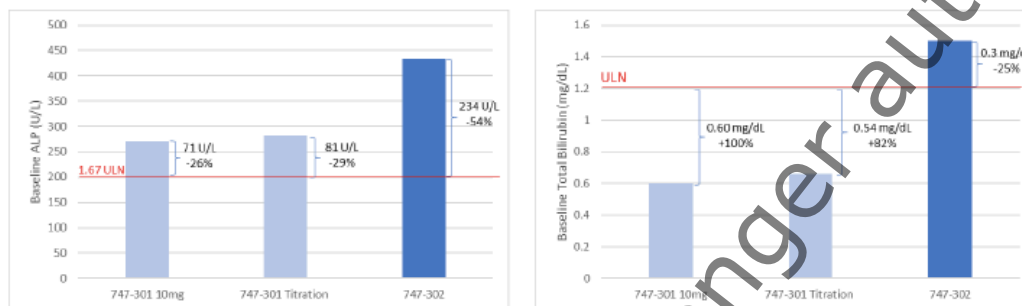
Subjects recruited into Study 747-301 had milder disease at an earlier stage and are representative of patients with PBC currently treated in routine clinical practice. Study 747-302 recruited subjects with

more advanced disease to enhance accrual of clinical events. This is supported by significant differences in baseline disease characteristics, the magnitude of change required to achieve biochemical thresholds of the primary response criteria in Study 747-301, the time course of ALP and total bilirubin, and real-world clinical practice patient characteristics.

As shown in Figure 4 and Figure 5, median baseline ALP and total bilirubin values were substantially higher in Study 747-302 versus 747-301.

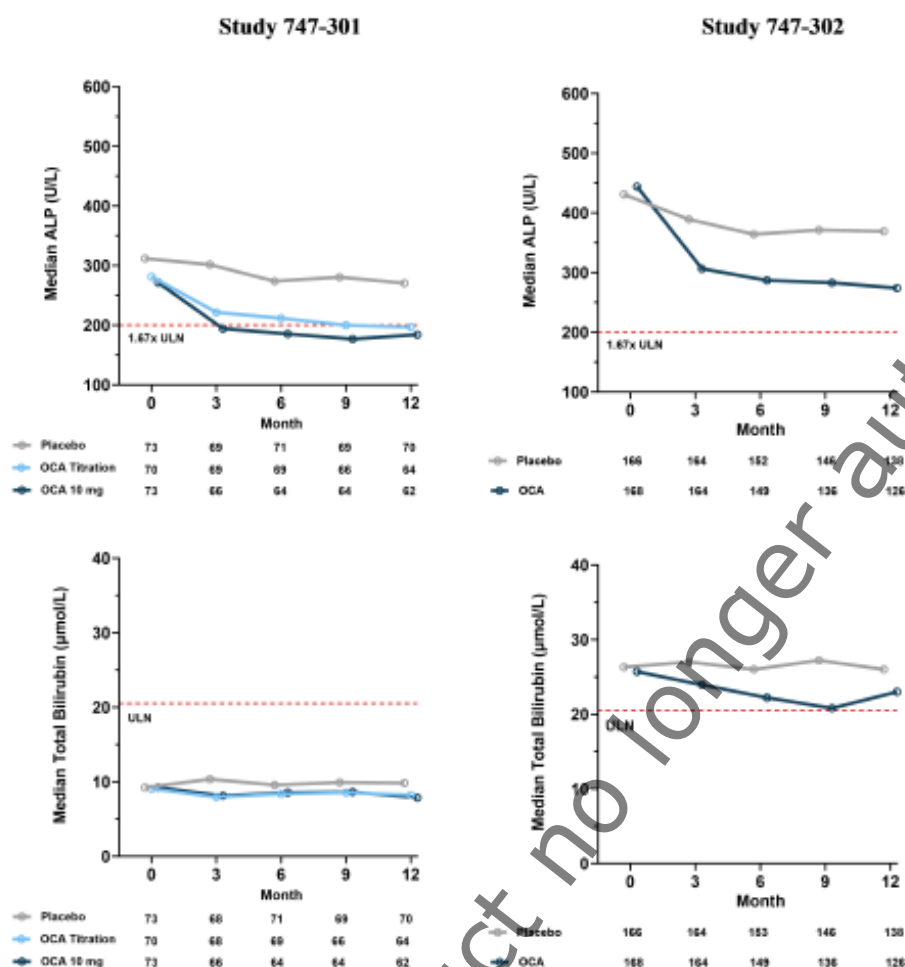
Figure 4 also shows that the percent reduction from baseline required to achieve the target ALP ($\leq 1.67 \times$ ULN) or total bilirubin ($< \text{ULN}$) thresholds from the primary response criteria of Study 747-301 were significantly different between studies.

Figure 4: Reduction from Median Baseline ALP and Total Bilirubin Required to Achieve 747-301 Endpoint (Responder)



Despite differences in baseline ALP and total bilirubin, clinically meaningful improvements in ALP and total bilirubin were observed in the OCA group compared to the placebo group in both studies (Figure 5). The magnitude of improvements in ALP were consistent for the OCA group for both studies, while a greater reduction in total bilirubin was observed for the OCA group in Study 747-302 compared to Study 747-301 (Table 1).

Figure 5: Median ALP (U/L) and Total Bilirubin (µmol/L) Over Time for Studies 747-301 and 747-302



Source: 747-301 CSR, Table 14.2.9.1.1; 747-302 CSR, Table 14.2.3.1

Table 1: Studies 747-301 and 747-302 - ALP and Total Bilirubin at Baseline and Month 12

	Study 747-301				Study 747-302	
	OCA Titration		OCA 10 mg		OCA	
	n	Median	n	Median	n	Median
ALP (U/L)						
Baseline	70	281.3	73	271.3	168	444.0
Month 12	64	196.6	62	184.2	126	274.0
Absolute Change		-85.5		-99.4		-99.0
Total Bilirubin (µmol/L)						
Baseline	70	9.1	73	9.2	168	25.7
Month 12	64	8.2	62	7.9	126	23.0
Absolute Change		-0.3		-0.4		-1.2

Source: 747-301 CSR, 14.2.9.1.1; 747-302 CSR, Table 14.2.3.1

As shown in Table 2 patient characteristics from European PBC and OCA registries provide supportive

evidence that the Study 747-301 subject population is more representative of the patient population treated with Ocaliva in real-world clinical practice than the Study 747-302 population. The median ALP levels of patients initiating Ocaliva in cohorts from Spain, Italy and the UK are similar to or lower than baseline ALP levels in Study 747-301.

Table 2: Median (IQR) ALP (U/L) in MAH Registrational Trials and European Registries of Patients Treated with OCA

	Randomized, Double-blind, Placebo-controlled Studies		European Registries OCA-treated Patients		
	747-301 N=216	747-302 N=334	Iberian Cohort Spain N=120	RECAPITULATE Italy N=441	UK-PBC N=349
ALP (U/L) Median (IQR)	286.6 (143.8, 811.0)	434.0 (262.0, 652.0)	244.0 (204.0, 361.0)	259.0 (203.0, 391.0)	343.4 (250.7, 469.4)
Total Bilirubin (mg/dL) Median (IQR)	0.54 (0.09, 2.30)	1.50 (1.00, 2.00)	0.7 (0.5, 1.1)	0.7 (0.5, 1.0)	0.55 (0.35, 0.90)

IQR=25th and 75th interquartile ranges

Source: 747-301 CSR Table 14.1.5.1.1; 747-302 CSR Table 14.1.3.1.1; Gomez 2020 (Iberian Cohort Spain); data on file (RECAPITULATE); Abbas 2023 (UK-PBC, total bilirubin), data on file (UK-PBC, ALP)

Biochemical Response Predicts Clinical Outcomes

Because of the high rate of treatment cross-over in Study 747-302, an analysis of biochemical response and correlation with clinical outcomes was conducted, independent of initial randomization status. As shown Table 3, irrespective of treatment group, there was an association between biochemical response (based on the Study 747-301 primary endpoint) and improved clinical outcomes (based on the Study 747-302 primary outcomes endpoint). This demonstrates that changes in biochemistries, specifically reductions in abnormal values of ALP and total bilirubin, which are known to reflect ongoing damage in progressive cholestatic disease, are predictive of improved clinical outcomes. The HR of 0.23 indicates a substantial reduction in the risk of liver transplant or death in subjects who achieve the biochemical response as initially described in Study 747-301.

Table 3: Time to the Event by Biochemical Response at Month 12: 747-301 Primary Endpoint Responder Criteria (ITT Population)

Statistics	Biochemical Responder ^a			Non-Biochemical Responder		
	Placebo	OCA	Total	Placebo	OCA	Total
Responder Definition: ALP <1.67x ULN and Total Bilirubin ≤ULN and ALP Decrease from Baseline of ≥15% at Month 12						
Number of Responders, N	4	17	21	162	151	313
Number of Subjects with the 747-302 Primary Endpoint Event, n (%)	1 (25.0)	2 (11.8)	3 (14.3)	79 (48.8)	69 (45.7)	148 (47.3)
Number of Subjects Censored, n (%)	3 (75.0)	15 (88.2)	18 (85.7)	83 (51.2)	82 (54.3)	165 (52.7)
Log Rank p-value ^b	0.006					
Hazard Ratio (95% CI) ^c	0.23 (0.07, 0.72)					

ALP=alkaline phosphatase, CI=confidence interval, ITT=intent to treat, OCA=obeticholic acid, ULN=upper limit of normal

^a A biochemical responder is defined as a subject who attains an ALP <1.67 times the ULN and total bilirubin ≤ULN and an ALP decrease of ≥15% from Baseline at Month 12 visit. Subjects missing values at Month 12 are considered non-responders.

^b Log-Rank p-value was based on log-rank test stratified by the treatment group.

^c Hazard ratio was estimated using stratified Cox's proportional hazards model with responder as an independent variable and the treatment group as strata. The results represent the ratio of Responder to Non-responder. A hazard ratio <1 indicates an advantage for Responder.

Source: 747-302 CSR, Table 14.2.9.1

This outcome benefit was observed across various established biochemical responder criteria (see response to Question 7).

Clinical Outcomes Benefit

The prespecified ITT analysis in Study 747-302 did not demonstrate a statistically significant difference between the OCA-treated group and placebo group on event-free survival for the Protocol Version 6 composite primary endpoint. The results from the prespecified analyses in Study 747-302 are not valid assessments of treatment benefit given the lack of adequate power due to poor enrollment, early termination for feasibility, inadequate number of outcome events, and systematic bias.

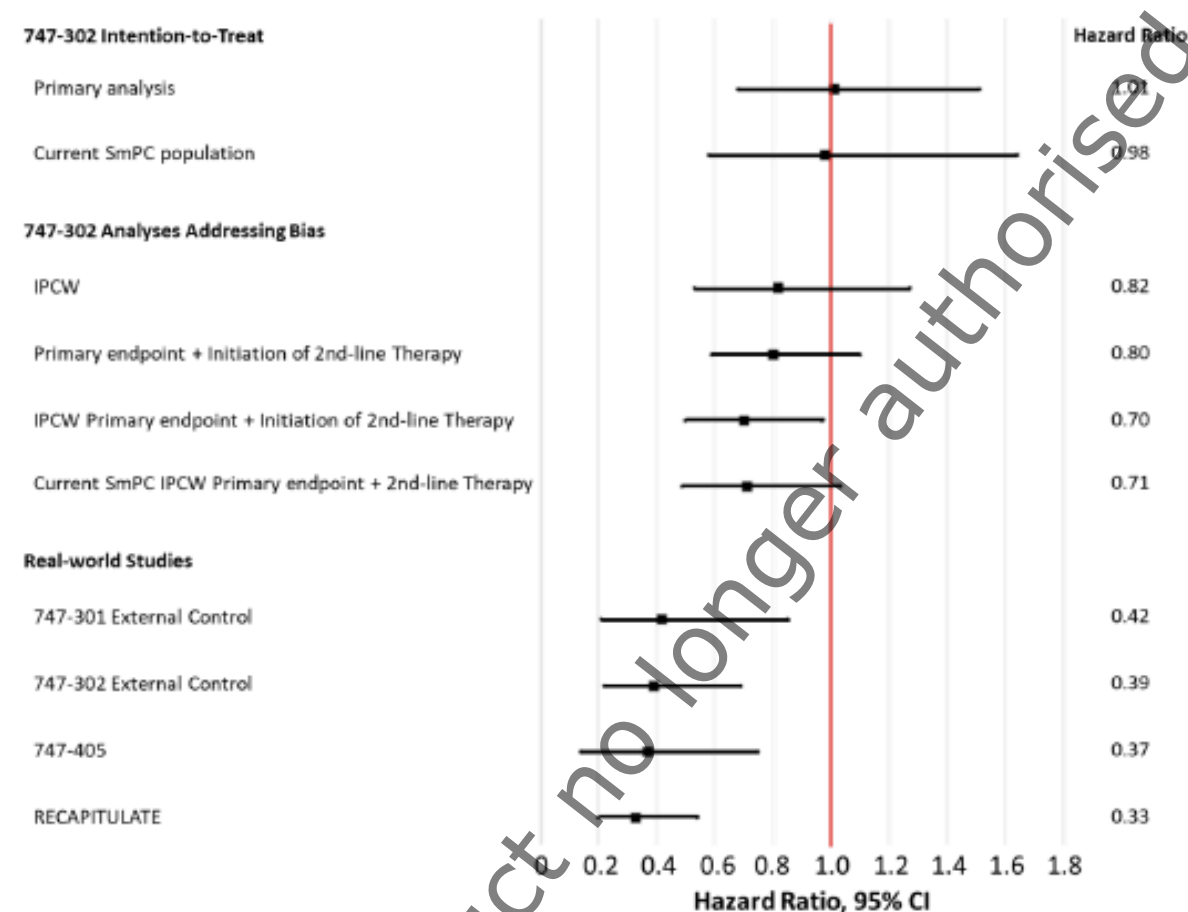
The MAH agrees that the RWE is not a “replacement” for Study 747-302. Instead, the MAH believes that a series of MAH-supported and independent studies provide consistent evidence of clinically meaningful OCA benefit in improving transplant-free and event-free survival in patients living with PBC with inadequate response or intolerant to UDCA, and should be included as part of CHMP’s assessment of OCA benefit:risk. The specifics of each of the studies cited by the MAH are included in response to Question 16 and are summarized below.

As presented in Figure 6, the clinical outcomes benefit of OCA treatment emerged as the MAH:

- Performed analyses that addressed bias, including inverse probability of censoring weighting (IPCW) and the inclusion of rescue medication in the primary endpoint
- Performed analyses that examined subgroups excluding subjects with more advanced disease, consistent with the current SmPC
- Conducted a comprehensive package of real-world studies

Taken together, the MAH has demonstrated that despite Study 747-302 lacking appropriate power to detect a treatment difference and containing significant bias, OCA demonstrates a reduction in serious and life-threatening outcome events compared to untreated subjects when focusing on the appropriate treatment subpopulation and adjusting for bias.

Figure 6: Study 747-302 - Hazard Ratio and 95% CI for Time to First Occurrence of Primary Endpoint (Death, Liver Transplant, or Hepatic Decompensation): 747-302 Intention-to-Treat; Analyses Addressing Bias; and Real-world Studies with Available Outcomes Data



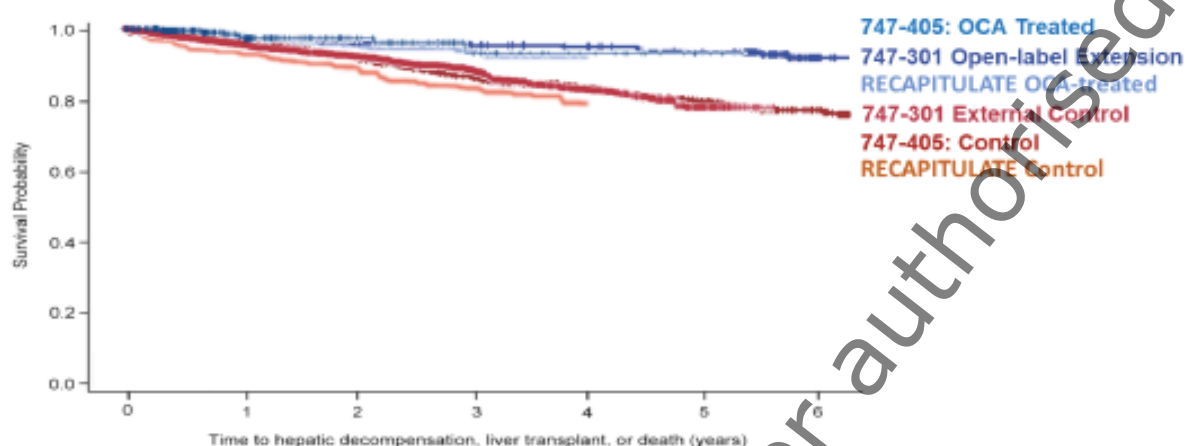
Current SmPC=Subjects in the compensated (indicated per current SmPC) population.

IPCW=inverse probability of censoring weighting

Initiation of second line therapy is defined as initiation of commercial OCA or initiation of UDCA for subjects who were monotherapy at baseline or initiation of fibrates for patients who were not on fibrates at baseline.

In additional support, Figure 7 shows the Kaplan-Meier (KM) survival curves for the 3 real-world studies with similar baseline populations of compensated subjects/patients: 747-301 with External Control; 747-405 and RECAPITULATE. It is noteworthy that the event rates (first occurrence of death, liver transplant or hepatic decompensation) of OCA-treated patients from a clinical trial, a US claims database, and an Italian patient registry are nearly superimposable, as are the event rates from the non-OCA-treated controls from a global registry, a US claims database, and an Italian patient registry. The consistency of both the KM survival curves, as well as the resulting hazard ratios, speaks to the stability of the observed treatment effect in a population consistent with the current SmPC.

Figure 7: Kaplan-Meier Curves of Time to First Occurrence of Death, Liver Transplant or Hepatic Decompensation from in Compensated Patients with PBC from Three Real-World Studies: 747-301 with External Controls, 747-405, and RECAPITULATE



Benefit Summary

- Subjects recruited into Study 747-301 were more representative of the patients currently treated in real-world clinical practice.
- Study 747-302 recruited a population of PBC patients with advanced disease at higher risk for liver-related clinical complications to enhance accrual of clinical events.
- Despite the advanced subject population and the challenges with study conduct, which introduced bias and lack of equipoise into Study 747-302, the biochemical response seen in Study 747-302 confirmed the observed biochemical benefit observed in Study 747-301.
- The profound decrease in outcome events noted in Study 747-302 biochemical responders (as defined by the Study 747-301 primary endpoint of ALP $<1.67 \times \text{ULN}$ and total bilirubin $< \text{ULN}$), independent of initial randomization status, confirms the association between ALP and total bilirubin and improved clinical outcomes.
- As the MAH sought to address study bias and the underpowered nature of Study 747-302 via ad hoc analyses, a clear trend of improvement in clinical outcomes is seen in subjects on OCA compared to placebo.
- Data both from MAH-supported and independent real-world and historical/external control studies support the findings of OCA benefit in Study 747-302 and further provide consistent evidence of clinically meaningful OCA benefit in substantial improvements in transplant-free and event-free survival.
 - OCA benefit is consistent across study populations, patient subgroups, study design and analysis, and was maintained throughout extensive sensitivity analyses. These 58% to 71% reductions in the relative risk of serious clinical events of all-cause death, liver transplants, and hepatic decompensation offer strong support that OCA treatment provides a clinically meaningful and significant benefit to appropriately treated PBC patients with a positive benefit:risk.
 - While MAH agrees that the RWE is not a “replacement” for Study 747-302, it is our position that CHMP should consider these results, in addition to those from 747-302, in their evaluation.

1.1.4. Clinical Safety

In Study 747-302, the safety population (N=334) included all randomized subjects who received at least one dose of investigational product (OCA or placebo). The safety population was the primary population used for safety analyses, in which only treatment-emergent events (TEAEs) were included (i.e., following exposure to the investigational product or within 30 days after the discontinuation of investigational product).

Treatment assignment was based on the randomization scheme at baseline. However, as previously reviewed, more subjects in the placebo group initiated commercially available PBC therapy (i.e., commercial Ocaliva, fibrates, or UDCA) while on study, significantly impacting the ability to appropriately characterize the safety of the prospectively randomized, controlled Study 747-302.

Despite the significant bias observed in Study 747-302, the MAH assessed the frequency of events between OCA and placebo in the overall, compensated (indicated per current SmPC), and decompensated (contraindicated per current SmPC) populations. Given the subjects in these various groups have more advanced PBC disease, and that it will not be feasible to establish the safety and efficacy of OCA in patients with more advanced PBC, the MAH has evaluated the safety profile in a revised SmPC indicated population that maximizes the benefit:risk profile.

The MAH is proposing to revise the SmPC indication for patients with PBC without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or decompensation event. In Study 747-302, 149 subjects met the revised SmPC indication and were included in the "proposed SmPC indicated population".

Treatment with OCA was generally well tolerated in patients with PBC who met the criteria of the proposed SmPC indication at baseline, and the overall safety profile was consistent with that observed in other PBC studies that excluded patients with more severe disease. The incidence of most treatment-emergent adverse events of special interest (TEAESIs) observed in OCA-treated subjects was markedly lower in the proposed SmPC indicated population compared to the overall safety population.

1.1.4.1. Overview of TEAEs

An overview of TEAEs by overall, compensated (indicated per current SmPC), and proposed SmPC indicated populations is presented in Table 4.

In comparison to the overall and compensated (indicated per current SmPC) populations, the proportion of serious TEAEs across treatment groups was lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), a total of 15 (18.5%) subjects in the OCA group and 17 (25.0%) subjects in the placebo group experienced a serious TEAE. Of which, 1 (1.2%) subject in the OCA group reported a TEAE of acute respiratory failure leading to death, which was considered not related to investigational product by the Investigator.

The incidence of any TEAEs was balanced across treatment groups (93.8% in the OCA group and 89.7% in the placebo group). Consistent with the overall and compensated populations, more subjects in the OCA group than the placebo group experienced severe TEAEs (45.7% versus 32.4%), treatment-related TEAEs (75.3% versus 55.9%), and TEAEs leading to dose reduction (24.7% versus 10.3%), which were mostly driven by pruritus. Pruritus is a known adverse drug reaction (ADR) per the current SmPC and was an adverse event of special interest (AESI) in Study 747-302.

Table 4: Study 747-302 - Overview of Treatment-Emergent Adverse Events by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Current SmPC		Proposed SmPC	
			Compensated (Indicated)		Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Any TEAE	158 (95.2)	162 (96.4)	122 (94.6)	130 (95.6)	61 (89.7)	76 (93.8)
Serious TEAE	53 (31.9)	53 (31.5)	40 (31.0)	33 (24.3)	17 (25.0)	15 (18.5)
TEAE Leading to Death	2 (1.2)	5 (3.0)	2 (1.6)	2 (1.5)	0	1 (1.2)
Severe TEAE	65 (39.2)	86 (51.2)	47 (36.4)	64 (47.1)	22 (32.4)	37 (45.7)
Treatment-Related TEAEs	111 (66.9)	133 (79.2)	80 (62.0)	107 (78.7)	38 (55.9)	61 (75.3)
TEAE Leading to IP Withdrawal	45 (27.1)	62 (36.9)	36 (27.9)	45 (33.1)	18 (26.5)	27 (33.3)
TEAE Leading to Dose Reduction	23 (13.9)	45 (26.8)	18 (14.0)	36 (26.5)	7 (10.3)	20 (24.7)
TEAE Leading to IP Interruption	43 (25.9)	48 (28.6)	36 (27.9)	34 (25.0)	17 (25.0)	21 (25.9)
TEAE Leading to Study Discontinuation	19 (11.4)	29 (17.3)	18 (14.0)	23 (16.9)	13 (19.1)	12 (14.8)

OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Hepatic Safety

A comprehensive evaluation of hepatic events was performed, including analyses of Investigator-reported, hepatic TEAEs (SMQ-based), evaluation of drug-induced serious hepatotoxicity (eDISH), adjudication of hepatic outcomes and hepatic safety events (e.g., potential drug-induced liver injury [DILI]) based on a broad set of hepatic trigger events (Investigator-reported TEAEs and pre-specified lab thresholds) to determine severity and causality by a blinded, independent adjudication committee.

A summary of the MAH's comprehensive evaluation is provided below and a detailed discussion is provided in Major Objection 2. Hepatic evaluations by overall, compensated (indicated per current SmPC), and proposed SmPC indicated populations is presented in Table 5.

The incidence of hepatic events observed in OCA group was markedly lower in the proposed SmPC indicated population in comparison to the overall safety population.

Table 5: Study 747-302 - Summary of Hepatic Safety: : Investigator-reported Hepatic TEAEs, eDISH, Adjudication of Hepatic Outcomes and Hepatic Safety Events by Overall, Compensated (indicated per current SmPC), and Proposed SmPC Indicated Populations

		Overall		Current SmPC		Proposed SmPC	
				Compensated (Indicated)		Indicated	
		PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Investigator-reported Hepatic TEAEs							
Subjects with at least 1 Hepatic TEAEs	n (%)	97 (58.4)	80 (47.6)	73 (56.6)	58 (42.6)	29 (42.6)	22 (27.2)
	IRY (PY)	40.855 (237.42)	26.42 (302.8)	35.814 (203.83)	21.215 (273.39)	25.754 (112.60)	11.844 (185.75)
Subjects with at least 1 Serious Hepatic TEAEs	n (%)	16 (9.6)	15 (8.9)	9 (7.0)	9 (6.6)	2 (2.9)	3 (3.7)
	IRY (PY)	4.620 (346.32)	3.646 (411.36)	3.042 (295.83)	2.483 (362.49)	1.385 (144.40)	1.396 (314.86)
Evaluation of Drug-induced Serious Hepatotoxicity (eDISH)							
Subjects meeting eDISH Hy's Law Criteria (All Post-Baseline Measurements)	n (%)	35 (21.1)	24 (14.3)	25 (19.4)	15 (11.0)	11 (16.2)	10 (12.3)
Subjects meeting eDISH Temple's Corollary Criteria (All Post-Baseline Measurements)	n (%)	28 (16.9)	24 (14.3)	28 (21.7)	23 (16.9)	22 (32.4)	18 (22.2)
Subjects meeting eDISH Cholestasis Criteria (All Post-Baseline Measurements)	n (%)	43 (25.9)	35 (20.8)	21 (16.3)	20 (14.7)	3 (4.4)	3 (3.7)
Adjudicated Hepatic Safety Events							
		Overall		Current SmPC		Proposed SmPC	
				Compensated (Indicated)		Indicated	
		PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
All Adjudicated Hepatic Safety Events	n (%) [e]	99 (59.6) [230]	85 (50.6) [189]	72 (55.8) [167]	59 (43.40) [123]	28 (41.2) [64]	29 (35.8) [58]
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥mild severity)	n (EAIR)	8 (2.225)	18 (4.521)	4 (1.377)	10 (2.824)	1 (0.685)	4 (1.910)
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥moderate severity)	n (EAIR)	7 (2.012)	12 (2.923)	3 (1.019)	5 (1.379)	1 (0.685)	2 (0.931)
Adjudicated Hepatic Outcomes							
EAIR of Hepatic Outcomes Adjudicated as ≥ Possibly Related to IP	n (%), IRY (PY)	2 (1.2), 0.564 (354.56)	10 (6.0), 2.391 (418.19)	1 (0.8), 0.334 (299.61)	6 (4.4) ^a , 1.640 (365.92)	1 (1.5), 0.689 (145.24)	3 (3.7) ^b , 1.403 (213.80)

^a Subject 115005 in the OCA group (compensated population) had ascites at baseline and would have been considered decompensated (contraindicated) at baseline. Ascites was reported in imaging/hospital notes, and these were not captured as part of the programmatic grouping, which used eCRF data.

^b Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for esophageal varices, there is a suggestion Subject 272004 had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

Investigator-reported Hepatic TEAEs

- Overall Safety Population (N=334)

The number of subjects with at least one hepatic TEAE was 80 (47.6%) in the OCA group and 97 (58.4%) in the placebo group.

- Proposed SmPC Indicated Population (N=149)
 - Incidence of hepatic PTs in the OCA group (27.2%) were lower than the placebo group (42.6%).
 - The difference between OCA-treated subjects and placebo is more pronounced when considering the incidence of exposure-adjusted hepatic TEAEs (11.844 per 100 PYs in the OCA group and 25.754 per 100 PYs in the placebo group).
 - No difference was observed between treatment groups of exposure-adjusted hepatic SAEs (1.396 per 100 PYs in the OCA group and 1.385 per 100 PYs in the placebo group).

Evaluation of Drug-induced Serious Hepatotoxicity (eDISH)

- Overall Safety Population (N=334)

More subjects in the OCA group (49.4%) are represented in the normal range for ALT and total bilirubin peak excursions compared to placebo (35.5%). Fewer subjects in the OCA group met criteria for the biochemical Hy's law range (peak ALT >3x ULN and peak total bilirubin >2x ULN) and cholestasis range (peak total bilirubin >2x ULN, and ALT <3x ULN).

- Proposed SmPC Indication (N=149)
 - More subjects in the OCA group (60.5%) were in the normal range for ALT and total bilirubin peak excursions compared to placebo (45.6%).
 - Fewer subjects in the OCA group (12.3%) met criteria for the biochemical Hy's law range compared to placebo (16.2%). Similar trends were observed for the cholestasis range (3.7% in the OCA group and 4.4% in the placebo group).

Adjudicated Hepatic Safety Events

As a retrospective assessment, hepatic safety events were identified via a set of biochemical and adverse event (SMQ based) triggers per the HSAC Charter. These events underwent clinical review by the HSAC of all available data (medical history, concomitant medications, vital signs, lab values, liver imaging, pathology reports, and noninvasive tests) for each identified subject to determine liver injury status (including causality and severity). The adjudication committees remained blinded to investigational product allocation.

Potential hepatic safety events (e.g., drug-induced liver injury [DILI]) were identified programmatically using SMQ searches of hepatic AEs, central and local laboratory data, and investigational product interruption records from the clinical database for hepatic injury. Hepatic AEs are defined as events included in the Hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, lab values, liver imaging and pathology reports, and NITs. Adjudication committees remained blinded to investigational product allocation.

Per the HSAC Charter, all potential hepatic safety events are then assessed for causality (investigational product relatedness) and severity based on the Drug-Induced Liver Injury Network (DILIN) index (Table 6).

Table 6: Study 747-302 - Hepatic Safety Adjudication Causality Assessment

Causality Assessment Score	Descriptor	Details
Insufficient Information	Insufficient details in case package to make any assessment	Cases that do not have enough information provided to be assigned one of the below 4 categories, will be designated as having insufficient information. Members will be asked to specify what additional information is required to complete the causality assessment.
Unlikely drug related	Confidence of causality assessment is <25%	A role for study drug is unlikely based on the available information. Another etiology is likely to be the cause of injury.
Possible drug related	Confidence of causality assessment is between 25% to 49%	The available evidence does not definitively exclude the possibility of a causal role for study drug, but another etiology is more likely to be the cause of injury.
Probable drug related	Confidence of causality assessment is between 50% to 74%	Causality is supported by the preponderance of evidence; the drug is more likely to be the causal agent rather than not. Testing rules out some/most other likely causes.
Highly likely drug related	Confidence of causality assessment is between 75% to 100%	The evidence is beyond a reasonable doubt (positive rechallenge)

- Overall Population (N=334)

- There were 189 hepatic safety events in 85 subjects in the OCA group compared to 230 events in 99 subjects in the placebo group.
- Of those events, 18 subjects had events positively adjudicated as possibly related (n=17) or probably related (n=1) events in the OCA group compared to 8 subjects (all possibly related) in the placebo group.
- Of the 18 subjects, 12 in the OCA group had events ≥ moderate severity compared to 7 subjects in the placebo group.

- Proposed SmPC Population (N=149)

- There were 58 hepatic safety events in 29 subjects in the OCA group compared to 64 events in 28 subjects in the placebo group.
- The majority of hepatic safety events in both treatment groups were mild severity, and the potential liver injury events assessed as ≥ moderate severity occurred in fewer subjects in the OCA group (10) than placebo group (12).

4 subjects had events positively adjudicated as possibly related in the OCA group compared to 1 subject in the placebo group. Of these subjects, 2 subjects had events ≥ moderate severity in the OCA group compared to 1 subject in the placebo group. Of the 2 subjects, 1 subject, a female, was found to have elevated transaminases (ALT and AST >5x baseline). Other liver biochemistry was stable and consistent with baseline. Elevated transaminases returned to baseline approximately 1 month after withdrawal of rifampicin and OCA. The Investigator judged the cause for the event to be most likely due to rifampicin. The other subject, a female, was

found to have an elevation in all liver biochemistries (ALT and AST > 5X ULN and total bilirubin > 3X ULN). She was diagnosed with cholecystolithiasis on Study Day 49 and underwent a laparoscopic cholecystectomy, subsequently all liver biochemistry had improved significantly. The subject was also taking ibuprofen and simvastatin at the time of the event.

- No subject with "possible" related potential hepatic events progressed to liver failure, suffered accelerated disease progression after the event, underwent liver transplantation or died during the study or the follow up period.
- All "possible" related potential hepatic events in the OCA group occurred within the first 3 months of investigational product, and no uniform pattern of liver injury was present.
- No subject had a hepatic safety event assessed as "probable" or "highly likely" by the HSAC, and all cases were reversible with discontinuation of OCA.

Adjudicated Hepatic Outcomes

All hepatic outcomes (EMA Composite Endpoint and FDA Expanded Endpoint as defined in Table 7) were adjudicated by a blinded, independent Hepatic Outcomes Committee (HOC) to determine whether they met the protocol-specified endpoint criteria.

Subsequently, per request from the US Food and Drug Administration (FDA), all EMA and FDA expanded hepatic outcome events underwent additional blinded clinical review retrospectively by an independent Hepatic Safety Adjudication Committee (HSAC) to determine causality (highly likely drug related, probable drug related, possible drug related, unlikely drug related, insufficient information).

Table 7: Study 747-302 - EMA Composite Endpoint and FDA Expanded Endpoints

EMA Composite Endpoint: All Subjects
• Death (all-cause) • Liver transplant • MELD score ≥ 15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: - Variceal bleed - Hepatic encephalopathy (as defined by a West Haven score of ≥ 2) - Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
FDA Expanded Endpoints:
Group 1 (applies to all subjects)
• Death (all-cause) • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of $>250/\text{mm}^3$ polymorph leukocyte (PMNs) in the ascitic fluid), or bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid) • Uncontrolled or refractory ascites (requiring large volume paracentesis) • Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club [Angeli 2019], portopulmonary syndrome, or hepatopulmonary syndrome) • MELD-Na score ≥ 15 if MELD-Na <12 at baseline • MELD score ≥ 15 if MELD-Na ≥ 12 at baseline

- Proposed SmPC Indication (N=149)

- EMA Composite Endpoint: A total of 1 subject with 1 event of liver transplant in the OCA group and 1 subject in the placebo group with 1 event of MELD ≥ 15 were considered possibly related to investigational product by the HSAC.
- FDA Expanded Endpoint: A total of 3 (3.7%) subjects with 4 events in the OCA group and 1 (1.5%) subject with 4 events in the placebo group were considered possibly related to investigational product by the HSAC.
- None of the OCA-treated or placebo subjects experienced a liver-related death. No cases were considered “probable” or “highly likely”.

Comprehensive evaluation of hepatic safety observed in clinical trials of OCA across indications has informed our understanding of OCA’s potential for hepatotoxicity. The majority of hepatic TEAEs have been reported in subjects with advanced PBC who either had evidence of decompensation or CSPH, which forms the basis for the proposed SmPC to further restrict the indication. Restricting the label per the proposed SmPC indication allows for an improved safety profile.

Additional analyses of post-marketing data from over 35,000 patient-years exposure show no increased hepatic events in patients with PBC treated with OCA.

Ocaliva Post-marketing Data: Hepatic Events

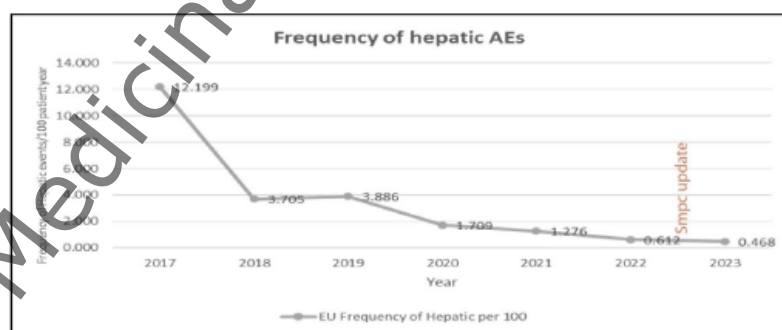
There has been no increased risk of hepatic events in post-marketing data. As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years.

Over the course of the marketed period for Ocaliva, there have been label refinements and changes to better define the appropriate treatment population compared to those subjects with more advanced disease that should not receive Ocaliva and should be contraindicated. A dramatic reduction in the frequency of hepatic AEs being reported occurred as these label changes per implemented. Between 2017 to 2023, the frequency of hepatic AEs reported per 100-patient years has dropped 30-fold. This signals that refinements in the label have worked to mitigate hepatic safety risk with Ocaliva.

In Figure 8, the frequency of exposure-adjusted incidence of hepatic safety reports has continuously decreased since the initial authorization of OCA.

- Prior to the SmPC update in June 2022, the frequency of exposure-adjusted incidence was 1.3 events per 100-patient-years.
- Following the change in the indicated patient population, the rate became 0.6 events per 100-patient years in 2022, a substantial reduction in the frequency of hepatic safety reports

Figure 8: Frequency of Hepatic Adverse Events “per 100-patient years” in EU



AE=adverse event; EU=European Union

Liver Transplants or Deaths

The MAH recognizes the significant imbalance in liver transplant and death events in Study 747-302. In the proposed SmPC indicated population: there were a total of 11 subjects in the OCA group (7 subjects had a liver transplant and 4 subjects had an all-cause death); and a total of 2 subjects in the placebo group (1 subject had a liver transplant and 1 subject had an all-cause death).

A comprehensive evaluation of liver transplant and death events in the 11 OCA-treated subjects and 2 placebo subjects was performed to assess the potential increased risk with OCA:

- Of the 11 subjects in the OCA group, a total of 1 subject had an event that was considered possibly related to investigational product by an independent, blinded adjudication by an HSAC (). Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that the subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC.
- The remainder of liver transplant and death events within proposed SmPC indicated population were adjudicated as unlikely related to investigational product.
- Upon subject-level review of Study 747-302, the majority of liver transplants and all-cause death events in the proposed SmPC indicated population had alternate diagnoses/comorbidities.
- The incidence of liver transplants and deaths in the placebo group from Study 747-302 was substantially lower than any of the other non-OCA treated groups from real world datasets. Meanwhile, the liver transplant and death event rates were consistent across real world datasets.
 - Real-world evidence (RWE) datasets
 - Over 35,000 patient-years of Ocaliva post-marketing exposure in PBC

Based on totality of assessments, the MAH concludes that the rate of liver transplant and death events in Study 747-302 was not consistent with post-marketing and real-world datasets, previous PBC studies, and external control studies. Furthermore, the totality of evidence supports a clinically meaningful and statistically significant transplant-free survival benefit of OCA use in the proposed SmPC indicated population.

A summary of the MAH's comprehensive evaluation is provided below and a detailed discussion is provided in Question 13.

Blinded HSAC Adjudication

The incidence of liver transplant and deaths was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). The incidence of liver transplants and deaths was higher for OCA-treated subjects in the compensated population (20 subjects) compared to OCA-treated subjects in the proposed SmPC indicated population (11 subjects).

Overall Safety Population

A total of 32 subjects randomized to the OCA group and 28 subjects in the placebo group had a liver transplant or death:

- There were 20 liver transplants, 13 deaths (all-cause), and 3 liver-related deaths in the OCA group and 18 liver transplants, 11 deaths (all cause), and 3 liver-related deaths in the placebo group.
- Independent, blinded adjudication by HSAC resulted in 4 liver transplants in the OCA group and 1 liver transplant in the placebo group that were considered possibly related to investigational product. The remaining liver transplant and death events in each treatment group were assessed by HSAC as unlikely.

Proposed SmPC Population

A total of 11 subjects in the OCA group and 2 subjects in the placebo group had a liver transplant or death:

- Of the 11 subjects in the OCA group, there were 7 liver transplants and 4 deaths of which one was liver related.
- Of the 2 subjects in the placebo group, 1 subject had a 1 liver transplant and 1 subject had a death (all cause).
- One subject in the OCA group had a liver transplant that was considered possibly related to investigational product by the HSAC. Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion this subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC.
- The remainder of liver transplant and death events within the proposed SmPC indicated population were adjudicated as unlikely related to investigational product by the HSAC.

Upon additional subject-level review, the majority of the subjects with a liver transplant or death in the proposed SmPC indicated population had alternate underlying diseases and/or causes which may have contributed to the outcome.

Table 8: Summary of Liver Transplants or Deaths (All-cause) by Overall and Baseline Disease Stage (ITT Population [N=334])

	Overall		Current SmPC		Proposed SmPC	
			Compensated (Indicated)		Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Liver Transplants or Deaths (All-cause)	28	32	15	20	2	11
Highly Likely Drug Related	0	0	0	0	0	0
Probable Drug Related	0	0	0	0	0	0
Possibly Related	1 (3.6)	4 (12.5)	0	3 (15.0)	0	1 (9.1)*
Unlikely Related	27 (96.4)	28 (87.5)	14 (100.0)	17 (85.0)	2 (100)	10 (90.9)
Insufficient Information	0	0	0	0	0	0
Liver Transplants						
Possibly Related	1	4	0	3	0	1
Unlikely Related	17	16	7	10	1	6
Deaths (All-cause)						
Possibly Related	0	0	0	0	0	0
Unlikely Related	11	13	7	7	1	4
Liver-related death						

	Overall		Current SmPC		Proposed SmPC	
			Compensated (Indicated)		Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Unlikely Related	4	3	3	2	0	1
Non-liver-related death						
Unlikely Related	7	10	4	5	1	3

* Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion Subject 272004 had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

Real-world Evidence/Historical Controls

The observed imbalance in liver transplants and deaths in Study 747-302 was not valid and reflected significant bias, particularly in favor of the placebo group. The MAH undertook 2 additional analyses to investigate this imbalance:

1. A comparison of the placebo group in the proposed SmPC indicated population in Study 747-302 real-world non-OCA treated patients with PBC, to understand the observed event rate relative to the known natural history of PBC.
2. An analysis of liver transplants in the US transplant registry before and after launch of commercial OCA, as the observed significant imbalance in liver transplants associated with OCA would manifest as increased transplants in the real world.

Results presented in Question 13 support the following conclusions:

- The liver transplants and death event rates observed in the placebo group in Study 747-302 did not reflect the high event rates seen in real-world analyses, which was consistent in multiple larger datasets.

- The liver transplant event rates observed in the OCA group in Study 747-302 was not consistent with the rates seen over time in a comprehensive liver transplant national registry. Remarkably, the percentage of liver transplants associated with PBC has decreased slightly over time despite the increasing number of patient-exposure years of OCA in the post-marketing setting.

Post-marketing Data

As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years.

- No increased risk of liver transplant or deaths has been observed in the post-marketing setting.
- Cumulatively, since marketing approval in 2016, 47 fatal reports due to hepatic events have been reported, and the majority were reported from patients who would now be contraindicated by the current SmPC. Cumulatively, 33 reports of liver transplants (31 with PT of liver transplant, and 2 with PT of liver transplant rejection) have been reported.

Cardiovascular Safety including MACE

A summary of the MAH's comprehensive evaluation is provided below and a detailed discussion is provided in Major Objection 2.

The totality of data from randomized clinical trials, RWE, and post-marketing data does not show a clear signal for an increased CV risk associated with OCA. Based on these data, the MAH is not proposing any additional risk minimization measures beyond the scope of the proposed SmPC.

Overall Safety Population

- In the overall population, there were 21 Cardiac Disorder TEAEs among 15 (8.9%) subjects in the OCA-treated group versus 14 among 9 (5.4%) subjects in the placebo group.

Proposed SmPC Population

- The majority of Cardiac Disorder TEAEs were observed in OCA-treated subjects at a lower rate in the proposed SmPC population.
- With the exception of palpitations, no Cardiac Disorder TEAE was reported by > 1 OCA-treated subject in the proposed SmPC population.
- There was no trend for an increased risk for atherosclerotic CV events such as coronary artery disease, angina, or myocardial infarction when evaluating individual CV PTs.
- 1 (1.2%) subject in the OCA group and 3 (4.4%) subjects in the placebo group reported an adjudicated Major Adverse Cardiovascular Events (MACE).
- There is no signal for an increased risk of adjudicated CV events.

Post-marketing Cardiovascular Safety

- The cumulative review of the post-marketing reports of atherosclerotic CV events secondary to changes in lipids did not alter the understanding of the MAH regarding CV safety for patients with PBC treated with OCA.
- No additional risk management measures are considered necessary to address risk associated with CV events. As mentioned in response to Question 5, the MAH commits to continue to monitor CV events with Ocaliva as a part of Signal detection activity. MAH will report back to the health authorities if there is a need for any further amendment in the future.

Renal Safety

A summary of the MAH's comprehensive evaluation is provided below and a detailed discussion is provided in Question 12.

The MAH evaluated renal TEAEs in OCA-treated subjects from Study 747-302 and postmarketing data respectively. From the totality of these analyses, the MAH concluded there is no increased risk of renal events in the proposed SmPC indicated population.

Overall Safety Population

- In the overall population, 17 (10.1%; EAIR of 4.159 subjects per 100 patient years) subjects had a renal TEAESI in the OCA group compared to 13 (7.8%; EAIR of 3.804 per 100 patient years) subjects in the placebo group.
- The most commonly reported renal TEAESI were Acute Kidney Injury (AKI) and hypoalbuminemia.
- Events of TTP point to both renal and cardiovascular SMQs.

Proposed SmPC Population

- 8 (8.9%; EAIR of 3.818 per 100 patient years) subjects in the OCA group and 4 (5.9%; EAIR of 2.877 per 100 patient years) subjects in the placebo group reported renal TEAESIs.
- Apart from the PT of TTP which was reported by 2 subjects in the OCA group (2.5%), the remaining renal events were reported by 1 OCA-treated subject (1.2%) each: AKI, hypoalbuminaemia, proteinuria, diabetic nephropathy, leukocyturia, and renal failure.
- None of these reported events were assessed as related with OCA either by investigator or MAH.
- In summary, there was no signal for an increased risk of renal TEAESIs with OCA treatment in Study 747-302.

Table 9: Study 747-302 - Treatment-Emergent Acute Kidney Injury in the Proposed SmPC Indicated Population

Subject ID	IP	Serious	Severity	Relatedness	Onset Day / Stop Date or Day of Death
207007	OCA 5 mg	No	Moderate	Not related	23 Aug 2016/ 10 Sep 2016 (death date)

Table 9: Study 747-302 - Treatment-Emergent Acute Kidney Injury in the Proposed SmPC Indicated Population

IP	Serious	Severity	Relatedness	Onset Day / Stop Date or Day of Death
OCA 5 mg	No	Moderate	Not related	23 Aug 2016/ 10 Sep 2016 (death date)

Post-marketing Renal Safety

- The analysis of postmarketing reports suggests that events of renal disease are more consistent with renal disease risk factors and natural history of PBC than direct effects of OCA.
- The cumulative review of the postmarketing reports did not change the understanding about the risk of renal impairment for patients with PBC treated with OCA.

Other Safety

AESIs of pruritus, dyslipidemia, and cholelithiasis/cholecystitis are discussed in Question 10.

Pruritus

- Pruritus is a known adverse drug reaction (ADR) per the current SmPC. The incidence for pruritus was higher in the OCA group (82.7%) compared to the placebo group (48.5%).
- The majority of pruritus events were mild to moderate and managed with temporary interruption of OCA treatment or use of medications such as antihistamines for control of symptoms. The incidence of serious pruritus TEAEs was low; 1 subject in the OCA group and none in the placebo group reported a serious TEAE of pruritus.

Dyslipidemia

- The incidence rate of dyslipidaemia TEAEs was similar across treatment groups (4.9% in the OCA group and 4.4% in the placebo group).
- The most frequently reported dyslipidaemia TEAE was low density lipoprotein increased (2 [2.5%] subjects in the OCA group and none in the placebo group).
- No subjects reported serious dyslipidaemia TEAEs or a TEAE leading to discontinuation.

Cholelithiasis/cholecystitis

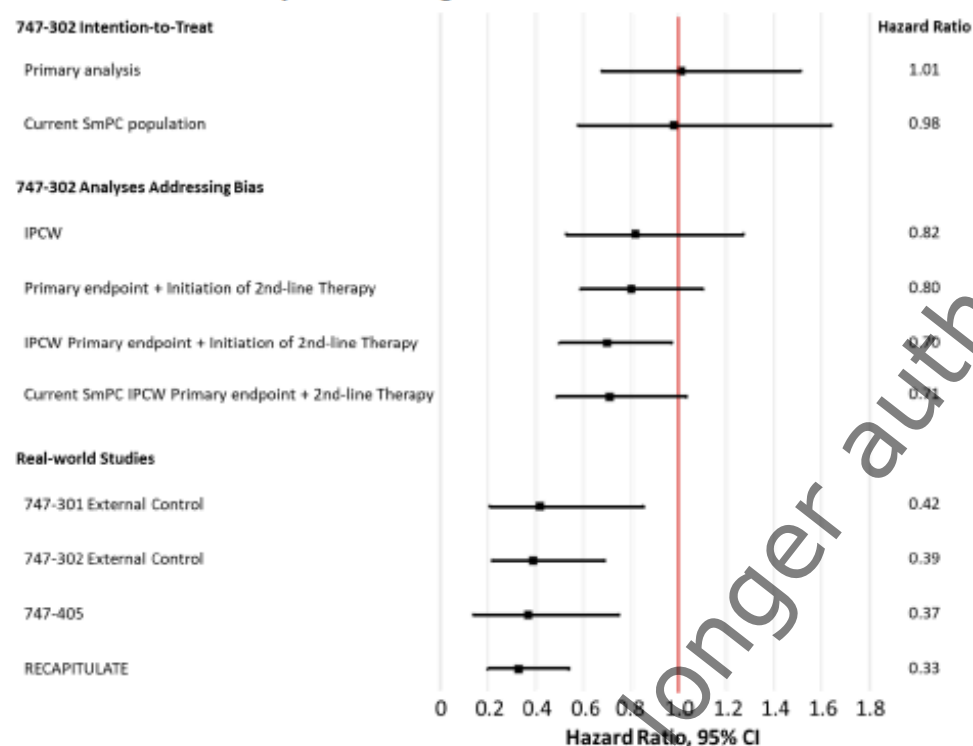
- A total of 3 (3.7%) subjects in the OCA group and 1 (1.5%) subject in the placebo group reported a cholecystitis/cholelithiasis TEAE.
- Cholelithiasis was the only PT reported across treatment groups.
- All cholecystitis/cholelithiasis TEAEs were mild to moderate in severity

Overall Benefit/Risk Assessment

In reviewing the totality of the data, including clinical studies, post-marketing data, and real-world evidence, OCA continues to demonstrate a favorable benefit:risk profile in the treatment of appropriate PBC patients as defined in the proposed SmPC label.

The MAH has demonstrated that despite feasibility challenges in Study 747-302 and observed bias, OCA has demonstrated benefit in biochemical response and clinical outcomes (Figure 6). Data both from MAH-supported and independent real-world and historical/external control studies support the findings of OCA benefit in Study 747-302 and further provide consistent evidence of clinically meaningful OCA benefit in improving transplant-free and event-free survival.

Figure 9: Hazard Ratio and 95% CI for Time to First Occurrence of Primary Endpoint (Death, Liver Transplant, or Hepatic Decompensation): 747-302 Intention-to-Treat; Analyses Addressing Bias; and Real-world Studies



Current SmPC=Subjects in the compensated (indicated per current SmPC) population.

The MAH recognizes there is some potential safety risk given imbalances observed in hepatotoxicity in the more advanced patients. While this observation was not observed in the post-marketing reports or real-world evidence, the MAH remains committed to ensure the safe use of OCA in the appropriate patient population. The observed imbalance in safety risk is reduced significantly by excluding the more severe patients, such as those with portal hypertension. Therefore, the MAH has proposed to further restrict the SmPC indicated population to those without evidence of portal hypertension. This will enhance the favorable benefit:risk profile for OCA.

Assessment of the MAH's response

Benefits of OCA treatment

Study 747.302 has failed to demonstrate a statistically significant and clinically relevant effect of OCA treatment in patients with PBC in reducing the risk of relevant clinical outcomes, i.e. the primary composite endpoint of death, liver transplant, or hepatic decompensation for the ITT population: HR 1.01 (95%CI 0.68, 1.51), p-value: 0.954. Notably, the results for the primary endpoint according to the liver disease status (compensated vs decompensated) show a numerical increment in the risk of event outcomes in decompensated patients treated with OCA (59.4% OCA vs 54.1% in placebo, HR 1.22 [95% CI: 0.65, 2.28]), though not statistically significant. By contrary, results were nearly identical in both treatment arms in the subgroup of compensated PBC patients (21.3% vs 21.7% OCA and placebo, respectively, HR 0.98 [95% CI: 0.58, 1.64]). Consistent results were observed across the spectrum of disease severity and relevant subgroups analysed, and in all the sensitivity analyses conducted. The MAH claims that the results from the prespecified analyses in Study 747-302 are not valid assessments of treatment benefit given the lack of adequate power due to poor enrolment, early termination for feasibility, inadequate number of outcome events, and systematic bias.

The study ended prematurely at 76% of anticipated enrolment, and with 96 of the targeted 127 (67%) adjudicated events observed, with 177 subjects ongoing at the time of Sponsor termination based on disposition. The MAH claims that this left the study underpowered to detect the proposed treatment effect. Although this can be agreed to some extent, it is highly unlikely that the observed lack of effect with nearly 70% of the planned number of events could have been reverted at all.

Furthermore, it is argued that due to the high treatment discontinuations and cross-over to effective treatments, which might have been due to unblinding in the placebo group, the study results might be biased. Although there could have been some differences in the timing of treatment discontinuation, similar rates of early treatment discontinuation were observed in both treatment arms (81.9% placebo vs 72% OCA discontinued treatment prematurely). It is also argued that subjects in the placebo group were more likely to initiate commercially available OCA treatment and that subjects in the placebo group who initiated commercial PBC treatments showed large and sustained decreases in ALP within 3 months of initiating second line therapy, as would be expected for subjects initiating an active treatment but not expected in subjects on placebo. However, according to the CSR, initiation of PBC treatment with a potential effect on ALP levels occurred in a small portion of subjects, and similar across treatment groups: incidence of initiating commercial Ocaliva in the placebo group (15%) compared with the OCA group (7%); whilst in OCA more subjects started bezafibrate (14% vs 7%), and no subjects started UDCA in any treatment group since the vast majority were on or past treatment. Although of a smaller magnitude, a decrease in ALP after switching to commercial treatments in OCA treated group was also reported (mean reduction 106.3 U/L placebo vs 67.5 U/L OCA). Moreover, no dramatic differences are observed between placebo and OCA treatment groups in the actual rate of treatment events while on treatment (39.6% placebo vs 35.4% OCA) or after IP discontinuation but still on study (45.8% vs 37.5%), with more subjects having the event in OCA after study discontinuation (14.6% placebo vs 27.1% OCA). Thus, although it can be agreed that the current estimation of the treatment effect might be confounded to some extent, should this occur it was in both treatment arms and not just in placebo. Therefore, any pot-hoc external comparison to overcome the failed study results becomes invalid.

Furthermore, the fact that placebo data from RWE show worse outcome results than those observed in the "pragmatic" placebo arm of the clinical trial raises serious doubts on its validity for comparative purposes. This worse outcome results in the "placebo" external cohorts could only be explained due to a high unlikely poor treatment management of PBC patients in clinical practice or, more likely, to differences in the actual prognosis of these cohorts. Thus, this underlines why comparisons with these external cohorts are not valid and limits their use as supportive evidence in this context.

So far, the only demonstrated effect of OCA treatment in PBC patients remains limited to quantitative reductions in biochemical parameters of highly uncertain clinical relevance. In the confirmatory trial, only a total of 21 (6.3%) patients enrolled in Study 747-302 met the primary endpoint as defined in the initial pivotal phase 3 Study 747-301 of an ALP $<1.67 \times \text{ULN}$ and total bilirubin $\leq \text{ULN}$ and ALP decrease from baseline of $\geq 15\%$. Indeed, the rate of responders was substantially lower compared to that previously reported and this was the case in both treatment arms, but rather noticeable in the OCA treated group: OCA 10.1% vs 2.4% placebo in Study 747-302 compared to OCA 34.0% vs 7% placebo in Study 747-301. No statistically significant differences were reported. At present, the predictive value of changes in ALP has not been demonstrated. The analyses conducted aimed to establish an association between biochemical response (based on the Study 747-301 primary endpoint) and improved clinical outcomes (based on the Study 747-302 primary outcomes endpoint) cannot be taken as demonstrative of the predictive value of these biochemical changes. Besides, the absence of concurrent changes in histological progression, and the worsening in relevant symptoms like pruritus and fatigue, add further uncertainty to the actual clinical benefits of OCA treatment.

In conclusion, the MAH has not confirmed that the changes in biochemical parameters following OCA treatment is associated with a clinical benefit for PBC patients.

Safety Risk

As initially noted, Study 747-302 shows a more concerning overall safety profile as compared to that reported in the initial submission, given the higher incidence rates of all types of TEAEs overall and compared to placebo treated patients. OCA treated patients showed a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death, both in the general safety population and the subset of patients with compensated liver disease. In addition, the higher rates observed in OCA treated patients for some relevant AESI like cardiovascular events (including adjudicated MACE), renal events (including AKI), DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events, both in the overall safety population and for the subset of patients with compensated disease were highlighted as a matter of major concern.

The MAH recognizes there is some potential safety risk given the imbalance observed in the overall safety population of Study 747-302 and cannot exclude a contributory role of OCA. Therefore, the MAH has proposed to further restrict the SmPC indicated population to patients with PBC without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or a prior decompensation event. This analysis was not pre-specified and the newly proposed target population for OCA is data driven by an otherwise limited subset of early stage PBC subjects of Study 747-302 (68 OCA vs 61 placebo). Thus, it is uncertain if the observed results in this subset of the study population represent an accurate estimation of their safety profile and thus if a "more benign" safety profile can be firmly concluded in them.

A reduction in the overall incidence of serious TEAEs (in newly proposed indication 18.5% OCA vs 25% placebo compared to the overall safety population 31.5% OCA vs 31.9% placebo) and TEAE leading to death (1.2% OCA vs 0 placebo in the restricted indication vs 3.0% OCA and 1.2% in the overall safety population) in the restricted PBC population is observed, with lower rates of serious TEAEs in OCA treated patients. The incidence of TEAEs leading to death remains slightly higher in OCA: 3.0% OCA vs 1.2% placebo in the overall population vs 1.2% OCA vs 0 placebo, but the number of events is too limited to firmly conclude. The lower incidence of serious TEAEs in the restricted PBC population is not totally unexpected considering that most serious TEAEs are related to the severity and progression of the underlying disease. By contrary, the incidence of severe TEAE (45.7% OCA vs 32.4% placebo), treatment related TEAEs (75.3% OCA vs 55.9% placebo), TEAE leading to IP withdrawal (33.3% OCA vs 26.5% placebo), to dose reductions (24.7% OCA vs 10.3% placebo), dose interruptions (25.9% OCA vs 25.0% placebo) or to treatment discontinuation (14.8% OCA vs 19.1% placebo) do not show relevant changes compared to those reported for the overall safety population. Indeed, most of them remain higher for OCA treated subjects, which is not reassuring. Incidence of thrombotic and cardiovascular disorders (6.2% OCA vs 2.9% placebo), , renal AESI (9.9% OCA vs 5.9% placebo), including events of AKI and renal failure, cholelithiasis (3.7% OCA vs 1.5% placebo), portal hypertensive gastropathy (3.7% OCA vs 0 placebo), DILI (2.5% OCA vs 0 placebo), liver transplant (1 case each in the early stage PBC population) or all-cause deaths (8 events in OCA vs 2 in placebo) are still observed more frequently in OCA treated subjects compared to placebo treated patients even in the newly proposed subset of early stage PBC patients. The number of events is sometimes too limited to firmly conclude, but the imbalance observed in the overall safety population remains in this restricted early stage PBC subset, which is concerning. Moreover, treatment is associated with significantly high incidences of pruritus (81.5% in OCA vs 47.1% placebo), which lead to treatment interruption in 23.5% OCA subjects and pharmacological treatment was required by 54.3% subjects in OCA (vs 7.4% and 27.9%, respectively, in placebo). OCA treatment in the newly proposed restricted population was also associated with higher gastrointestinal disorders (63% OCA vs 50% placebo), including higher rates of severe cases, and fatigue (9.9% OCA vs 7.4% placebo). All of them may have a significant negative impact in patient's health condition. It is also noted that the similar rates of hepatic TEAEs observed in OCA and placebo treated subjects in the newly proposed early stage PBC population raise doubts on the actual benefit of treatment since lower rates

might have been expected by a treatment aimed to modify the disease progression.

In summary, even if an apparent less toxic safety profile is seen in the proposed restricted subset of PBC patients, still an increased toxicity and poor tolerability of OCA treatment is noted in the subset of patients with an early stage, mostly asymptomatic and slow progressive condition. Moreover, it is important to note that this population was not pre-specified but it is data driven and it is comprised by a low number of patients. This hampers the proper interpretation of the reported results, as these might well be biased. In addition, the anticipated long-term exposure in clinical practice and difficulties to identify and exclude patients at risk of relevant events, add further concerns. In the absence of a demonstrated clinical benefit, the identified risks, and doubts on the reliability of the estimation, in an otherwise asymptomatic or mildly symptomatic early stage PBC population, are considered not acceptable.

The MAH has not confirmed the efficacy and safety of OCA in the treatment of PBC neither in the current indication nor in a restricted one, and thus SOB#1 is not fulfilled. As a consequence, the requested variation is not approvable (MO).

Safety

Question 2

The hepatic and CV AE profile appears particularly concerning. In addition to the broad discussion requested above, the MAH should specifically discuss the following:

1. The observed higher incidence of DILI and other hepatic AEs (e.g. blood bilirubin increased, varices oesophageal, ascites, portal hypertensive gastropathy) in OCA treated patients, including those with compensated liver disease, is of concern. Please comment, including the possibility to implement any risk minimisation measures.
2. The higher rate of CV AEs in OCA treated patients, including higher rates of adjudicated MACE, both in the overall safety population and in the compensated subset, is worrisome, even if most events were considered not related to OCA by the investigators. Contrary to previous findings, dyslipidaemia was less frequently reported in OCA treated patients in this study. However, no information is presented for changes in HDL cholesterol. The increased incidence of CV events, including MACE, in patients treated with OCA is a major concern and deserves further discussion on possible associated factors, including changes in lipid parameters among others.

Summary of the MAH's response

In the context of the totality of evidence on the benefit:risk, the MAH considers the safety profile acceptable with the proposed risk minimization measure to revise the current SmPC population and contraindicate patients with decompensated cirrhosis (CP-B, CP-C), a prior decompensated event, or compensated cirrhosis with clinical evidence of portal hypertension at baseline.

The hepatic and CV safety profile of OCA in the proposed SmPC indicated population improved in comparison to the overall and compensated populations in Study 747-302. Due to the significant bias observed in Study 747-302, the MAH has further investigated the safety profile of OCA in over 35,000 patient-years of Ocaliva post-marketing exposure in PBC. The MAH is also currently conducting a real-world safety analysis of patients with PBC (Study 747-405).

The response to the Major Objection is presented below according to the points highlighted by the Committee.

Overview of Hepatic Safety Events and Other Hepatic TEAEs

CHMP asked that the MAH address the "...observed higher incidence of DILI and other hepatic AEs (e.g., blood bilirubin increased, varices oesophageal, ascites, portal hypertensive gastropathy) in OCA treated patients, including those with compensated liver disease."

A comprehensive evaluation of hepatic safety events was performed in Study 747-302, including analyses of Investigator-reported hepatic TEAEs (SMQ-based), and retrospective adjudication of a broad set of hepatic safety events as triggered by Investigator-reported TEAEs and pre-specified lab thresholds, by an independent adjudication committee (data not previously included in the MAA submission dated 22 Dec 2022). The adjudication committee remained blinded to investigational product allocation and assessed the potential hepatic safety events, assigned likelihood of causality and degree of severity, and provided potential etiology for all cases.

A summary of the hepatic evaluations in Study 747-302 by overall, compensated (indicated per current SmPC) and proposed SmPC indicated populations is presented in Table 10.

In comparison to the overall population, the incidence of adjudicated potential hepatic safety events and other hepatic TEAEs noted by the CHMP in the OCA group was markedly lower with no meaningful difference between OCA and placebo treated subjects in the proposed SmPC indicated population.

Table 10: Study 747-302 - Summary of Hepatic Safety: Investigator-reported Hepatic TEAEs and Adjudicated Hepatic Safety Events by Overall, Compensated (indicated per current SmPC), and Proposed SmPC Indicated Populations

		Overall		Current SmPC		Proposed SmPC	
				Compensated (Indicated)		Indicated	
		PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Investigator-reported Hepatic TEAEs							
Subjects with at least 1 Hepatic TEAEs	n (%)	97 (58.4)	80 (47.6)	73 (56.6)	58 (42.6)	29 (42.6)	22 (27.2)
	IRY (PY)	40.855 (237.42)	26.42 (302.8)	35.814 (203.83)	21.215 (273.39)	25.754 (112.60)	11.844 (185.75)
Subjects with at least 1 Serious Hepatic TEAEs	n (%)	16 (9.6)	15 (8.9)	9 (7.0)	9 (6.6)	2 (2.9)	3 (3.7)
	IRY (PY)	4.630 (346.32)	3.646 (411.36)	3.042 (295.83)	2.483 (362.49)	1.385 (144.40)	1.396 (214.86)
Adjudicated Hepatic Safety Events							
All Adjudicated Hepatic Safety Events	n (%) [e]	99 (59.6) [230]	85 (50.6) [189]	72 (55.8) [167]	59 (43.40) [123]	28 (41.2) [64]	29 (35.8) [58]
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥mild severity)	n (EAIR)	8 (2.325)	18 (4.521)	4 (1.377)	10 (2.824)	1 (0.685)	4 (1.910)
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥moderate severity)	n (EAIR)	7 (2.012)	12 (2.923)	3 (1.019)	5 (1.379)	1 (0.685)	2 (0.931)

AE=adverse event; IP=investigational product; IRY=number of patients with event per 100 patient year; EAIR=number of patients with event per 100 patient year; OCA=obeticholic acid; PBO = placebo; PY=patient-years; SmPC=Summary of Product Characteristic; TEAE=Treatment-Emergent Adverse Event

Adjudicated Hepatic Safety Events (e.g., DILI)

- Overall Population

There were 189 hepatic safety events in 85 subjects in the OCA group compared to 230 events in 99 subjects in the placebo group. Of those events, 18 subjects had events positively adjudicated as possibly

related (n=17) or probably related to investigational product (n=1) events in the OCA group compared to 8 subjects (all possibly related) in the placebo group.

Of the 18 subjects, 12 in the OCA group had events $\geq$ moderate severity compared to 7 subjects in the placebo group.

- Proposed SmPC Indicated Population

There were 58 potential liver injury events in 29 subjects in the OCA group compared to 64 events in 28 subjects in the placebo group. The majority of potential liver injury events in both treatment groups were mild of severity, and the potential liver injury events assessed as $\geq$ moderate severity occurred in fewer subjects in the OCA group (10) than placebo group (12).

4 subjects had potential liver injury events adjudicated as possibly related in the OCA group compared to 1 subject in the placebo group. Of these subjects, 2 female subjects had events $\geq$ moderate severity in the OCA group compared to 1 subject in the placebo group. One subject was found to have elevated transaminases (ALT and AST $>5\times$ baseline). Other liver biochemistry was stable and consistent with baseline. Elevated transaminases returned to baseline approximately 1 month after withdrawal of rifampicin and OCA. The Investigator judged the cause for the event to be most likely due to rifampicin. The other subject was found to have an elevation in all liver biochemistries (ALT and AST $> 5\times$ ULN and total bilirubin $> 3\times$ ULN). She was diagnosed with cholecystolithiasis on Study Day 49 and underwent a laparoscopic cholecystectomy, subsequently all liver biochemistry had improved significantly. The subject was also taking ibuprofen and simvastatin at the time of the event.

No subject had potential liver injury assessed as probable or highly likely by the HSAC, and all cases were reversible with discontinuation of OCA. No subject with possible related potential liver injury progressed to liver failure, suffered accelerated disease progression after the event, underwent liver transplantation or died during the study or the follow up period.

All possible related potential liver injury events in the OCA group occurred within the first 3 months of investigational product, and no uniform pattern of liver injury was present.

Investigator-reported Hepatic TEAESIs

Overall Population

A total of 80 (47.6%) subjects in the OCA group and 97 (58.4%) subjects in the placebo group. Of these, 4 (2.4%) in the OCA group and none in the placebo group reported a PT of drug-induced liver injury.

Proposed SmPC Indicated Population

The incidence of hepatic TEAESIs in the OCA group (27.2%) was lower than in the placebo group (42.6%). Of these, 2 (2.5%) in the OCA group and none in the placebo group reported a PT of drug-induced liver injury.

The difference between subjects in the OCA and placebo groups is more pronounced when considering the incidence of exposure-adjusted hepatic TEAESIs (11.844 per 100 PYs in the OCA group and 25.754 per 100 PYs in the placebo group).

No difference was observed between treatment groups of exposure-adjusted hepatic serious TEAESIs (1.396 per 100 PYs in the OCA group and 1.385 per 100 PYs in the placebo group).

Additional analyses of post-marketing data from over 35,000 patient-years exposure show no increased hepatic events in patients with PBC treated with OCA.

Ocaliva Post-marketing Data: Hepatic Events

There has been no increased risk of hepatic events in post-marketing data. As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years. There

has been a decrease in hepatic reports globally. Between 2017 to 2023, the frequency of hepatic AEs reported per 100-patient years has dropped 30-fold.

Comprehensive evaluation of hepatic safety events observed in clinical trials of OCA across indications has informed our understanding of OCA's potential for hepatotoxicity. The majority of hepatic TEAEs have been reported in subjects with advanced PBC who either had evidence of decompensation or CSPH, which forms the basis for our proposed SmPC to further restrict the indication. Restricting the label per the proposed SmPC indication allows for an improved safety profile.

-Study 747-302: Adjudicated Hepatic Safety Events and Other Hepatic TEAEs

Adjudicated Hepatic Safety Events

As a retrospective assessment, hepatic events were identified via a set of biochemical and adverse event (SMQ based) triggers per Hepatic Safety Adjudication Charter (HSAC). These events underwent clinical review by the HSAC of all available data (medical history, concomitant medications, vital signs, lab values, liver imaging, pathology reports, and noninvasive tests) for each identified subject to determine liver injury status (including causality and severity). The adjudication committees remained blinded to investigational product allocation and assessed the potential for liver injury, assigned likelihood of causality and degree of severity, and provided potential etiology for all cases.

Potential hepatic injury events (e.g., DILI) were identified programmatically using SMQ searches of hepatic AEs, central and local laboratory data, and investigational product interruption records from the clinical database for hepatic injury. Hepatic AEs are defined as events included in the Hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, lab values, liver imaging and pathology reports, and non-invasive tests (NITs). Adjudication committees remained blinded to investigational product allocation.

Per the HSAC Charter, all cases adjudicated as potential evidence for liver injury are then assessed for causality (investigational product relatedness) and severity based on the Drug-Induced Liver Injury Network (DILIN) index (Table 11).

Table 11: Study 747-302 - Hepatic Safety Adjudication Causality Assessment

Causality Assessment Score	Descriptor	Details
Insufficient Information	Insufficient details in case package to make any assessment	Cases that do not have enough information provided to be assigned one of the below 4 categories, will be designated as having insufficient information. Members will be asked to specify what additional information is required to complete the causality assessment.
Unlikely drug related	Confidence of causality assessment is <25%	A role for study drug is unlikely based on the available information. Another etiology is likely to be the cause of injury.
Possible drug related	Confidence of causality assessment is between 25% to 49%	The available evidence does not definitively exclude the possibility of a causal role for study drug, but another etiology is more likely to be the cause of injury.
Probable drug related	Confidence of causality assessment is between 50% to 74%	Causality is supported by the preponderance of evidence; the drug is more likely to be the causal agent rather than not. Testing rules out some/most other likely causes.
Highly likely drug related	Confidence of causality assessment is between 75% to 100%	The evidence is beyond a reasonable doubt (positive rechallenge)

Blinded case level assessments of all hepatic events in the overall, compensated (indicated per current SmPC), and proposed SmPC indicated populations are presented in Table 12. A listing of the possibly related potential liver injury events in the proposed SmPC indicated population are described below and presented in Table 13.

All hepatic events had sufficient information for a causality assessment. There was 1 subject in the OCA group and 1 subject in the placebo group with hepatic events that were not assessable for a severity assessment.

The incidence of hepatic trigger events submitted for adjudication was lower in the OCA group (189 events) than the placebo group (230 events). Similarly, in the proposed SmPC indicated population, the incidence of hepatic trigger events was numerically lower in the OCA group (58 events) than the placebo group (64 events).

The incidence of hepatic safety events that were positively adjudicated as possible related to investigational product by the HSAC in the OCA group was lower in the proposed SmPC indicated population compared to the overall population:

- 38 events in 17 (10.1%) OCA-treated subjects in the overall population versus 9 events in 4 (4.9%) OCA-treated subjects in the proposed SmPC indicated population (brief narratives for these subjects are provided below).

In the proposed SmPC indicated population, the majority of the hepatic safety events were mild (22.2% in the OCA group and 20.6% in the placebo group) and moderate (9.9% in the OCA group and 16.2% in the placebo group). In the OCA group, 1 subject had a moderate-severe hepatic safety event (see below for mini narrative).

There were no hepatic safety events in the proposed SmPC indicated population assessed as probable or definite by the HSAC. The majority of subjects with possible causality were using concomitant

medications known to be potentially hepatotoxic at the time of the potential liver injury event and all "possible" events were reversible with discontinuation of OCA.

OCA:

- One female subject was found to have elevated transaminases (ALT and aspartate aminotransferase [AST] >5x baseline) on 02 Aug 2017 (Study Day 92). Other liver biochemistry was stable and consistent with baseline. Concomitant and potential hepatotoxic medication included rifampicin, which was initiated on Study Day 15. Rifampicin and investigational product were stopped, and the subject was admitted for a liver biopsy. Synthetic liver function remained normal, and no subsequent endpoint was reached. Elevated transaminases returned to baseline approximately 1 month after withdrawal of rifampicin and OCA. The Investigator judged the cause of the potential liver injury event to be most likely rifampicin.
- One female subject was found to have an elevation in all liver biochemistries (ALT and AST >5x ULN and total bilirubin >3x ULN) on 22 Jun 2018 (Study Day 80). The subject had been diagnosed with cholecystolithiasis on 22 May 2018 (Study Day 49). It is unclear from the documentation whether there were any gallstone-related or obstructive symptoms. Investigational product was ceased on 22 Jun 2018 (Study Day 80) and the subject underwent a laparoscopic cholecystectomy on 02 Aug 2018 (Study Day 121). On 12 Aug 2018 (Study Day 131) all liver biochemistry had improved significantly; no further blood tests are available for review (end of study [EOS]). The subject was also taking ibuprofen and simvastatin at the time of the event.
- One female subject experienced a significant elevation in alkaline phosphatase (ALP) (ALP >1000 U/L and >5% increase from baseline) on Study Day 91 with a lesser degree of gamma-glutamyl transferase (GGT), total bilirubin, ALT, and AST elevation. OCA was dose reduced to 10 mg every other day on Study Day 135. ALP remained persistently elevated, and OCA was withdrawn on Study Day 241 due to pruritis and rash. There was mild improvement in peak ALP after OCA withdrawal, but ALP did not return to baseline and remained >1000 U/L with a >15% increase from baseline. There was no associated synthetic liver function abnormality and the subject did not reach any endpoint by the end of study.
- One female subject experienced a single occasion of elevated ALT, AST (ALT/AST >3x baseline and >5x ULN), and GGT, without total bilirubin or ALP changes on Study Day 92. No changes were made to OCA dosing. Subsequent labs showed resolution of lab abnormalities without OCA dechallenge.

Placebo:

- One female subject with an elevation of predominantly GGT (467 U/L from baseline value of 261 U/L) and total bilirubin (2.5 mg/dL from baseline value of 1.4 mg/dL) with more modest elevation of ALT, AST, and ALP on Study Day 104. Investigational product was discontinued and the event was judged by the Investigator as probably related to investigational product. Concomitant medications included rifampicin at the time of the event. Laboratory results after Study Day 104 were unavailable.

Table 12: Study 747-302 - Summary of Hepatic Safety Events by Highest Causality and Highest Severity by Blinded HSAC Assessments by Overall, Compensated, and Proposed SmPC Indicated Population

n (%) [e]	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Hepatic Safety Events	99 (59.6) [230]	85 (50.6) [189]	72 (55.8) [167]	59 (43.4) [123]	28 (41.2) [64]	29 (35.8) [58]
Highest Causality by Blinded HSAC						
Highly Likely Drug Related	0	0	0	0	0	0
Probable Drug Related	0	1 (0.6) [4]	0	0	0	0
Possible Drug Related	8 (4.8) [22]	17 (10.1) [38]	4 (3.1) [11]	10 (7.4) [22]	1 (1.5) [4]	4 (4.9) [9]
Unlikely Drug Related	91 (54.8) [205]	67 (39.9) [141]	68 (52.7) [154]	49 (36.0) [101]	27 (39.7) [62]	25 (30.9) [49]
Insufficient Information	0	0	0	0	0	0
Highest Severity by Blinded HSAC						
Mild	41 (24.7)	37 (22.0)	36 (27.9)	34 (25.0)	14 (20.6)	18 (22.2)
Moderate	46 (27.7)	33 (19.6)	29 (22.5)	16 (12.5)	11 (16.2)	8 (9.9)
Moderate-Severe	4 (2.4)	8 (4.8)	3 (2.3)	4 (2.9)	1 (1.5)	2 (2.5)
n (%) [e]	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Severe	7 (4.2)	5 (3.0)	3 (2.3)	3 (2.2)	1 (1.5)	0
Fatal	0	1 (0.6)	0	0	0	0
Not Assessable	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)

AE=adverse event; e=number of events; HSAC=Hepatic Safety Adjudication Committee; IP=investigational product; OCA=obeticholic acid; PBO=placebo; PH=evidence of portal hypertension; SmPC=Summary of Product Characteristic

Table 13: Study 747-302 - Listing of Subjects in the OCA group with Potential Liver Injury Assessed as at Least Possible Potential Liver Injury Event by the Blinded HSAC in the Proposed SmPC Indicated Population (N=149)

Subject ID	IP	Blinded HSAC Highest Severity	Days OCA start to injury onset	ALT/ AST elevated	ALP/ GGT elevated	Bilirubin elevation above BL	Alternate Diagnosis / Concomitant Medications	MAH Clinical Comments
136002	OCA	Moderate-severe	85	Y	N	N	Rifampicin	Investigator assessment: most likely due to Rifampicin
162004	OCA	Moderate	80	Y	N	Y	Ibuprofen, Simvastatin, Biliary stone passage	Cholecystolithiasis Dx D49 Unexpectedly high GGT at screening No blood tests after cholecystectomy
219036	OCA	Mild	91	N	Y	N	-	Very high ALP at screening, other liver biochemistry at ULN (fluctuating), significant spike in ALT but no major elevation in other liver biochemistry and no synthetic function impairment (Bili, Alb, INR). ALP remained high despite IP cessation
238006	OCA	Mild	97	Y	N	N	Intercurrent illness	Mild, OCA continued throughout (5 years), no further events, good response
297004	PBO	Moderate	104	N	Y	Y	Rifampicin	-

Alb=albumin; Bili=bilirubin; BL=baseline; HSAC=Hepatic Safety Adjudication Committee; INR= international normalized ratio; IP=investigational product; N=No; OCA=obeticholic acid; PBO=placebo; SmPC=Summary of Product Characteristics; Y=Yes
Source: Data on file

Table 13: Study 747-302 - Listing of Subjects in the OCA group with Potential Liver Injury Assessed as at Least Possible Potential Liver Injury Event by the Blinded HSAC in the Proposed SmPC Indicated Population (N=149)

IP	Blinded HSAC Highest Severity	Days OCA start to injury onset	ALT/ AST elevated	ALP/ GGT elevated	Bilirubin elevation above BL	Alternate Diagnosis / Concomitant Medications	MAH Clinical Comments
OCA	Moderate-severe	85	Y	N	N	Rifampicin	Investigator assessment: most likely due to Rifampicin
OCA	Moderate	80	Y	N	Y	Ibuprofen, Simvastatin, Biliary stone passage	Cholelithiasis Dx D49 Unexpectedly high GGT at screening No blood tests after cholecystectomy
OCA	Mild	91	N	Y	N	-	Very high ALP at screening, other liver biochemistry at ULN (fluctuating), significant spike in ALT but no major elevation in other liver biochemistry and no synthetic function impairment (Bili, Alb, INR). ALP remained high despite IP cessation
OCA	Mild	97	Y	N	N	Intercurrent illness	Mild, OCA continued throughout (5 years), no further events, good response
PBO	Moderate	104	N	Y	Y	Rifampicin	-

Alb=albumin; Bili=bilirubin; BL=baseline; HSAC=Hepatic Safety Adjudication Committee; INR= international normalized ratio; IP=investigational product; N=No; OCA=obeticolic acid; PBO=placebo; SmPC=Summary of Product Characteristics; Y=Yes
Source: Data on file

Other Hepatic TEAEs

Other hepatic TEAEs noted by the CHMP (i.e., DILI, blood bilirubin increased, varices oesophageal, ascites, portal hypertensive gastropathy) are summarized by overall, compensated (indicated per current SmPC), and proposed SmPC indicated population in Table 14.

In comparison to the overall and compensated populations, hepatic TEAEs observed in OCA-treated subjects reduced in the proposed SmPC indicated population.

- Blood bilirubin increased: 20 (11.9%) OCA-treated subjects in the overall population, 14 (10.3%) OCA-treated subjects in the compensated population, and 4 (4.9%) OCA-treated subjects in the proposed SmPC indicated population
- Varices oesophageal: 20 (11.9%) OCA-treated subjects in the overall population, 16 (11.8%) OCA-treated subjects in the compensated population, and 4 (4.9%) OCA-treated subjects in the proposed SmPC indicated population
- Ascites: 18 (10.7%) OCA-treated subjects in the overall population, 9 (6.6%) OCA-treated subjects in the compensated population, and 1 (1.2%) OCA-treated subject in the proposed SmPC indicated population
- Portal hypertensive gastropathy: 14 (8.3%) OCA-treated subjects in the overall population, 11 (8.1%) OCA-treated subjects in the compensated population, and 3 (3.7%) OCA-treated subjects in the proposed SmPC indicated population

- DILI: 4 (2.4%) OCA-treated subjects in the overall population, 3 (2.2%) OCA-treated subjects in the compensated population, and 2 (2.5%) OCA-treated subjects in the proposed SmPC indicated population; Investigator-reported DILI events were adjudicated as described above: 1 subject with an event was positively adjudicated (possibly related; moderate in severity).

There were no serious hepatic TEAEs of varices oesophageal, ascites, and portal hypertensive gastropathy in the proposed SmPC indicated population. There was 1 OCA-treated subject with a serious hepatic TEAE of blood bilirubin that was considered unlikely related to investigational product by the Investigator and 1 OCA-treated subject with a serious hepatic TEAE of DILI (Section 1.2.1.1.1).

Table 14: Study 747-302 - Other Hepatic Treatment-Emergent Adverse Events Specified per the CHMP in Overall, Compensated, and On-label per Proposed SmPC (Safety Population [N=334])

Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Subjects with at least 1 Hepatic TEAE	97 (58.4)	80 (47.6)	73 (56.6)	58 (42.6)	29 (42.6)	22 (27.2)
Blood bilirubin increased	25 (15.1)	20 (11.9)	18 (14.0)	14 (10.3)	8 (11.8)	4 (4.9)
Varices oesophageal	28 (16.9)	20 (11.9)	23 (17.8)	16 (11.8)	6 (8.8)	4 (4.9)
Ascites	21 (12.7)	18 (10.7)	12 (9.3)	9 (6.6)	3 (4.4)	1 (1.2)
Portal hypertensive gastropathy	7 (4.2)	14 (8.3)	4 (3.1)	11 (8.1)	0	3 (3.7)
Drug-induced liver injury	0	4 (2.4)	0	3 (2.2)	0	2 (2.5)

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence of portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Ocaliva Post-marketing Data: Hepatic Events

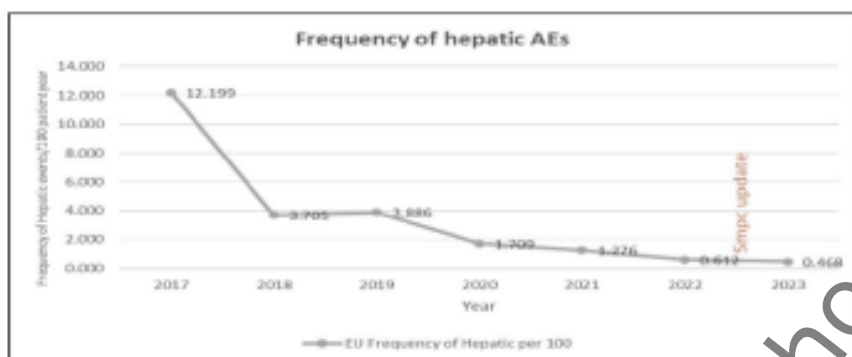
OCA was granted accelerated approval under the trade name Ocaliva by the US FDA on 27 May 2016, and received conditional approval by the European Commission on 12 Dec 2016, by Health Canada on 24 May 2017, and is now approved in 43 countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. As of May 2023, the estimated cumulative global exposure from marketing experience is over 35,000 patient-years.

Over the course of the marketed period for Ocaliva, there have been label refinements and changes to better define the appropriate treatment population compared to those subjects with more advanced disease that should not receive Ocaliva and should be contraindicated. A dramatic reduction in the frequency of hepatic AEs being reported occurred as these label changes per implemented. Between 2017 to 2023, the frequency of hepatic AEs reported per 100-patient years has dropped 30-fold. This signals that refinements in the label have worked to mitigate hepatic safety risk with Ocaliva.

In Figure 8, the frequency of exposure-adjusted incidence of hepatic safety reports has continuously decreased since the initial authorization of OCA.

- Prior to the SmPC update in June 2022, the frequency of exposure-adjusted incidence was 1.3 events per 100-patient-years.
- Following the change in the indicated patient population, the rate became 0.6 events per 100-patient years in 2022, a substantial reduction in the frequency of hepatic safety reports.

Figure 8: Frequency of Hepatic Adverse Events “per 100-patient years” in EU



AE=adverse event; EU=European Union.

Represented the same figure 8 as above for easy reference.

Per the changes now being proposed to the SmPC, OCA would be contraindicated in adult patients with PBC with decompensated cirrhosis, a prior decompensation event, or in patients with compensated cirrhosis who have evidence of portal hypertension. Although differentiation of progressive liver disease from potential drug-induced liver injury relies on clinical assessment by experts, there is an increased rate of reported liver safety events in patients with advanced PBC. These advanced patients would be contraindicated in the proposed labeling.

Cardiovascular Safety

CHMP raises two separate but related issues regarding the CV safety of OCA:

3. Effect of OCA on CV events, including MACE
4. Effect of OCA on lipid profiles

Overview of Cardiovascular Safety

A comprehensive analysis of CV events was performed based on the CV SOC, evaluating Cardiac Disorder TEAEs and SAEs. A separate analysis of CV events based on SMQ criteria was also undertaken. Apart from the investigator reported TEAE and AESI analyses, an independent committee of experts adjudicated CV events based on capture of a broad set of triggers, including TEAEs, labs (e.g. troponin), ECGs, and review of hospitalizations, to provide a rigorous evaluation of CV events. Based on the known effect of FXR-agonism on lipids and observed changes in lipoproteins observed in early clinical trials of OCA, lipoproteins were measured at study visits. Finally, Framingham risk scores (FRS), a tool used to predict 10-year risk for coronary heart disease, was also evaluated at baseline and on treatment.

In addition, CV events were also analyzed in post-marketing data to further assess any potential CV risks in patients with PBC treated with OCA.

CV Safety

Overall Population

A total of 15 (8.9%) subjects in the OCA group and 9 (5.4%) subjects in the placebo group reported a Cardiac Disorder TEAE.

In a broad SMQ of embolic and thrombotic events for CV AESIs, the incidence of overall CV TEAESIs was higher in the OCA group (9.5%) compared to placebo (4.2%).

5 (3.0%) subjects in the OCA group and 3 (1.8%) subjects in the placebo group reported an adjudicated MACE.

- Proposed SmPC Indicated Population

A total of 6 (7.4%) subjects in the OCA group and 4 (5.9%) subjects in the placebo group reported a Cardiac Disorder TEAE.

The incidence of CV TEAESIs was higher in the OCA group (6.2%) compared to placebo (2.9%). However, there was no trend for an increased risk for atherosclerotic CV events such as coronary artery disease, angina, or myocardial infarction when evaluating individual CV PTs.

Rates for serious TEAESIs were low in both groups; 1 OCA-treated subject reported a CVA event in the setting of confirmed TTP; both events were considered unlikely related to investigational product by the Investigator.

There is no clear signal for an increased CV risk based on analyses of the adjudicated CV events in a rigorous manner. A total of 1 (1.2%) subject in the OCA group and 3 (4.4%) subjects in the placebo group reported an adjudicated MACE.

Mean FRS was 7% in the OCA group and 9% in the placebo group at baseline. Mean FRS remained <10% at Month 12 and Month 42 in both groups.

Table 15: Study 747-302 - Summary of CV Events

		Overall		Compensated (Current per SmPC Indicated)		Proposed SmPC Indicated	
		PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Subjects with at least 1 Cardiac Disorder TEAE	n (%)	9 (5.4)	15 (8.9)	8 (6.2)	7 (5.1)	4 (5.9)	6 (7.4)
Subjects with at least 1 CV TEAESI	n (%)	7 (4.2)	16 (9.5)	5 (3.9)	11 (8.1)	2 (2.9)	5 (6.2)
Subjects with at least 1 Serious CV TEAESI	n (%)	3 (1.8)	7 (4.2)	2 (1.6)	4 (2.9)	1 (1.5)	2 (2.5)
Subjects with at least 1 Adjudicated CV TEAE	n (%)	3 (1.8)	5 (3.0)	3 (2.3)	2 (1.5)	3 (4.4)	1 (1.2)

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event; TEAESI=Treatment-Emergent Adverse Event of Special Interest.

Lipid Profile

- Decreases in LDLc over time in both OCA and placebo groups were likely due to frequent use of fibrates.
- The early, small decrease in HDLc attenuated over the course of treatment with OCA and is unlikely to impact long-term CV risk.

Ocaliva Postmarketing Data: CV Events

- The cumulative review of the post-marketing reports of atherosclerotic CV events secondary to changes in lipids did not alter the understanding of the MAH regarding CV safety for patients with PBC treated with OCA.

In summary, the totality of data from randomized clinical trials, RWE, and post-marketing data does not show a clear signal for an increased CV risk associated with OCA. Based on these data, the MAH is not proposing any additional risk minimization measures beyond the scope of the proposed SmPC.

Study 747-302: CV Safety

Cardiovascular TEAEs

A summary of CV TEAEs by SOC and PT for the overall, compensated, and proposed SmPC is presented in Table 16.

In the overall population, there were 21 Cardiac Disorder PTs among 15 (8.9%) patients in the OCA-treated group versus 14 among 9 (5.4%) patients in the placebo group. The most frequent Cardiac Disorder PT was palpitations: 5 (3%) patients in the OCA group versus 2 (1.2%) in placebo (palpitation is a known ADR in the SmPC). All other Cardiac Disorder events occurred in <2% of either treatment group.

In comparison to the overall population, 6 (7.4%) subjects in the OCA group and 4 (5.9%) subjects in the placebo group reported a Cardiac Disorder PT in the proposed SmPC population. The majority of Cardiac Disorder TEAEs were observed in OCA-treated subjects at a lower rate in the proposed SmPC population compared to the overall population.

With the exception of palpitations, no other Cardiac Disorder PT was reported by >1 OCA treated subject in the proposed SmPC population.

Table 16: Study 747-302 - Treatment-Emergent Adverse Events by Overall and Baseline Disease Stage in System Order Class of Cardiac Disorders

SOC Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	Placebo N=166	OCA N=168	Placebo N=129	OCA N=136	Placebo N=68	OCA N=81
Cardiac Disorders	9 (5.4)	15 (8.9)	8 (6.2)	7 (5.1)	4 (5.9)	6 (7.4)
Palpitations	2 (1.2)	5 (3.0)	1 (0.8)	3 (2.2)	0	3 (3.7)
Angina pectoris	1 (0.6)	2 (1.2)	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)
Coronary artery disease	0	2 (1.2)	0	0	0	0
Left ventricular hypertrophy	0	2 (1.2)	0	0	0	0
Myocardial infarction	0	2 (1.2)	0	1 (0.7)	0	0
Arrhythmia	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)
Atrial fibrillation	1 (0.6)	1 (0.6)	1 (0.8)	0	0	0
Bradycardia	0	1 (0.6)	0	1 (0.7)	0	0
Cardiovascular disorder	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)
Myocarditis	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)
Pericardial effusion	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)
Sinus bradycardia	0	1 (0.6)	0	0	0	0
Supraventricular extrasystoles	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)
Atrioventricular block second degree	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0
Bundle branch block right	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0
Cardiac failure	3 (1.8)	0	3 (2.3)	0	2 (2.9)	0
Cardiac failure congestive	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0
Diastolic dysfunction	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0
Extrasystoles	1 (0.6)	0	1 (0.8)	0	0	0

SOC Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	Placebo N=166	OCA N=168	Placebo N=129	OCA N=136	Placebo N=68	OCA N=81
Hypertensive heart disease	1 (0.6)	0	1 (0.8)	0	0	0

CSR=clinical study report; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; SOC=system organ class; TEAE=Treatment-Emergent Adverse Event

Notes: TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

Adverse events were coded using MedDRA Version 24.0.

For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302 CSR, Tables 14.3.1.2.2, 14.3.3.1.2.2.1, 14.3.1.2.2.2

Cardiovascular TEAEs and Serious TEAEs

CV TEAEs and serious CV TEAEs are summarized by overall, compensated (on-label per current SmPC) and on-label per proposed SmPC populations in Table 17 and Table 18.

CV AEIs were defined by the embolic and thrombotic events broad Standardized MedDRA Queries (SMQ), ischaemic heart disease broad SMQ, or central nervous system vascular disorders narrow SMQ. CV AEIs captured a broad range of atherosclerotic events which are of primary interest, as well as several non-atherosclerotic events such as venous thrombotic events and TTP, which do not have an underlying lipid-related pathophysiology. TTP was captured for both CV and renal SMQs. For this reason, the cases of TTP are described separately under renal AEIs Question #10.

While the rate for overall CV TEAEs was higher in the OCA group compared to placebo, there was no trend for an increased risk for atherosclerotic CV events such as coronary artery disease, angina, or myocardial infarction when evaluating individual CV PTs. Rates for serious TEAEs were low in both groups; 1 OCA-treated subject reported a CVA in the setting of confirmed TTP. Details for this case are described in Question #10.

Adjudicated outcomes for CV events provide the most rigorous analysis of CV risk based on a comprehensive CV adjudication process.

Table 17: Study 747-302 - Cardiovascular Treatment-Emergent AEIs in ≥1 OCA-treated Subject by Preferred Term in Overall, Compensated, and Proposed SmPC (Safety Population [N=334])

Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Subjects with at least 1 Cardiovascular TEAE	7 (4.2)	16 (9.5)	5 (3.9)	11 (8.1)	2 (2.9)	5 (6.2)
Angina pectoris	1 (0.6)	2 (1.2)	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)

Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Cerebrovascular accident	1 (0.6)	2 (1.2)	0	2 (1.5)	0	1 (1.2)
Coronary artery disease	0	2 (1.2)	0	0	0	0
Myocardial infarction	0	2 (1.2)	0	1 (0.7)	0	0
Subarachnoid haemorrhage	0	2 (1.2)	0	0	0	0
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	2 (1.5)	0	2 (2.5)
Portal vein thrombosis	0	1 (0.6)	0	1 (0.7)	0	0
Pulmonary embolism	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.7)	0	0
Reversible cerebral vasoconstriction syndrome	0	1 (0.6)	0	0	0	0
Thrombophlebitis	0	1 (0.6)	0	1 (0.7)	0	0
Thrombosis	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)
Venous recanalization	0	1 (0.6)	0	1 (0.7)	0	0
Venous thrombosis	0	1 (0.6)	0	1 (0.7)	0	1 (1.2)

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension;
SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Table 18: Study 747-302 - Cardiovascular Serious Treatment-Emergent AESIs in ≥1 OCA-treated Subject by Preferred Term in Overall, Compensated, and Proposed SmPC (Safety Population [N=334])

Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Subjects with at least 1 Serious Cardiovascular TEAE	3 (1.8)	7 (4.2)	2 (1.6)	4 (2.9)	1 (1.5)	2 (2.5)
Cerebrovascular accident	0	2 (1.2)	0	2 (1.5)	0	1 (1.2)
Coronary artery disease	0	2 (1.2)	0	0	0	0
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	2 (1.5)	0	2 (2.5)
Angina pectoris	0	1 (0.6)	0	0	0	0
Myocardial infarction	0	1 (0.6)	0	0	0	0
Pulmonary embolism	1 (0.6)	1 (0.6)	1 (0.8)	1 (0.7)	0	0
Subarachnoid haemorrhage	0	1 (0.6)	0	0	0	0
Mesenteric vein thrombosis	1 (0.6)	0	0	0	0	0
Paraplegia	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension;
SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Adjudicated Cardiovascular Events

All suspected MACE, including CV death, non-fatal myocardial infarction, non-fatal stroke, and additional CV events were adjudicated by an independent CV adjudication committee in a blinded fashion.

Potential events were identified programmatically using searches for fatal events, hospitalizations, and SMQ based searches for CV TEAEs. SMQ trigger events included ischaemic heart disease, cardiac failure, Torsade de pointes/QT prolongation, arrhythmia related investigations, signs and symptoms, cardiac arrhythmia terms [including bradyarrhythmias and tachyarrhythmias], and central nervous system haemorrhages and cerebrovascular conditions. Events were reviewed in conjunction with evaluation of

medical history, concomitant medications, vital signs, prespecified lab values, and ECGs. Adjudication committee members remained blinded to investigational product treatment assignment (CAC Charter, Version 7).

Adjudicated MACE is summarized by overall, compensated (on-label per current SmPC) and on-label per proposed SmPC populations in Table 19.

Overall

Overall, 5 (3.0%) subjects in the OCA group and 3 (1.8%) subjects in the placebo group reported an adjudicated MACE.

Proposed SmPC

In comparison to the overall population, the incidence of MACE observed in OCA-treated subjects was reduced significantly in the proposed SmPC population.

In the Proposed SmPC population, 1 (1.2%) subject in the OCA group and 3 (4.4%) subjects in the placebo group reported an adjudicated MACE. One subject treated with OCA, reported an adjudicated CVA event in the setting of confirmed TTP. Details for this case are provided in Question #10, Section 2.8.3.4.5. Considering the presentation of stroke in the setting of TTP, it is unlikely that the TTP event was related to OCA treatment, consistent with the Investigator's assessment.

In summary, when considering the proposed SmPC population, there is no clear signal for an increased CV risk based on rigorous analyses of the adjudicated CV events.

Table 19: Study 747-302 - Summary of Adjudicated Cardiovascular Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Subject with at least 1 Adjudicated CV TEAE	3 (1.8)	5 (3.0)	3 (2.3)	2 (1.5)	3 (4.4)	1 (1.2)
Revascularization Procedure	0	2 (1.2)	0	0	0	0
Stroke	0	2 (1.2)	0	2 (1.5)	0	1 (1.2)
Cardiovascular Death	0	1 (0.6)	0	0	0	0
Preferred Term, n (%)	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Myocardial Infarction	0	1 (0.6)	0	0	0	0
Arrhythmia	1 (0.6)	0	1 (0.8)	0	1 (1.5)	0
Heart Failure	2 (1.2)	0	2 (1.6)	0	2 (2.9)	0

OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Changes in Serum Markers of Lipids

LDLc

In study 747-301, mean baseline LDLc levels were >ULN (2.59 mmol/L or 100 mg/dL) for all treatment groups (3.6 mmol/L for 10 mg OCA, 3.5 mmol/L for Titration OCA, and 3.6 mmol/L for placebo). Consistent with FXR-related effects and previously observed findings from early phase studies, at week

2, a transient increase in LDLc was observed in the OCA groups, which returned to baseline levels by Month 3 and remained stable for the duration of treatment, with no difference from placebo between Month 3 and Month 12 (Figure 10). This small, transient increase in LDLc is unlikely to have an impact on long-term CV risk.

A different pattern for changes in lipids was observed in Study 747-302. Mean baseline LDLc was slightly higher in study 747-302 (mean LDLc 4.0 mmol/L) compared to study 747-301 (mean LDLc 3.6 mmol/L). In 747-302, a transient increase in LDLc was observed in the placebo group in the first month, with decreases in LDLc over time in both OCA and placebo groups (Figure 11).

While this pattern of lipid changes is not consistent with either the natural history of PBC or known biologic effects of OCA, the frequent use of antipruritic medications, which also lower LDLc (specifically cholestyramine, bezafibrate and fenofibrate), may have contributed to the observed decreases in LDLc in this study. As shown in Table 20, a larger proportion of subjects (higher in the OCA group compared to the placebo group) used antipruritic medications (i.e., fibrates) during the study, which likely explains the pattern of LDLc decrease in both groups, and especially the greater LDLc lowering in OCA-treated subjects, who were more likely to use fibrates. Of note, more subjects in the placebo group reported use of a statin during the study compared to the OCA group.

Mean (SD) LDLc (mmol/L)

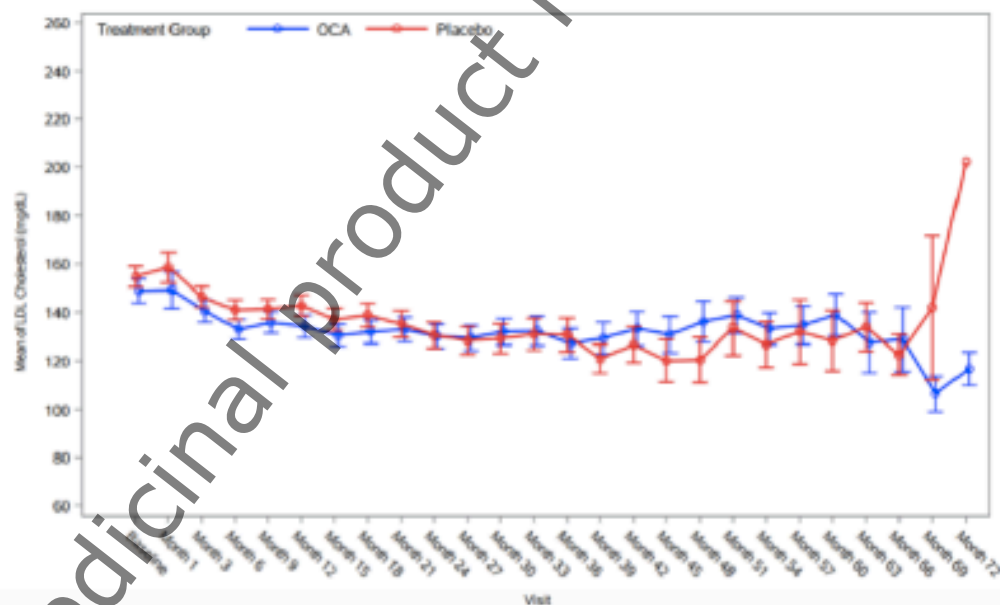
Time (Month)

Legend: Placebo (white circle), Titration OCA (orange triangle), 10 mg OCA (teal square)

Time (Month)	Placebo (mmol/L)	Titration OCA (mmol/L)	10 mg OCA (mmol/L)
0	3.6	3.6	3.6
3	3.6	3.6	3.6
6	3.6	3.6	3.6
9	3.4	3.4	3.4
12	3.6	3.6	3.6

Note: To convert from mmol/L to mg/dL, LDL is multiplied by 38.61

Figure 11: LDL Cholesterol by Treatment Group in Study 747-302



Number of Subjects	Visit																									
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
001	155	71	160	139	126	116	107	102	97	86	82	74	63	61	51	45	41	41	36	29	28	23	12	5	3	3
002	162	72	161	149	136	121	100	94	80	71	58	51	48	41	37	30	25	20	17	16	10	8	5	4	2	1

Table 20: Study 747-302 - Concomitant Medications: Lipid-modifying Agents

ATC 2 Class Preferred Term	Placebo N=166	OCA N=168	Overall N=334
Lipid modifying agents	86 (51.8)	99 (58.9)	185 (55.4)
Colestyramine	35 (21.1)	58 (34.5)	93 (27.8)
Bezafibrate	12 (7.2)	24 (14.3)	36 (10.8)
Atorvastatin	15 (9.0)	12 (7.1)	27 (8.1)
Fenofibrate	16 (9.6)	10 (6.0)	26 (7.8)
Simvastatin	7 (4.2)	13 (7.7)	20 (6.0)
Rosuvastatin	5 (3.0)	5 (3.0)	10 (3.0)
Atorvastatin calcium	7 (4.2)	2 (1.2)	9 (2.7)
Ezetimibe	5 (3.0)	3 (1.8)	8 (2.4)
Colesevelam hydrochloride	4 (2.4)	2 (1.2)	6 (1.8)
Colestipol hydrochloride	2 (1.2)	3 (1.8)	5 (1.5)
Rosuvastatin calcium	4 (2.4)	1 (0.6)	5 (1.5)
Evolocumab	2 (1.2)	2 (1.2)	4 (1.2)
Pravastatin	2 (1.2)	1 (0.6)	3 (0.9)
Colesevelam	0	2 (1.2)	2 (0.6)
Colestipol	1 (0.6)	1 (0.6)	2 (0.6)
Lovastatin	1 (0.6)	1 (0.6)	2 (0.6)
Aspartame;colestyramine	1 (0.6)	1 (0.6)	1 (0.3)
Astaxanthin;berberine;folic acid;monascus purpureus;policosanol;ubidecarenone	1 (0.6)	0	1 (0.3)
Astaxanthin;folic acid;monascus purpureus;policosanol;ubidecarenone	1 (0.6)	0	1 (0.3)
Atorvastatin calcium trihydrate;ezetimibe	1 (0.6)	0	1 (0.3)
Fish oil	1 (0.6)	0	1 (0.3)
Nicotinic acid	0	1 (0.6)	1 (0.3)
Omega-3 fatty acids	1 (0.6)	0	1 (0.3)
Pitavastatin	0	1 (0.6)	1 (0.3)
Pitavastatin calcium	1 (0.6)	0	1 (0.3)
Salmon oil	0	1 (0.6)	1 (0.3)

OCA=obeticolic acid; ATC=Anatomical Therapeutic Chemical

Notes: Concomitant medications were defined as all medications taken by subjects on or after the first dose of study treatment. Percentages were based on number of subjects in the Safety Population within each treatment group and overall.

A subject with multiple events within a given anatomical therapeutic chemical or preferred term was counted only once per anatomical therapeutic chemical or preferred term.

Source: 747-302 CSR, Table 14.3.3.1

HDLc

As requested by CHMP, HDLc by visit and by treatment group from Study 747-301 is presented in Figure 12. Mean baseline HDLc levels were 2.1 mmol/L in the 10 mg OCA group, 2.1 mmol/L in the Titration OCA group, and 1.8 mmol/L in the placebo group. The majority of subjects were above the LLN for HDLc. A small decrease in mean HDLc was observed from baseline in the OCA group, evident at Week 2, which attenuated over time through Month 12. At Month 12, the mean HDLc levels in the placebo and OCA titration groups were the same (1.8 mmol/L) and remained within normal range.

In Study 747-302, mean baseline HDLc was similar across treatment groups (1.9 mmol/dL in the OCA group and 1.8 mmol/dL in the placebo group) and similar to levels observed in Study 747-301 (Figure 13). HDLc remained stable in the placebo group through approximately Month 36, after which increases were seen, but were associated with small sample size and differential dropout. In the OCA group, HDLc decreased from 1.9 mmol/dL to 1.7 mmol/dL at Month 1, with a gradual trend to baseline levels from Month 12 to Month 60 (between 1.8 mmol/dL and 2.0 mmol/dL).

Of note, this degree of small decrease in HDLc has not been shown to impact CV risk (Gülec 2020).

Figure 12: HDL Cholesterol by Treatment Group in Study 747-301

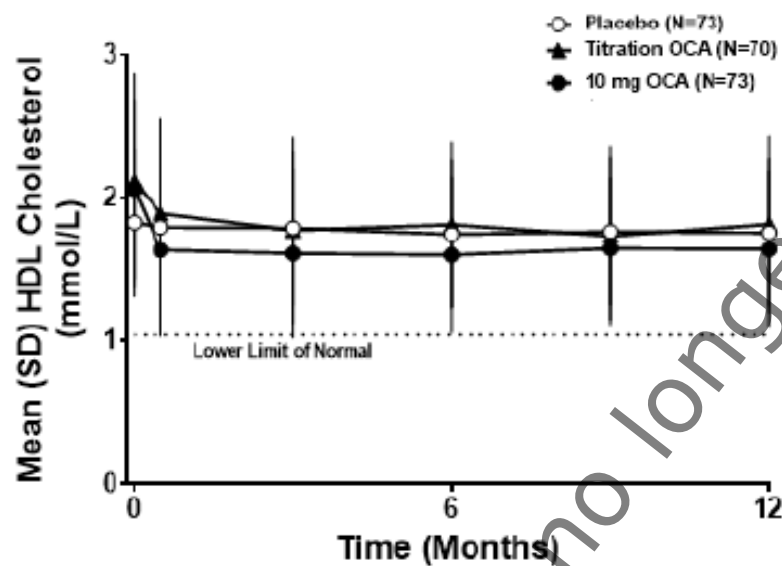
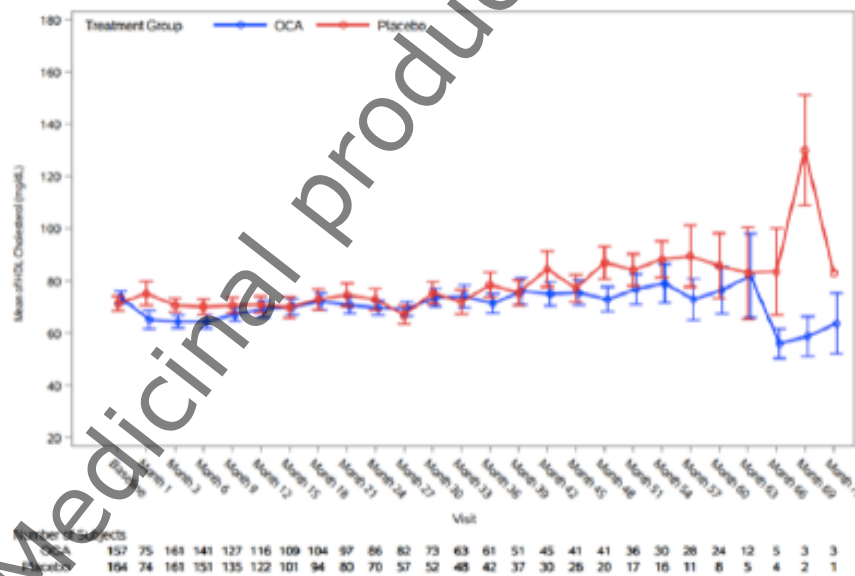


Figure 13: HDL Cholesterol by Treatment Group in Study 747-302



In summary, the transient increase in LDLc and the small decrease in HDLc, which attenuate with continued treatment with OCA, are unlikely to negatively impact long-term CV risk.

Framingham Risk Scores

Framingham risk scores (FRS) by visit are presented in Table 21.

Overall

Overall, mean (SD) FRS was 9% (9) in the OCA group and 10% (11) in the placebo group at baseline. No clear trends or significant differences were observed in FRS between treatment groups for any baseline disease stage.

Proposed SmPC

In the Proposed SmPC population, mean (SD) FRS was 7% (6) in the OCA group and 9% (9) in the placebo group at baseline. FRS remained <10% at Month 12 and Month 42 in the OCA and placebo groups.

Table 21: Summary of Framingham Risk Score in Study 747-302 by Visit by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Compensated (Indicated per current SmPC)		Proposed SmPC Indicated	
	PBO N=166	OCA N=168	PBO N=129	OCA N=136	PBO N=68	OCA N=81
Baseline						
n	160	155	124	126	66	76
Mean (SD)	10.201 (10.628)	8.701 (9.113)	9.382 (9.441)	8.744 (9.622)	8.607 (9.492)	7.142 (6.225)
SE	0.840	0.732	0.848	0.857	1.168	0.714
Median (Q1, Q3)	6.676 (3.891, 12.444)	6.104 (3.592, 11.024)	6.957 (3.709, 12.095)	6.088 (3.595, 10.180)	5.303 (3.390, 9.418)	5.580 (3.527, 7.901)
Min, Max	0.572, 61.615	0.690, 75.545	0.572, 61.139	0.690, 75.545	0.572, 61.139	0.690, 38.874
Month 12						
n	114	116	92	99	47	59
Mean (SD)	10.334 (9.718)	8.854 (10.021)	10.385 (9.486)	8.723 (10.258)	9.004 (9.165)	7.100 (6.625)
SE	0.910	0.930	0.989	1.031	1.337	0.863
Median (Q1, Q3)	7.602 (4.074, 12.813)	5.681 (3.202, 10.336)	7.602 (4.444, 13.036)	5.634 (3.127, 10.707)	5.323 (3.184, 10.609)	5.357 (2.790, 7.345)
Min, Max	0.596, 51.559	0.608, 82.821	0.596, 48.535	0.608, 82.821	0.596, 42.074	0.608, 32.652
Month 42						
n	26	40	25	35	16	22
Mean (SD)	9.111 (6.796)	9.003 (6.456)	9.346 (6.827)	9.281 (6.685)	7.420 (5.702)	9.161 (6.987)
SE	1.333	1.021	1.365	1.130	1.426	1.490
Median (Q1, Q3)	7.885 (4.086, 12.574)	7.886 (4.049, 10.632)	8.141 (4.226, 12.574)	7.897 (4.049, 11.191)	5.303 (3.895, 10.617)	8.055 (3.530, 11.761)
Min, Max	0.954, 26.859	1.725, 24.847	0.954, 26.859	1.725, 24.847	0.954, 22.300	1.725, 24.847

BP= blood pressure; FRS=Framingham Risk Score; HDL=high density lipoprotein; Max=maximum; Min=minimum; OCA=obeticolic acid; Q=quartile; USPI=United States Prescribing Information

Notes: FRS was derived using data after initiation of treatment and through discontinuation of study treatment or within 30 days after the discontinuation of study treatment. Data after a patient began commercial OCA were excluded.

The 10-year cardiovascular disease risk (%) for women=[1 - 0.95012^{exp(B - 26.1931)}] × 100%, where B=2.32888 × ln (age) + 1.20904 × ln (total cholesterol) - 0.70833 × ln (high-density lipoprotein cholesterol) + 2.76157 × ln (systolic blood pressure if not treated) + 2.82263 × ln (systolic blood pressure if treated) + 0.52873 (if current smoker) + 0.69154 (if diabetic).

Ocaliva Post-marketing Data: CV Events

OCA was granted accelerated approval under the trade name Ocaliva by the US FDA on 27 May 2016 and received conditional approval by the European Commission on 12 Dec 2016 and by Health Canada on 24 May 2017. Ocaliva is now approved in 43 countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. As of May 2023, the estimated cumulative global exposure from marketing experience is over 35,000 patient-years.

No increased risk of CV events has been observed in the post-marketing setting.

Cumulatively, since marketing approval in 2016, 136 CV reports, which included 170 CV events, have been reported globally.

The most frequently reported CV events were PTs of cerebrovascular accident (29), myocardial infarction (22), aphasia (15), dysarthria (7), cerebral haemorrhage (6), TIA (6), and thrombosis (6).

Twelve CV cases with a fatal outcome were reported. Ten of these cases were assessed as not related or unlikely related to Ocaliva. The remaining 2 fatal cases were assessed as possibly related to Ocaliva; one report was from a patient with advanced PBC disease who would now be contraindicated per the current SmPC, and one fatal event of cerebral haemorrhage after a fall was confounded by concomitant use of an anticoagulant medication.

In summary, the totality of data from randomized clinical trials, RWE, and post-marketing data does not show a clear signal for an increased CV risk associated with OCA. Based on these data, the MAH is not proposing any additional risk minimization measures beyond the scope of the proposed SmPC.

Assessment of the MAH's response

Hepatic Safety

Evaluation of hepatic safety events was performed in Study 747-302, including analyses of Investigator-reported hepatic TEAEs (SMQ-based), and retrospective adjudication of a broad set of hepatic safety events as triggered by Investigator-reported TEAEs and pre-specified lab thresholds, by an independent adjudication committee (not previously reported to CHMP). Based on these data, compared to the overall population the incidence of hepatic TEAEs and other hepatic TEAEs noted by the CHMP in the OCA group were markedly lower with no meaningful difference between OCA and placebo treated subjects in the proposed SmPC indicated population (investigator-reported hepatic TEAE: 27.2% OCA vs 42.6% placebo in the proposed SmPC and 47.6% OCA vs 58.4% placebo in the overall population; adjudicated hepatic safety events: 35.8% OCA vs 41.2% placebo in the proposed SmPC and 50.6% OCA vs 59.6% placebo in the overall population). Not unexpectedly, the incidence of positively adjudicated hepatic events were reduced in the restricted indication (4.9%) with respect to the overall safety population (10.1%), and similar rates of severe and exposure adjusted hepatic TEAEs are seen in OCA and placebo. A reduction in the overall incidence of hepatic events in subjects with an early stage PBC condition is not unexpected given that these events can be anticipated with the progression of the underlying disease. However, for a treatment aimed to modify disease progression, a reduction in the risk of hepatic TEAEs with respect to placebo arm would have been expected. Thus, although an increased hepatic toxicity of OCA treatment cannot be concluded based on these data, the roughly similar rates of hepatic events are not reassuring at all.

As requested, other hepatic TEAEs noted by the CHMP (i.e., DILI, blood bilirubin increased, varices oesophageal, ascites, portal hypertensive gastropathy) were also analysed and presented. As expected, the incidences of most of these hepatic events, which are related to the severity and progression of the PBC condition, were reduced in the restricted early stage PBC population compared

to the overall safety population (BR increased 4.9% vs 11.9%, varices oesophageal 4.9% vs 11.9%, portal hypertensive gastropathy 3.7% vs 8.3%), whilst the rate of DILI events remain unchanged (2.5% vs 2.4%). In the restricted population, the incidence of BR increased, varices oesophageal and ascites was lower in OCA vs placebo, which is reassuring. However, hepatic events of portal hypertensive gastropathy and DILI events were only reported for OCA treated patients in an otherwise mild, early stage PBC subpopulation, which is concerning.

Information from postmarketing on hepatic events show that the frequency of hepatic AEs reported per 100-patient years has dropped 30-fold between 2017 to 2023. However, this does not necessarily reflect a decrease in hepatic events linked to SmPC restrictions, as claimed by the MAH, but well reflect just a change in the main source of reporting data, where clinical trials decrease over time whilst spontaneous reporting is the main source in the late years. It is not surprising that the rate of spontaneous reporting decreases over time, particularly considering that most of these hepatic events would be expected during the progression of PBC. Adherence to current restrictions in the SmPC has not been measured, and thus, the effectiveness of current RMM remains undetermined.

The MAH proposes a restriction in the indication for OCA to the treatment of primary biliary cholangitis (PBC) without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or a prior decompensation event, in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA in order to minimise these risks. Even if an apparent more acceptable hepatic safety profile is seen in this restricted population, data are limited (n=149) and results come from post-hoc analyses, thus no firm conclusions can be drawn. Even in this restricted population, rather similar rates of hepatic TEAEs and serious hepatic TEAEs are observed in OCA vs placebo treated subjects, which is not totally reassuring. Furthermore, some relevant hepatic events like portal hypertensive gastropathy and DILI events are still reported during OCA treatment in an otherwise mild and early stage PBC population. This is further discussed under MO1, considering the totality of the safety findings. (See MO1).

Information in the SmPC Section 4.4 should be duly revised to properly reflect the increased risk of hepatic TEAESI during OCA treatment, including a recommendation to interrupt treatment in patients progressing to more advanced PBC stages where OCA is contraindicated (OC).

CV safety

A higher rate of CV AEs was seen in OCA (8.9%) vs placebo (5.4%) treated patients, including higher rates of adjudicated MACE (3.0% OCA vs 1.8% placebo) and embolic and thrombotic events for CV AESIs (9.5% OCA vs 4.2% placebo) in the overall safety population. A similar trend was seen in the compensated subset of PBC patients.

Apart from the investigator reported TEAE and AESI analyses, an independent committee of experts adjudicated CV events based on capture of a broad set of triggers, including TEAEs, labs (e.g. troponin), ECGs, and review of hospitalizations, to provide a rigorous evaluation of CV events. Lipoproteins were measured at study visits. Based on these data, in comparison to the overall population, the incidence of cardiac disorder TEAE, CV TEAESI and serious CV TEAESI was reduced in the newly proposed restricted SmPC population: 7.4% OCA vs 5.9% placebo, 6.2% OCA vs 2.9 % placebo, 2.5% OCA vs 1.5% placebo, respectively. However, still numerically higher rates of these common events are seen in OCA treated subjects. The most frequent Cardiac Disorder PT was palpitations: 5 (3%) patients in the OCA group versus 2 (1.2%) in placebo (palpitation is a known ADR in the SmPC). In the restricted population, palpitation remains as the only cardiac disorder reported by >1 OCA patient (3 patients, 3.7% vs 0 subjects in placebo). The incidence of TTP, venous thrombosis and cerebrovascular accident remains higher in the restricted PBC population (6.2% OCA vs 2.9% placebo).

A retrospective adjudication of CV TEAE reduces the incidence of MACE events in the overall safety population (3.0 OCA vs 1.8% placebo), but a shift in trend is observed in the proposed SmPC population: (3 events) 1.2% OCA and (1 event) 4.4% placebo. This is reassuring, but due to the low numbers of events, results should be taken with caution.

The previously observed findings in lipid parameters from early phase studies, which included a transient increase in LDLc at week 2 observed in the OCA groups, which returned to baseline levels by Month 3 and remained stable for the duration of treatment, and transient HDL decreases, were not seen in the confirmatory trial. The MAH argues that decreases in LDLc over time in both OCA and placebo groups were likely due to frequent use of fibrates, whilst the early, small decrease in HDLc attenuated over the course of treatment with OCA and is unlikely to impact long-term CV risk.

In the post-marketing setting, cumulatively, since marketing approval in 2016, 136 CV reports, which included 170 CV events, have been reported globally. The most frequently reported CV events were PTs of cerebrovascular accident (29), myocardial infarction (22), aphasia (15), dysarthria (7), cerebral haemorrhage (6), TIA (6), and thrombosis (6). Twelve CV cases with a fatal outcome were reported, 10 considered not related.

Although firm conclusions cannot be drawn, the numerical imbalance observed in Study 747-301 with respect to CV events, including MACE and other thrombotic events, remains in the confirmatory trial. Restricting the population to those on early stage do not solve the concern, since still these events were reported commonly and more frequently in OCA than in placebo treated subjects, except for MACE events, but numbers are too limited to firmly conclude. Thus, at present, the increased risk of CV events cannot be ruled out neither in the overall nor in the restricted PBC population. Considering the early stage of PBC condition, the high incidence of CV and thrombotic events in OCA treated patients is concerning. The lack of information in Section 4.4 is not acceptable. A proposal to reflect the risk should be presented (OC).

Based on the data presented, an increased risk of portal hypertension, DILI, thrombotic and CV events in OCA treated subjects may exist even in the restricted early PBC population. This is concerning and should be properly reflected in the SmPC. Besides, this restricted population is data driven, which hampers interpretation of the reported results.

Issue not solved, but not further pursued within this procedure.

SmPC changes to reflect the identified risks are deemed required.

Other concerns

Clinical aspects (Efficacy and Safety)

Study 747-301 (LTSE)

Question 3

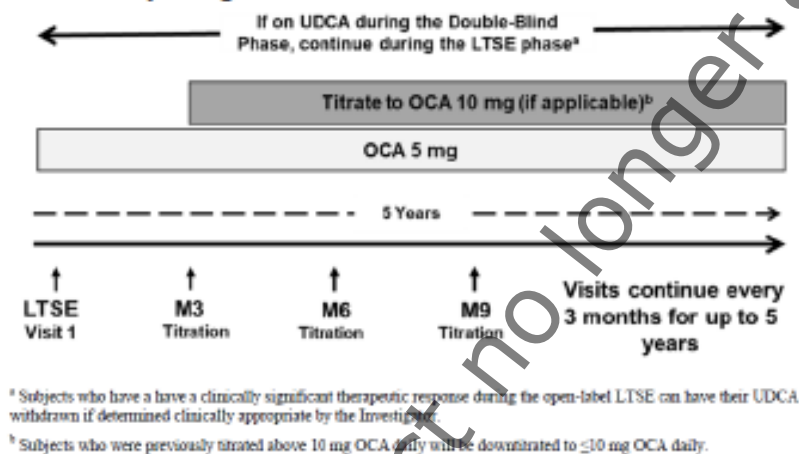
Patients randomized to placebo in Study 747-301 crossed over to OCA treatment and all patients were followed for up to an additional 5 years (747-301 LTSE). A more comprehensive presentation of the relevant efficacy and safety results (focusing on SAEs and AESIs) of this study should be provided.

Summary of the MAH's response

Study 747-301 was the Phase 3, 12-month, double-blind, placebo-controlled trial that was submitted in the original application to support the Conditional Marketing Authorisation (CMA) based on establishing a reduction in serum alkaline phosphatase (ALP). The study enrolled subjects in early-stage primary biliary cholangitis (PBC) with ALP $\geq 1.67 \times$ upper limit of normal (ULN) or total bilirubin $> \text{ULN}$ but $< 2 \times \text{ULN}$, and without presence of clinical complications of PBC or clinically significant hepatic decompensation. Following the 12-month double-blind, placebo-controlled period of Study 747-301, all subjects, including those who received placebo, were eligible to participate in an open-label LTSE and were followed for up to an additional 5 years (747-301 LTSE). The first subject was randomized to the double-blind phase in March 2012 and the last subject completed the LTSE Phase of the study in December 2018. Thus, at the time of the CMA approval in December 2016, all subjects were in the LTSE Phase.

The Month 12 Visit from the double-blind phase served as the Day 1 Visit of the LTSE Phase as shown in Figure 14.

Figure 14: Study Design 747-301 LTSE



LTSE=long-term safety extension; M=month; OCA=obencholic acid; UDCA=ursodeoxycholic acid
Source: Source: 747-301 LTSE CSR

Key study design aspects of 747-301 LTSE included:

- Subject treatment allocation in the double-blind Phase was not made available until the entire study was unblinded. Accordingly, all subjects starting in the LTSE phase were initially started on the 5 mg dose, i.e., subjects who received placebo started OCA therapy, those already on 5 mg continued on the same dose, while those who received 10 mg at the end of the double-blind phase were titrated down to 5 mg. Using this approach, blinding of the entire study was maintained and data on the effects of down titrating from 10 mg to 5 mg were also obtained.
- All subjects continued at a 5 mg dose for a minimum of 3 months. Subsequent to the LTSE Month 3 visit, OCA doses could be titrated (incrementally from 5 mg to 10 mg to 15 mg, up to 25 mg OCA at a frequency of no more than one up-titration every 3 months). However, effective with Protocol Version 5 (21 Mar 2018), the protocol was amended to align with marketing doses (i.e., 5 mg or 10 mg once daily). Any subject receiving a dose higher than 10 mg was down titrated to ≤ 10 mg daily.
- Any of these subjects who had a clinically significant therapeutic response during the LTSE phase could have had their ursodeoxycholic acid (UDCA) withdrawn if determined clinically appropriate by the Investigator. Subjects who received investigational product as monotherapy in the double-blind phase were to receive OCA as a monotherapy in the LTSE phase.

747-301 LTSE – Disposition and Demographics

LTSE – Disposition

A total of 217 subjects were enrolled into the double-blind phase of the study; 198 subjects completed the double-blind phase, of which 193 subjects enrolled into the LTSE phase. The MAH decided to stop the LTSE phase early (before the last subject had completed) as it was determined that the LTSE had met its clinical objectives by demonstrating sustained efficacy of OCA after long-term treatment for up to 72 months with no unexpected safety findings with longer-term administration of OCA in this population.

Subject disposition is summarized in Table 22 for the overall subject population.

Overall, there was good retention in the study. A total of 158 (82%) subjects completed 4 years of follow-up on study and 111 (60%) subjects completed the protocol as specified following administrative termination/closure of the study after 6 years. The largest number of subjects excluded for a single cause were due to discontinuation of the study due to study closure by the MAH (83 [43%] subjects). Twenty (10%) subjects discontinued due to an adverse event (AE) (either pruritus or other AE), and 12 (6%) subjects withdrew consent. Two subjects in the LTSE phase (one during the study and another after the study was closed) died; both deaths were considered by the Investigator as unrelated to OCA. An additional subject had died in the double-blind phase (considered as unlikely related to OCA by the Investigator and the MAH).

Table 22: 747-301 LTSE – Subject Disposition: All Subjects (N=193)

Number of Subjects, n (%)	Total OCA
Subjects Enrolled in LTSE Phase	193
Strata 1: ALP > 3× ULN and/or AST > 2× ULN and/or Bilirubin > 1× ULN, Intolerant to UDCA	8 (4)
Strata 2: ALP ≤ 3× ULN and AST ≤ 2× ULN and Bilirubin ≤ 1× ULN, Intolerant to UDCA	4 (2)
Strata 3: ALP > 3× ULN and/or AST > 2× ULN and/or Bilirubin > 1× ULN, Currently taking UDCA	57 (30)
Strata 4: ALP ≤ 3× ULN and AST ≤ 2× ULN and Bilirubin ≤ 1× ULN, Currently taking UDCA	124 (64)
Double-Blind Phase Treatment	
Placebo	66 (34)
Titration OCA ^a	63 (33)
Subjects that uptitrated from 5 mg to 10 mg OCA	33 (17)
Subjects that remained at 5 mg OCA	30 (16)
10 mg OCA	64 (33)
Safety Population ^b	193 (100)
2-year Completers ^c	174 (90)
3-year Completers ^d	165 (85)
4-year Completers ^e	158 (82)
5-year Completers ^f	116 (60)
Primary Reason for Discontinuation from the LTSE Phase	
Withdrew consent	12 (6)
Was unable to provide required blood samples	0
Developed any exclusion criterion, including pregnancy	0
Death during LTSE Phase ^g	1 (<1)
Discontinued due to pruritus	8 (4)
Was discontinued due to other clinical or laboratory adverse event	12 (6)
Was lost to follow-up	6 (3)
Was discontinued due to administrative reason(s)	0
Was discontinued due to major protocol violation/non-compliance	1 (<1)
Was discontinued due to other reason	90 (47)
Trial closure in country by MAH	83 (43)
PI decision	5 (3)
Discontinuation due to Liver transplantation ^h	1 (<1)
Pregnancy	1 (<1)

AST=aspartate transaminase; LTSE=long-term safety extension; OCA=obeticholic acid; PI=Principal Investigator; UDCA=ursodeoxycholic acid; ULN=upper limit of normal

Percentages are based on the number of subjects enrolled in the LTSE phase.

^a Subjects randomized to the Titration OCA treatment group received 5 mg OCA as their starting dose. Only Titration OCA subjects eligible for titration at Month 6 uptitrated to 10 mg OCA, while subjects ineligible for titration remained at their starting dose of 5 mg OCA.

- ^b All subjects who received any amount of OCA during the LTSE phase.
- ^c All subjects who were exposed to OCA for at least 2 years.
- ^d All subjects who were exposed to OCA for at least 3 years.
- ^e All subjects who were exposed to OCA for at least 4 years.
- ^f All subjects who were exposed to OCA for at least 5 years.
- ^g Subject 183004 died on study with death as the reason for discontinuation. One additional subject died within 30 days of the end of the LTSE phase of the study (165002), but the subject is not accounted for with death as a reason for discontinuation as they had already been discontinued due to trial closure. A third subject died during the double-blind phase (Section 2.1.3.3).
- ^h The subject represented in this row as "Discontinuation due to liver transplant" is Subject 142017. In addition, Subject 162005 was discontinued from the study due to placement on liver transplant list (captured as PI decision; subject underwent transplant within 30 days of end-of study). One additional subject (Subject 109004) received liver transplant within 30 days of the end of the study, but reason for discontinuing was adverse event of hepatic decompensation (details on these subjects can be found in Section 2.1.3.7).

Source: 747-301 LTSE CSR, Table 14.1.1 and Table 14.4.1.2

- ^b All subjects who received any amount of OCA during the LTSE phase.
- ^c All subjects who were exposed to OCA for at least 2 years.
- ^d All subjects who were exposed to OCA for at least 3 years.
- ^e All subjects who were exposed to OCA for at least 4 years.
- ^f All subjects who were exposed to OCA for at least 5 years.
- ^g Subject 1 died on study with death as the reason for discontinuation. One additional subject died within 30 days of the end of the LTSE phase of the study (2), but the subject is not accounted for with death as a reason for discontinuation as they had already been discontinued due to trial closure. A third subject died during the double-blind phase (Section 2.1.3.3).
- ^h The subject represented in this row as "Discontinuation due to liver transplant" is Subject 4. In addition, Subject 6 was discontinued from the study due to placement on liver transplant list (captured as PI decision; subject underwent transplant within 30 days of end-of study). One additional subject (Subject 1) received liver transplant within 30 days of the end of the study, but reason for discontinuing was adverse event of hepatic decompensation (details on these subjects can be found in Section 2.1.3.7).

Source: 747-301 LTSE CSR, Table 14.1.1 and Table 14.4.1.2

747-301 LTSE – Populations Analysed

Except where noted, only subjects who enrolled in the LTSE phase were considered for analysis in this report. The Safety Population included 193 subjects who received at least 1 dose of OCA during the LTSE phase.

747-301 LTSE – Demographics and Baseline Characteristics

Key demographic and baseline characteristics (baseline at the time of enrolment in the double-blind phase) of the 193 subjects enrolled in the LTSE are summarized by for Total OCA in Table 23.

For the total population, the mean age was 55.4 years, with a range from 29 to 83 years. A total of 83% of subjects were <65 years of age. As expected with PBC, the study population was predominantly female (92%) and white (94%). The majority of the population was European (67%), followed by North American (29%), and Australian (4%).

The mean body weight and body mass index were 69.70 kg and 26.05 kg/m², respectively, with 82% of subjects being <30 kg/m². The majority (93%) of the population was on UDCA at baseline. The majority of subjects enrolled in the 747-301 LTSE had features of mild to moderate PBC. Baseline bilirubin was >ULN in 8% of subjects, while baseline ALP, alanine transaminase (ALT), and aspartate aminotransferase (AST) were >3x ULN in 27%, 24%, and 10% of subjects, respectively.

Table 23: 747-301 LTSE – Demographic and Baseline Characteristics: Safety Population (N=193)

	Total OCA (N=193)
Age (years)	
n	193
Mean (SD)	55.4 (10.01)
SEM	0.72
Median	55.0

	Total OCA (N=193)
Q1, Q3	49.0, 63.0
Min, Max	29, 83
Age subgroups, n (%)	
<65 years	161 (83)
>65 years	32 (17)
<30 years	1 (<1)
30 to 39 years	10 (5)
40 to 49 years	41 (21)
50 to 59 years	71 (37)
60 to 69 years	58 (30)
70 to 79 years	11 (6)
>80 years	1 (<1)
Sex, n (%)	
Male	16 (8)
Female	177 (92)
Race/Ethnicity, n (%)	
White	181 (94)
Non-White	12 (6)
Black	3 (2)
Asian	2 (1)
Hispanic	4 (2)
Other	3 (2)
Multiple Races Checked	0
Region, n (%)	
Europe	129 (67)
North America	56 (29)
Australia	8 (4)
On UDCA at Baseline, n (%)	180 (93)
Bilirubin >ULN	16 (8)
ALP >3x ULN	52 (27)
ALT >3x ULN	46 (24)
AST >3x ULN	19 (10)

OCA=obeticholic acid; SD=standard deviation; SEM=standard error of the mean; UDCA=ursodeoxycholic acid; ULN=upper limit of normal

Note: Percentages are based on the number of subjects assigned to each treatment group.

Source: 747-301 LTSE CSR, Table 14.1.2, 14.1.3

747-301 LTSE - Efficacy

Composite Endpoint of Alkaline Phosphatase and Total Bilirubin

The double-blind phase primary efficacy composite endpoint (the percentage of subjects with ALP $<1.67\times$ ULN and total bilirubin $\leq$ ULN and an ALP decrease of $\geq 15\%$ from baseline) was evaluated in the LTSE to assess the long-term efficacy of OCA in subjects with PBC, including durability of response. The percentage of subjects achieving the primary efficacy composite endpoint in the LTSE phase is presented in Figure 15.

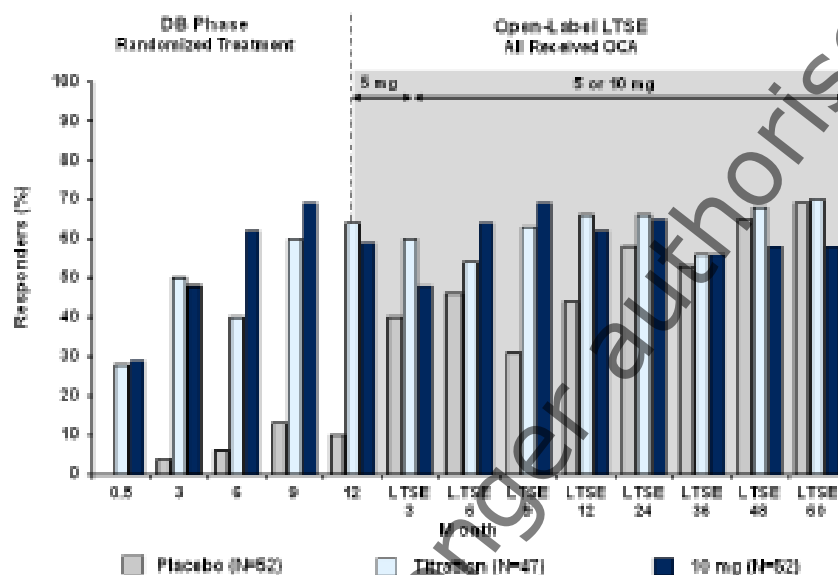
For subjects previously randomized to OCA and who continued treatment with OCA in the LTSE, the percentage of subjects achieving the primary composite endpoint at the end of the double-blind phase, i.e., Month 12 (51% for 5-10 mg OCA and 56% for 10 mg OCA), was sustained over the subsequent open-label period.

A decrease in responders from Month 12 of the double-blind phase (LTSE baseline) to Month 3 LTSE was observed for subjects previously treated with 10 mg OCA, which was expected as the protocol required all subjects to initiate the LTSE at 5 mg OCA, including subjects who were randomized to 10 mg OCA. An improved response was subsequently observed at LTSE Month 6, consistent with protocol guidance that subjects were allowed to uptitrate after LTSE Month 3 and further reinforces 10 mg OCA provides incremental efficacy compared with 5 mg OCA.

For subjects who received placebo during the double-blind phase and entered the LTSE, similar increases in responders from the double-blind baseline were observed at LTSE Month 3 that paralleled those of OCA during the double-blind placebo phase. Namely, a robust response was observed from LTSE baseline (9%) to LTSE Month 3 (34%), which was increased over the subsequent months of the LTSE treatment phase. Importantly, a response rate of approximately 50% was maintained through LTSE Month 60, irrespective of dose or treatment group.

Figure 15: 747-301 LTSE – Percentage of Subjects Achieving Primary Efficacy Composite Endpoint Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N = 193)

ALP <1.67× ULN, Total Bilirubin ≤ULN, and ALP Decrease of ≥15% from Double-Blind Baseline



DB=double-blind; LTSE=long-term safety extension; OCA=chenodeoxycholic acid; UDCA=ursodeoxycholic acid; ULN=upper limit of normal

A responder was ALP <1.67× ULN and total bilirubin ≤ULN, and ALP decrease of ≥15% from double-blind baseline. For all subjects, double-blind baseline is the mean of all available evaluations before double-blind treatment.

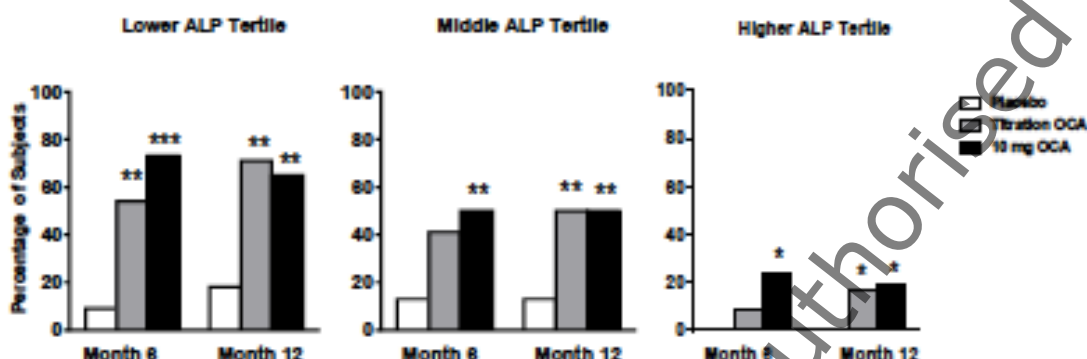
Source: 747-301 LTSE CSR, Table 14.2.1

747-301 Double-Blind - Composite Endpoint of Alkaline Phosphatase and Total Bilirubin by Baseline ALP Tertile

The percentage of double-blind subjects achieving the primary composite endpoint at the end of the double-blind phase was 47% in the OCA 10 mg group, 46% in the OCA titration group, and 10% in the placebo group. In the double-blind phase of the study only, the effect of OCA was also evaluated based on baseline ALP tertiles (<250.5 U/L [lower], ≥250.5 U/L to <339.6 U/L [middle], and ≥339.6 U/L [higher]). As shown in Figure 16, a greater percentage of OCA-treated subjects achieved the primary composite endpoint compared with placebo-treated subjects across all 3 ALP tertiles (lower tertile: 18% placebo, 71% OCA titration, and 65% OCA 10 mg; middle tertile: 13% placebo, 50% OCA titration, and 50% OCA 10 mg; upper tertile: 0% placebo, 17% OCA titration, 19% OCA 10 mg). As expected, the percentage of subjects achieving an endpoint was inversely proportional to the degree of severity (i.e., the highest percentage of subjects achieving the primary composite endpoint was in the lowest tertile).

Figure 16: 747-301 Double-Blind - Percentage of Subjects Achieving Primary Composite Endpoint Summarized by Baseline ALP Tertile: ITT Population (N = 216)

Responder Criteria: ALP <1.67x ULN and Total Bilirubin ≤ULN, and ALP decrease of ≥15% from Baseline



Lower ALP Tertile = Baseline ALP <250.5 U/L:

Middle ALP Tertile = Baseline ALP ≥250.5 U/L to <339.6 U/L:

Higher ALP Tertile = Baseline ALP ≥339.6 U/L:

Placebo n = 22, Titration OCA n = 24, OCA 10 mg n = 26

Placebo n = 24, Titration OCA n = 22, OCA 10 mg n = 26

Placebo n = 27, Titration OCA n = 24, OCA 10 mg n = 21

CMH=Cochran-Mantel-Haenszel; ITT=intent-to-treat; OCA=obeticholic acid

*p <0.05, **p <0.01, ***p <0.0001; P-values for comparing treatments were obtained using CMH General Association test stratified by randomization strata factor.

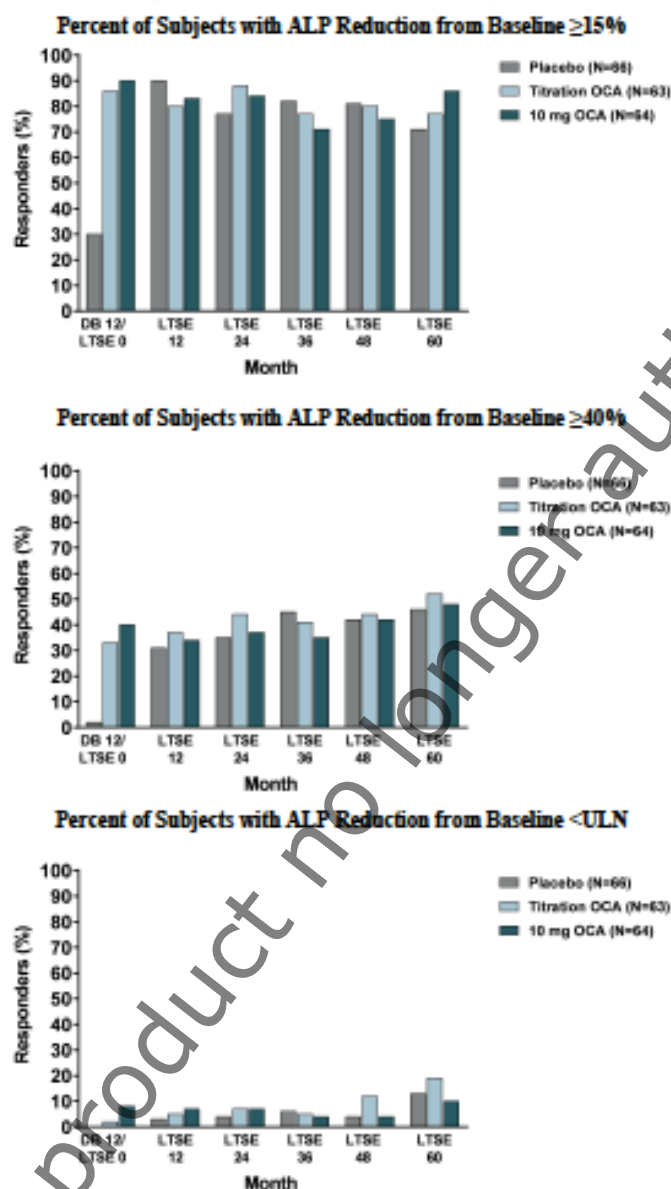
Source: CSR 747-301, Section 14, Table 14.2.3.12

747-301 LTSE – ALP Responder Analyses

The original mean double-blind baseline ALP values were comparable across treatment groups, ranging from 307.47 (10 mg OCA) U/L to 328.42 U/L (placebo).

Percentages of subjects achieving ALP reductions of ≥ 15% and ≥ 40% over time are summarized in Figure 17 for the safety population. By LTSE Month 12, about 80% of subjects had experienced a clinically significant 15% reduction in ALP. At LTSE Month 12, placebo subjects who started OCA in the LTSE saw an increased proportion of responders across both ALP thresholds. This was consistent with the responder rates observed with OCA treatment during the double-blind phase, which was sustained in the 5-10 mg OCA and 10 mg OCA groups throughout the LTSE. By LTSE Month 60, nearly 50% of OCA-treated subjects saw a ≥ 40% improvement in ALP. Notably, a decrease of ALP of > 40% in patients with PBC has been associated with survival rates comparable to healthy matched control populations (Parés 2006).

Figure 17: 747-301 LTSE – Responder Analysis Based on ALP at Double-Blind Baseline in Subjects Using Observed Data: Safety Population (N=193)



DB=double-blind; LTSE=long-term safety extension; OCA=obeticholic acid; UDCA=ursodeoxycholic acid; ULN=upper limit of normal.

A responder was defined by a decrease in ALP of $>15\%$ from double-blind baseline, $>40\%$ from double-blind baseline, or ALP $< \text{ULN}$.

ALP ULN = $\leq 118 \text{ U/L}$ [females] and $\leq 124 \text{ U/L}$ [males]

Source: 747-301 LTSE CSR, Table 14.2.2

747-301 LTSE – ALP and Bilirubin Time Course

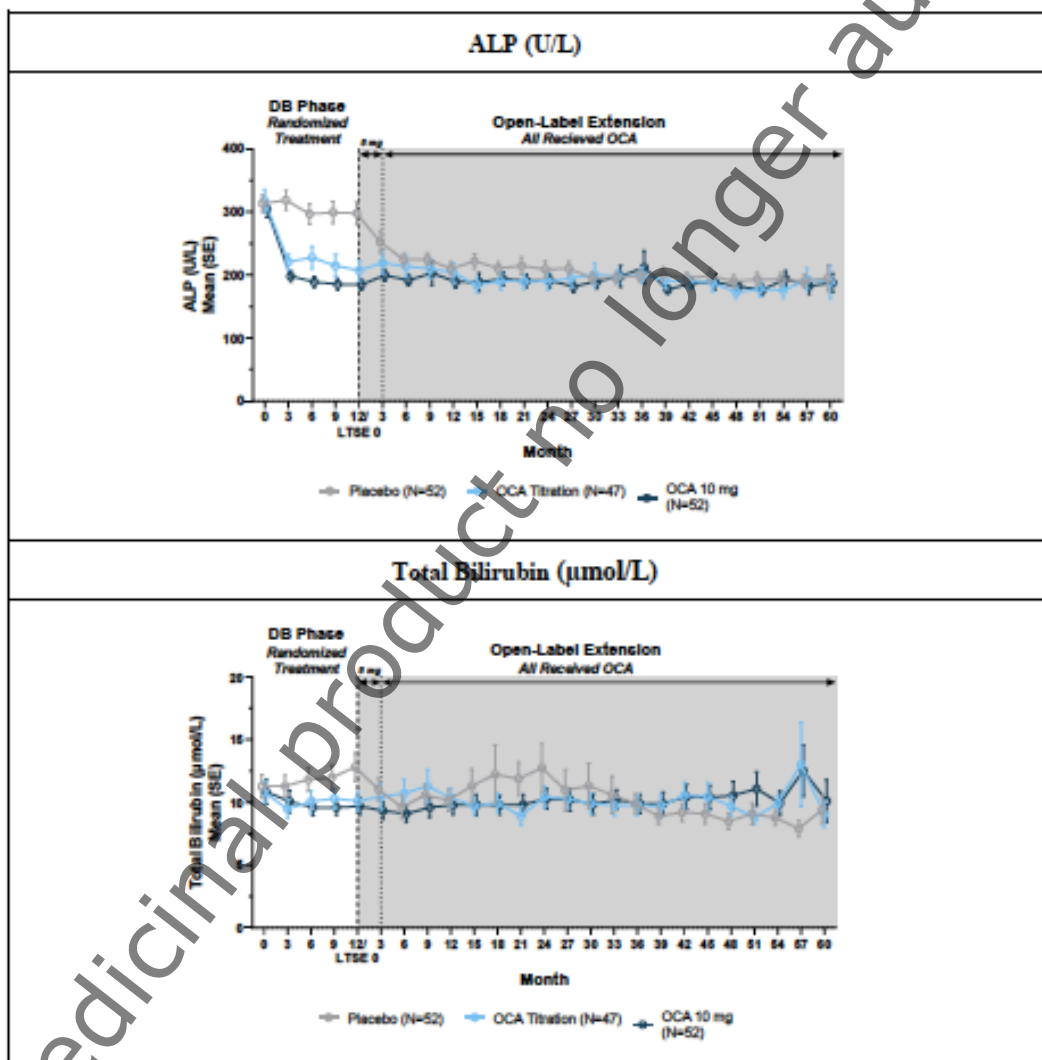
ALP and bilirubin values over time and change from baseline are summarized in Figure 18.

The clinically meaningful and statistically significant reductions from baseline in ALP observed in OCA-treated subjects through the initial 12-month, double-blind phase were sustained with continued treatment in the LTSE. Notably, absolute means approached $1.67 \times \text{ULN}$, which has been correlated with improved transplant-free survival (Lammers 2014) and remained generally stable through LTSE Month 60. For subjects who received placebo during the double-blind phase and entered the LTSE, similar statistically significant reductions in ALP from the double-blind baseline were observed as early as LTSE

Month 3 that paralleled those of OCA during the double-blind placebo phase, with reductions sustained through end of study.

The double-blind baseline mean total bilirubin values were comparable across treatment groups, ranging from 10.434 $\mu\text{mol/L}$ (5-10 mg OCA) to 11.807 $\mu\text{mol/L}$ (placebo). During the double-blind treatment phase, total bilirubin levels tended to increase from baseline in placebo subjects. Following initiation of OCA in the LTSE, mean total bilirubin concentrations in placebo subjects declined and reached levels that were comparable to or below baseline in the double-blind phase. These changes were not statistically significant. For subjects treated with OCA during the double-blind period, continued OCA treatment maintained total bilirubin concentrations at or below baseline throughout the LTSE. Maintaining bilirubin levels at or below ULN has been shown to improve liver-related outcomes over time (Murillo-Perez 2020).

Figure 18: 747-301 LTSE – Mean (SE) ALP and Total Bilirubin Values Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)



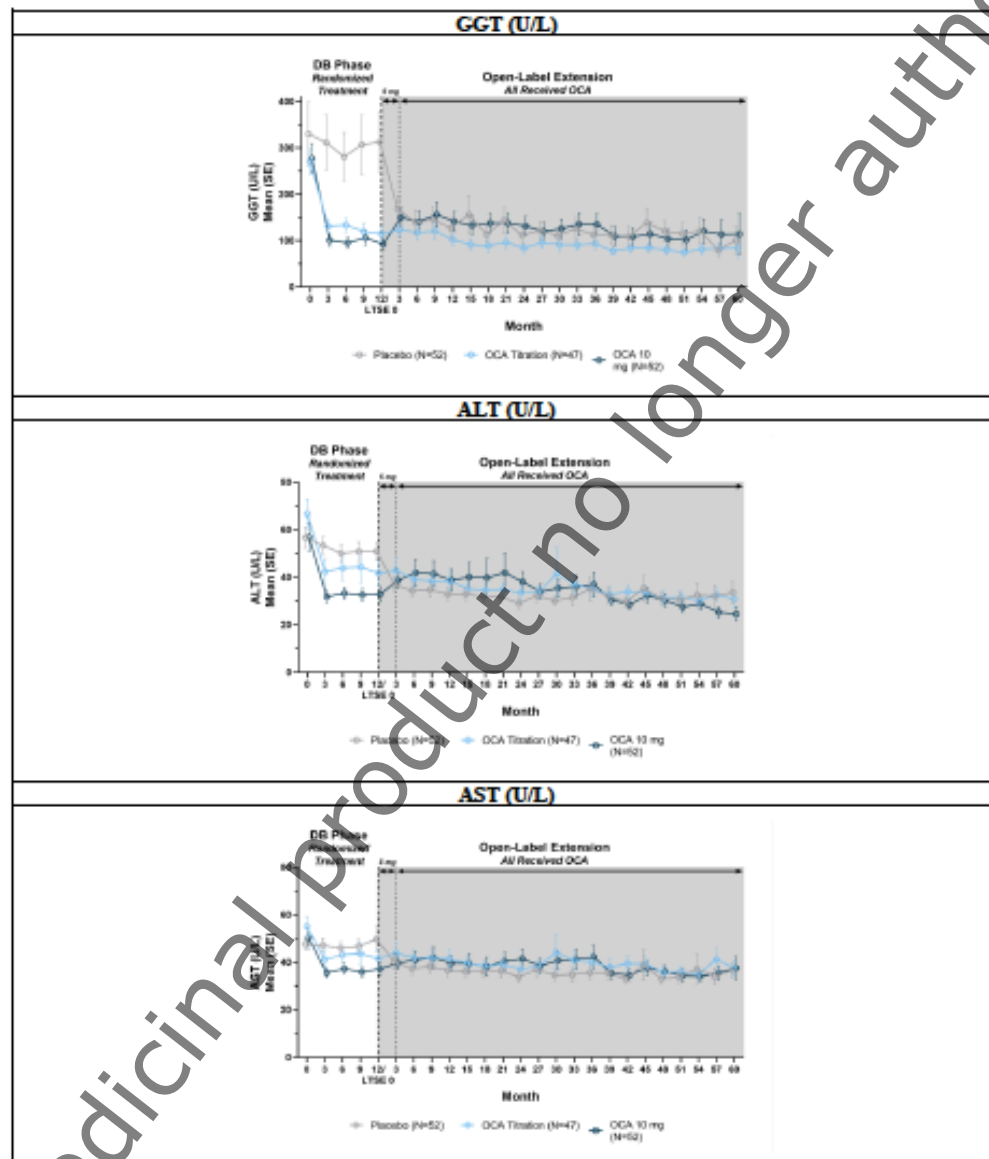
DB = double-blind; LTSE = long-term safety extension; OCA = obeticholic acid; SE = standard error; UDCA = ursodeoxycholic acid.
For all subjects, double-blind baseline is the mean of all available evaluations before double-blind treatment.
Source: 747-301 LTSE CSR, Table 14.2.3

747-301 LTSE – Other Efficacy Clinical Laboratory Endpoints

GGT, ALT, and AST

Gamma glutamyl transferase (GGT), ALT, and AST values over time and change from baseline are summarized in Figure 19. The clinically meaningful and statistically significant reductions from baseline in GGT, ALT, and AST observed in OCA-treated subjects through the initial 12-month, double-blind phase were sustained with continued treatment in the LTSE through Month 60. For subjects who received placebo during the double-blind period and entered the LTSE, similar statistically significant reductions from the double-blind baseline were observed for all 3 parameters at LTSE Month 3 that paralleled those of OCA during the double-blind placebo period. In this group, improvements were also maintained through Month 60.

Figure 19: 747-301 LTSE – GGT, ALT, and AST Values Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)



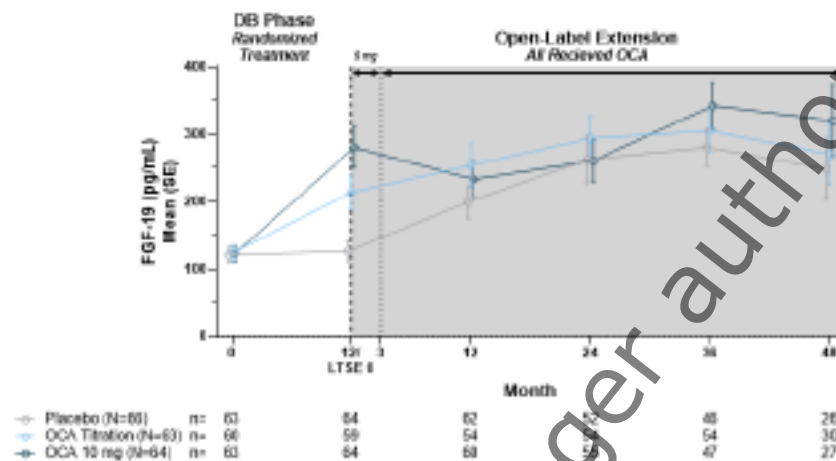
ALT=alanine aminotransferase; AST=aspartate aminotransferase; DB=double-blind; GGT=gamma-glutamyl transferase; LTSE=long-term safety extension; OCA = obeticholic acid; SE = standard error; UDCA = ursodeoxycholic acid
For all subjects, double-blind baseline is the mean of all available evaluations before double-blind treatment.
Source: 747-301 LTSE CSR, Table 14.2.3

747-301 LTSE – Markers of Farnesoid X Receptor Activation

Statistically significant increases from baseline in fibroblast growth factor 19 (FGF-19) observed in OCA-treated subjects through the initial 12-month, double-blind phase were sustained with continued treatment in the LTSE through Month 48 (Figure 20). For subjects who received placebo during the

double-blind period and entered the LTSE, similar statistically significant increases from the double-blind baseline were observed at LTSE Month 12 that paralleled those of OCA during the double-blind placebo period. These results are consistent with OCA-mediated farnesoid X receptor activation resulting in greater FGF-19 concentration which were sustained and durable through the duration of treatment.

Figure 20: 747-301 LTSE – FGF-19 in All Subjects Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)



DB=double-blind; FGF-19=fibroblast growth factor-19; LTSE=long-term safety extension; OCA=obeticholic acid; SE=standard error; UDCA=ursodeoxycholic acid

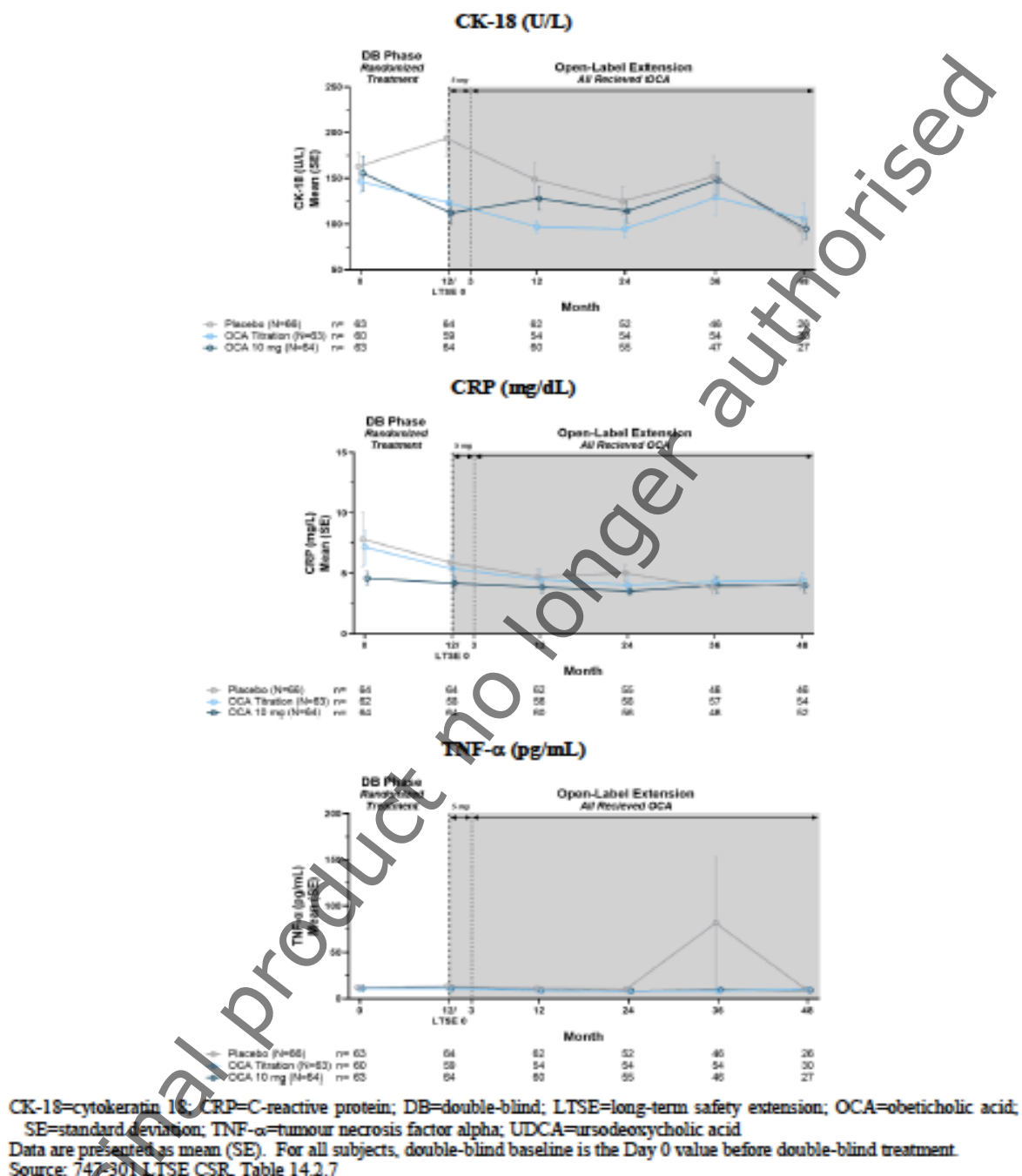
Data are presented as mean (SE). For all subjects, double-blind baseline is the Day 0 value before double-blind treatment.

Source: 747-301 LTSE CSR, Table 14.2.7

747-301 LTSE - Markers Inflammation

Statistically significant reductions from baseline in markers of inflammation cytokeratin 18 (CK-18), C-reactive protein (CRP), and tumour necrosis factor alpha (TNF- α) were observed in OCA-treated subjects through the initial 12-month, double-blind phase and were sustained with continued treatment in the LTSE (Figure 21). For subjects who received placebo during the double-blind period and entered the LTSE, similar statistically significant reductions from the double-blind baseline were observed for TNF- α at LTSE Month 12 that paralleled those of OCA during the double-blind period. CK-18 and CRP were also decreased from double-blind baseline in placebo subjects at LTSE Month 12 and beyond; however, these values did not reach statistical significance.

Figure 21: CK-18, CRP, and TNF- α Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)

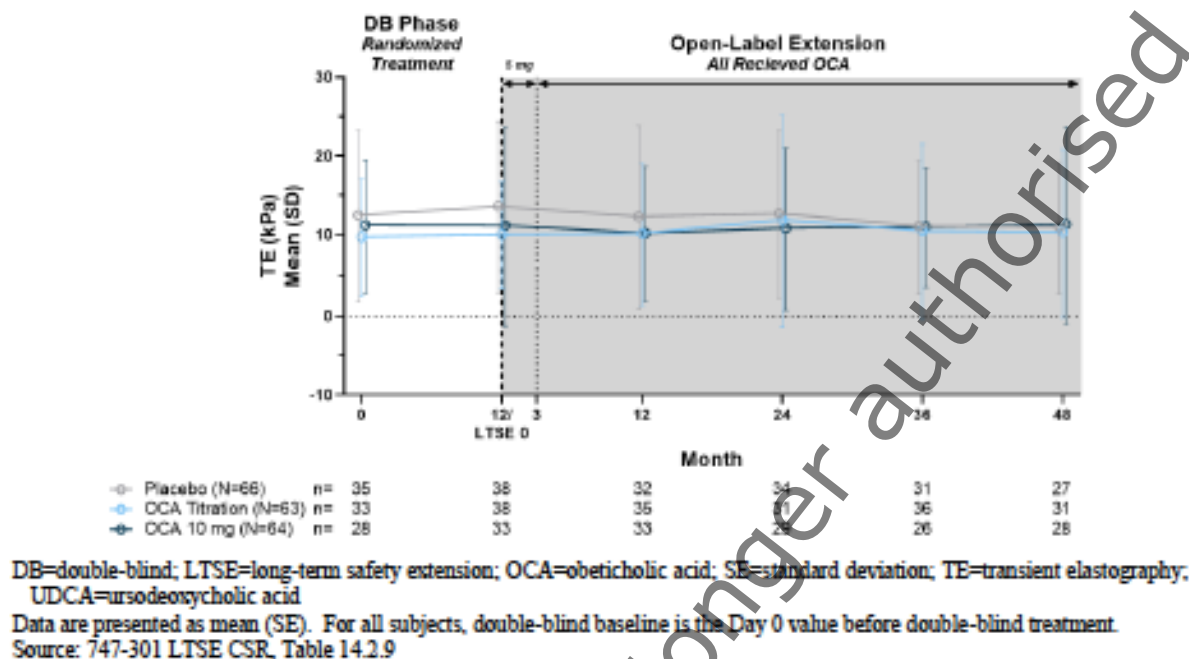


747-301 LTSE – Liver Stiffness as Assessed by Transient Elastography (TE)

Across treatment groups, mean double-blind baseline hepatic stiffness values ranged from 9.74 kPa (5-10 mg OCA) to 12.50 kPa (placebo), and median double-blind baseline hepatic stiffness values were 6.3 kPa (5-10 mg OCA) to 9.00 kPa (placebo) (747-301 LTSE CSR, Table 14.2.9). These values are consistent with F2-F3 fibrosis, based on the following thresholds: $\geq$ F1 7.1 kPa; $\geq$ F2 8.8 kPa; $\geq$ F3 10.7 kPa; $\geq$ F4 16.9 kPa (Corpechot 2012). As was the case in the double-blind phase of the study, there was no statistically significant progression of hepatic stiffness observed during the LTSE as measured by TE (Figure 22). Stabilization or improvement in liver stiffness over time by TE have been shown to be

associated with significant reductions in adverse hepatic outcomes (Corpechot 2022)

Figure 22: Transient Elastography Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)



747-301 LTSE – Liver Biopsy and Histology

A protocol-defined biopsy substudy (n=17) was performed in subjects assessing baseline biopsies (up to 1 year before the start of the double-blind phase) and after 3 years of OCA treatment (LTSE Month 24 for OCA randomized subjects and LTSE Month 36 for placebo randomized subjects).

Fibrosis shifts from double-blind baseline by fibrosis subgroup are summarized in Table 24.

Three years of OCA treatment was generally associated with an improvement or no worsening of histologic fibrosis in subjects with PBC. Specifically, 4 subjects experienced a worsening of fibrosis and 7 subjects experienced an improvement in fibrosis, including 2 subjects with incomplete cirrhosis improving to septal fibrosis.

Table 24: Fibrosis – Shift from Double-Blind Baseline to Follow-up for Double-Blind Biopsy Subgroup: All Subjects

Follow-up (n=17)	Total OCA (N=19) Baseline					
	F0	F1	F2	F3	F4	F5
	No Fibrosis	Portal/Periportal Fibrosis without Septa	Portal/Periportal Fibrosis with Septa	Septal Fibrosis	Incomplete Cirrhosis	Cirrhosis
F0: No Fibrosis	0	0	0	0	0	0
F1: Portal/Periportal Fibrosis without Septa	0	2 (12)	2 (12)	1 (6)	0	0
F2: Portal/Periportal Fibrosis with Septa	0	1 (6)	1 (6)	0	0	0
F3: Septal Fibrosis	0	0	1 (6)	3 (18)	2 (12)	1 (6)
F4: Incomplete Cirrhosis	0	0	0	1 (6)	0	1 (6)
F5: Established Cirrhosis	0	0	0	0	1 (6)	0

OCA=obeticholic acid

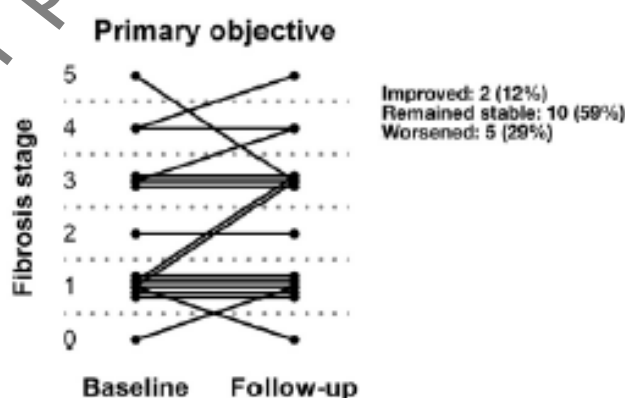
Data are presented as n (%) of subjects. For all subjects, double-blind baseline is the screening visit before double-blind treatment.

Source: 747-301 LTSE CSR, Table 14.2.15.1

A post hoc reanalysis of the biopsy substudy was conducted with a consensus read from 2 pathologists using the most modern histologic scoring system for PBC (Nakanuma Histologic Staging) and automated second harmonic generation imaging for collagen morphometry.

The results of the post hoc reanalysis (Bowlus 2019), were generally consistent with per-protocol assessment, with the majority of subjects experiencing an improvement or no worsening in histologic fibrosis (71%). Additionally, it was found that the majority of subjects had or experienced or exhibited improvements or no worsening in ductopenia (82%), ductular reaction (82%), interface hepatitis (100%), and lobular hepatitis (94%), all of which are key histologic features of PBC. Finally, automated collagen morphometry assessments revealed that after 3 years of OCA treatment, subjects had reductions in collagen area ration, collagen fiber density, and collagen reticulation index. Overall, the results of the post hoc reanalysis were indicative that long-term OCA treatment in patients with PBC is associated with improvement or stabilization across a spectrum of histologic features of PBC.

Figure 23: Histologic Analysis of Liver Fibrosis Stage in the Paired Histology Population (N=17)



Fibrosis stage (F0-F5) from baseline to follow-up evaluation per the PBC Obeticholic Acid International Study of Efficacy prespecified score system (primary endpoint in the paired histology population)

Adapted from Bowlus 2020

747-301 LTSE – Efficacy Conclusions

Study 747-301 enrolled subjects with ALP $\geq 1.67 \times$ ULN or total bilirubin $> \text{ULN}$ but $< 2 \times \text{ULN}$, and without presence of clinical complications of PBC or clinically significant hepatic decompensation. This population is representative of what is expected in actual clinical target practice and consistent with the current and proposed SmPC.

The efficacy associated with continued treatment with OCA was durable and consistent with the effects observed in the double-blind phase. For subjects originally randomized to OCA, continued treatment was associated with sustained improvements in liver biochemistry. For subjects originally randomized to placebo, there were clinically significant improvements in liver biochemistry following the initiation of OCA nearly identical to the changes observed in subjects randomized to OCA in the double-blind phase. Specifically, long-term treatment with OCA, up to 6 years in subjects with PBC resulted in clinically meaningful improvements as assessed by the primary efficacy endpoint—the composite ALP and total bilirubin endpoint that supported initial approval of OCA for the treatment of PBC. In addition, improvements in markers of cholestasis, inflammation, and hepatocellular injury were observed along with improvement or no worsening of histologic fibrosis. Improvements in markers of fibrosis and apoptosis observed during the double-blind phase were all maintained with long-term treatment.

- Response to the composite endpoint, which has been accepted as an endpoint reasonably likely to predict clinical benefit in patients with PBC, was maintained with long-term OCA treatment up to 6 years.
- The mean improvements in ALP were sustained with long-term treatment. Notably, absolute mean values of ALP approached $1.67 \times \text{ULN}$, which has been correlated with improved transplant-free survival (Lammers 2014).
- By LTSE Month 60, nearly 50% of OCA-treated subjects saw a $\geq 40\%$ improvement in ALP, which has been associated with survival rates comparable with healthy-matched control populations (Parés 2006).
- OCA treatment was associated with long-term maintenance of total bilirubin concentrations at or below baseline. These longer-term bilirubin data provide clinically relevant context of disease progression given that total bilirubin does not deteriorate until later stage of disease. These results are significant as maintenance of bilirubin levels at or below ULN has been shown to be associated with improved liver related outcomes over time (Murillo-Perez 2020).
- The clinically meaningful and statistically significant reductions from baseline in GGT, ALT, and AST observed in OCA-treated subjects through the initial 12-month, double-blind phase were sustained with continued treatment in the LTSE.
- Other markers of hepatocellular injury and inflammation, including CK-18, CRP, and TNF- α , were reduced following initiation of OCA and sustained with continued treatment during the LTSE.
- There was no significant progression of hepatic stiffness observed during the LTSE as measured by TE. Worsening of liver stiffness by TE has been shown to be associated with adverse long-term outcomes in PBC.
- A biopsy substudy ($n=17$) was performed in subjects who had liver biopsies at baseline and after 3 years of OCA treatment. OCA treatment was generally associated with an improvement or no worsening of histologic fibrosis in subjects with PBC. Results of the post hoc reanalysis of the biopsy substudy were indicative that long-term OCA treatment in patients with PBC is associated with improvement or stabilization across a spectrum of histologic features of PBC.

747-301 LTSE – Safety

The Safety Population included all subjects who received at least one dose of OCA during the LTSE phase. Treatment assignment was based on the treatment actually received. The Safety Population (N=193) was used for the analysis of all safety data. In this section, all safety parameters are presented by Total OCA.

LTSE – Exposure: A total of 193 subjects received at least 1 dose of OCA during the LTSE (Table 25). The median number of days on OCA was 1924.0 days (5.3 years) from initiation of OCA regardless of if it was in the double-blind or LTSE phase. The median weighted average daily OCA dose for Total OCA was 8.3 mg (SD 3.42). Forty-two (22%) subjects received OCA >10 mg daily at some point during the study (Subjects were allowed to be titrated up to 25 mg OCA prior to Protocol Version 5 (21 Mar 2018) to align with marketing doses).

LTSE – Brief Summary of Adverse Events

An overall summary of treatment emergent adverse events (TEAEs) during the LTSE phase is provided in Table 26. Overall, 189 (98%) subjects had at least 1 TEAE. A total of 105 (54%) subjects had a severe TEAE (incidence largely driven by pruritus), 64 (33%) subjects had a moderate TEAE, 20 (10%) subjects had a mild TEAE, and 150 (78%) subjects had a treatment-related TEAE. Two (1%) subjects had a TEAE that led to death; 61 (32%) subjects had at least 1 serious TEAE, and 25 (13%) subjects had a TEAE that led to discontinuation.

Table 26: 747-301 LTSE – Overall Summary of Treatment-Emergent Adverse Events During LTSE Phase – Crude Incidence Rate: Safety Population (N=193)

	Total OCA (N=193)
Subjects Reporting at Least 1 TEAE, n (%)	189 (98)
Total Number of TEAEs	3059
By Severity ^a , n (%)	
Mild	20 (10)
Moderate	64 (33)
Severe	104 (54)
Missing	1 (<1)
By Relationship ^b , n (%)	
Not Related	16 (8)
Unlikely	23 (12)
Possibly Related	58 (30)
Probably Related	65 (34)
Definitely	27 (14)
Missing	0
At Least One Related and Severe TEAE ^c , n (%)	50 (26)
Leading to Investigational Product Withdrawal or Study Discontinuation, n (%)	25 (13)
Subjects Reporting at Least 1 Serious TEAE, n (%)	61 (32)
Total Number of Serious TEAEs	109
By Severity ^a , n (%)	
Mild	1 (<1)
Moderate	18 (9)
Severe	42 (22)
Missing	0
By Relationship ^b , n (%)	
Not Related	35 (18)
Unlikely	24 (12)
Possibly Related	2 (1)
Probably Related	0
Definitely	0
Missing	0
Leading to Death, n (%)	2 (1)

AE=adverse event; LTSE=long-term safety extension; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Percentages are based on the number of subjects assigned to each treatment group. A TEAE during LTSE phase was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of LTSE OCA.

^a Subjects reporting more than 1 TEAE were counted only once per dose group at the highest severity.

747-301 LTSE – Frequent Adverse Events

TEAEs that occurred in $\geq 5\%$ of subjects in the total group are summarized in Table 27. The AE profile in the LTSE phase was consistent with that reported in the double-blind phase as well as in previous studies with OCA; no new findings were noted.

The most common TEAE by Medical Dictionary for Regulatory Activities (MedDRA) preferred term was pruritus (132 [68%] subjects). Most TEAEs were considered resolved at the end of the LTSE.

Table 27: 747-301 LTSE – Treatment-Emergent Adverse Events Occurring in $\geq 5\%$ of Subjects in the Total Group by System Organ Class and Preferred Term - Crude Incidence Rate: Safety Population (N=193)

System Organ Class Preferred Term, n (%)	Total OCA (N=193)
All TEAE	189 (98)
Skin and subcutaneous tissue disorders	145 (75)
Pruritus	132 (68)
Skin lesion	13 (7)
Infections and infestations	140 (73)
Urinary tract infection	46 (24)
Nasopharyngitis	44 (23)
Upper respiratory tract infection	29 (15)
Influenza	28 (15)
Sinusitis	20 (10)
Bronchitis	15 (8)
Respiratory tract infection	13 (7)
Pneumonia	12 (6)
Cystitis	11 (6)
Herpes zoster	11 (6)
Gastroenteritis	9 (5)
Gastrointestinal disorders	129 (67)
Nausea	31 (16)
Diarrhoea	29 (15)
Abdominal pain	25 (13)
Abdominal pain upper	24 (12)
Constipation	21 (11)

System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Dyspepsia	18 (9)
Gastrooesophageal reflux disease	15 (8)
Abdominal distension	11 (6)
Varices oesophageal	11 (6)
Haemorrhoids	11 (6)
Ascites	10 (5)
Vomiting	10 (5)
Gastritis	10 (5)
Toothache	9 (5)
Musculoskeletal and connective tissue disorders	116 (60)
Arthralgia	37 (19)
Back pain	25 (13)
Osteopenia	20 (10)
Pain in extremity	18 (9)
Osteoarthritis	16 (8)
Osteoporosis	11 (6)
Musculoskeletal pain	10 (5)
Myalgia	10 (5)
Neck pain	9 (5)
General disorders and administration site conditions	94 (49)
Fatigue	49 (25)
Oedema peripheral	24 (12)
Pyrexia	13 (7)
Influenza like illness	9 (5)
Injury, poisoning and procedural complications	83 (43)
Procedural pain	12 (6)
Nervous system disorders	68 (35)
Headache	30 (16)
Dizziness	11 (6)
Respiratory, thoracic and mediastinal disorders	62 (32)
Cough	30 (16)
Psychiatric disorders	42 (22)
Insomnia	16 (8)
Depression	11 (6)
Blood and lymphatic system disorders	39 (20)
Anaemia	18 (9)

System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Vascular disorders	36 (19)
Hypertension	17 (9)
Eye disorders	33 (17)
Dry eye	9 (5)
Hepatobiliary disorders	32 (17)
Cholelithiasis	9 (5)

AE=adverse event; LTSE=long-term safety extension; OCA=obeticolic acid; TEAE=treatment-emergent adverse event
Percentages are based on the number of subjects assigned to each treatment group. A TEAE during LTSE phase was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of LTSE OCA. At each level of summation (overall, system organ class, preferred term), subjects reporting more than 1 TEAE were counted only once per dose group.

Source: 747-301 LTSE CSR, Table 14.3.1.2

747-301 Deaths

Three subjects died across both phases of the study, 2 in the LTSE phase and 1 in the double-blind phase.

Two subjects died during the LTSE, and both deaths were considered not related to OCA by the Investigator and the MAH.

--Subject 1 (Preferred Term: Sepsis)

Cause of Death: Bacterial endocarditis with multiorgan failure after cardiac surgery

A male subject was admitted to the hospital with infective endocarditis related to a bioprosthetic aortic valve (approximately 6 months after the start of the LTSE phase of the study). The subject's hospital course was dominated by complications of bacterial endocarditis (perivalvular abscess, splenic infarction, bacterial pneumonitis). The subject underwent aortic valve replacement with another bioprosthesis and total splenectomy due to splenic infarction. The subject died approximately 3 weeks after cardiac surgery due to multi-organ failure in the setting of ongoing sepsis (infective endocarditis). The event (Preferred Term: Sepsis) was considered by the Investigator and MAH as not related to OCA.

--Subject 2 (Preferred Term: Jaundice)

Cause of Death: Alcoholic hepatitis with multiorgan failure

A female subject was noted to have a sudden severe spike in total bilirubin on end-of-treatment blood tests. Clinically, she presented with onset of severe jaundice 58 months after the start of the LTSE phase of the study. A week later she was admitted to the hospital for increasing jaundice in the setting of an increased alcohol intake over the preceding months. The subject had signs of encephalopathy, and over the course of the hospitalization, had a gradual deterioration with increasing jaundice, hepatorenal syndrome, and confirmed acute alcoholic hepatitis. The subject had completed the study through study closure and died about 3 weeks after OCA and study discontinuation due to alcoholic hepatitis with multiorgan failure (hepatic, renal, encephalopathy) with a background of primary biliary cholangitis without evidence of advanced cirrhotic liver disease prior to the event of alcoholic hepatitis. The event (Preferred Term: Jaundice) was considered by the Investigator and MAH as not related to OCA.

An additional subject died in the double-blind phase and the fatal event was considered as unlikely related to OCA by the Investigator and the MAH.

--Subject 3 (Preferred Term: Cardiac failure)

Cause of Death: Recurrent heart failure in subject with severe, longstanding cardiovascular disease

A male subject experienced a serious adverse event of cardiac failure and was hospitalized approximately 7 months after the start of the double-blind phase of the study. The subject had a long history of cardiovascular disease with hypertension, multiple myocardial infarctions, recurrent episodes of heart failure, atrial fibrillation, and chronic renal impairment prior to enrolment into the study (since 1993). The event of worsening heart failure (cardiac failure) was considered resolved at the time of hospital discharge. Approximately 5 weeks later, the subject had a second event of cardiac failure and was hospitalized again. The subject was discharged home and readmitted to the hospital approximately 1 month later for worsening symptoms of heart failure and investigational product dosing was discontinued. During this admission the subject was placed on an "End of life care pathway" and his symptoms were palliated. He died and the primary cause of death was noted as congestive cardiac failure and ischaemic heart disease, prior myocardial infarction. Secondary causes of death were listed as chronic kidney disease and PBC. The event (Preferred Term: Cardiac Failure) was considered by the Investigator and MAH as unlikely related to investigational product.

The above described in the LTSE and double-blind phases deaths were unexpected and unrelated to the subjects' underlying liver disease. All subjects had stable synthetic liver function and no evidence of decompensation at baseline.

LTSE – Other Serious Adverse Events

Serious TEAEs that occurred in >1 subject in the total group are summarized by Total OCA in Table 28. Overall, 61 (32%) subjects had a serious TEAE.

The only serious TEAEs reported in more than 1 subject were osteoarthritis (in 6 subjects), oesophageal varices haemorrhage (in 4 subjects), radius fracture and pneumonia (in 3 subjects each), and pancreatitis, procedural pain, atrial fibrillation, and anaemia (in 2 subjects each). Two of the serious TEAEs (atrial fibrillation and cardiac failure congestive) were considered by the Investigator to be possibly related to OCA; all other serious TEAEs were considered not related or unlikely related.

All serious TEAEs resolved with or without sequelae except for the 2 deaths in the LTSE phase described in Section 2.1.3.3 and the serious TEAEs of chronic myeloid leukaemia and breast cancer, which were ongoing at the end of the study.

Table 28: 747-301 LTSE – Serious Treatment-Emergent Adverse Events Occurring in >1 Subject in the Total Group by System Organ Class and Preferred Term – Crude Incidence Rate: Safety Population (N=193)

System Organ Class Preferred Term, n (%)	Total OCA (N=193)
All Serious TEAE	61 (32)
Gastrointestinal disorders	17 (9)
Oesophageal varices haemorrhage	4 (2)
Pancreatitis	2 (1)
Injury, poisoning and procedural complications	15 (8)
Radius fracture	3 (2)
Procedural pain	2 (1)
Infections and infestations	12 (6)
Pneumonia	3 (2)
Musculoskeletal and connective tissue disorders	9 (5)
Osteoarthritis	6 (3)
Cardiac disorders	5 (3)
Atrial fibrillation	2 (1)
Blood and lymphatic system disorders	3 (2)
Anaemia	2 (1)

AE=adverse event; LTSE=long-term safety extension; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Percentages are based on the number of subjects assigned to each treatment group. A TEAE during LTSE phase is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of LTSE OCA. At each level of summation (overall, preferred term), subjects reporting more than 1 serious TEAE are counted only once per dose group.
Source: 747-301 LTSE CSR, Table 14.3.1.6

LTSE – Treatment-Emergent Adverse Events that Led to Study Discontinuation

TEAEs that led to study discontinuation and occurred in >1 subject in the total group are summarized by Total OCA in Table 29. Overall, 26 (13%) subjects had a TEAE that led to discontinuation. The only TEAEs that led to discontinuation reported in more than 1 subject were pruritus (in 14 subjects) and oesophageal varices haemorrhage and fatigue (in 2 subjects each).

Several of the TEAEs that led to discontinuation were considered by the Investigator to be possibly or probably related to OCA, while 5 TEAEs (in 3 subjects) were considered definitely related: pruritis and neurodermatitis in one subject, pruritus in a second and pruritus and quality of life decreased in the third.

About half of TEAEs that led to discontinuation resolved with or without sequelae after discontinuation of OCA. All the other TEAEs remained ongoing (or led to death in 2 LTSE subjects [deemed by the Investigator as not related to OCA]) at the time of study discontinuation.

Table 29: 747-301 LTSE – Treatment-Emergent Adverse Events that Led to Discontinuation Occurring in >1 Subject in the Total Group by System Organ Class and Preferred Term – Crude Incidence Rate: Safety Population (N=193)

System Organ Class Preferred Term, n (%)	Total OCA (N=193)
All TEAE	26 (13)
Skin and subcutaneous tissue disorders	15 (8)
Pruritus	14 (7)
Gastrointestinal disorders	3 (2)
Oesophageal varices haemorrhage	2 (1)
General disorders and administration site conditions	4 (2)
Fatigue	2 (1)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event
Percentages are based on the number of subjects assigned to each treatment group. A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of OCA. At each level of summation (overall, system organ class, preferred term), subjects reporting more than 1 TEAE were counted only once per dose group.
Source: 747-301 LTSE CSR, Table 14.3.1.7

Pruritus Events

Overall, 151 (78%) subjects had an event. No subject had a serious TEAE of pruritus. Pruritus TEAEs that led to discontinuation were reported in 14 subjects. Of these, 7 subjects had TEAEs that were severe (1 subject was listed as "Drug Interrupted," but end of study indicated that the subject was withdrawn from the study due to a TEAE, so written as though investigational product was withdrawn), 5 were moderate, and 2 were mild.

Table 30: 747-301 LTSE – Pruritus Treatment-Emergent Adverse Events During the Long-Term Safety Extension Phase – Crude Incidence Rate: Safety Population (N=193)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Pruritus	151 (78)
Eye disorders	2 (1)
Eye pruritus	2 (1)
Gastrointestinal disorders	1 (<1)
Anal pruritus	1 (<1)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Reproductive system and breast disorders	2 (1)
Vulvovaginal pruritus	2 (1)
Skin and subcutaneous tissue disorders	151 (78)
Prurigo	1 (<1)
Pruritus	150 (78)
Pruritus allergic	1 (<1)
Pruritus generalized	5 (3)
Rash pruritic	4 (2)

AE=adverse event; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Percentages are based on the number of subjects assigned to each treatment group. Subjects reporting more than 1 AE within a special interest category, system organ class, or preferred term were counted only once per dose group.

A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of OCA.

TEAEs are sorted alphabetically. Pruritus is any event with preferred term including "Prur".

Source: 747-301 LTSE CSR, Table 14.3.1.8.3

Throughout treatment, more pruritus days were mild than moderate or severe. This aligns with the mean (SD) visual analogue scale values remaining in the mild range through the duration of treatment from OCA baseline. Pruritus frequency and severity remained steady after approximately 3 months of OCA treatment.

Hepatic-Related Events

-Assessment of SMQ of Hepatic Disorders

An assessment of overall treatment-emergent hepatic disorders was conducted using the Standardised MedDRA Query (SMQ) of Hepatic Disorders, excluding the following sub-SMQs: Congenital, familial, neonatal, and genetic disorders of the liver; Liver infections; and Pregnancy-related hepatic disorders.

Hepatic-related TEAEs during the LTSE phase are summarized in Table 31.

Overall, 47 (24%) subjects (Total OCA) had a hepatic-related event. The most common events were oesophageal varices in 11 (6%), ascites in 10 (5%), and hepatic cirrhosis in 7 (4%) subjects which generally reflected disease progression.

Table 31: 747-301 LTSE – Hepatic-Related Treatment-Emergent Adverse Events During the Long-Term Safety Extension Phase – Crude Incidence Rate: Safety Population (N=193)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Hepatic Disorders	47 (24)
Eye disorders	1 (<1)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Ocular icterus	1 (<1)
Gastrointestinal disorders	16 (8)
Ascites	10 (5)
Gastric varices	1 (<1)
Oesophageal varices haemorrhage	4 (2)*
Portal hypertensive gastropathy	5 (3)
Varices oesophageal	11 (6) ^b
Hepatobiliary disorders	20 (10)
Hepatic cirrhosis	7 (4)
Hepatic cyst	2 (1)
Hepatic failure	1 (<1)
Hepatic lesion	1 (<1)
Hepatic pain	1 (<1)
Hepatic steatosis	1 (<1)
Hepatomegaly	4 (2)
Hyperbilirubinaemia	1 (<1)
Jaundice	3 (2)
Liver tenderness	1 (<1)
Perihepatic discomfort	1 (<1)
Portal hypertension	3 (2)
Investigations	17 (9)
Alanine aminotransferase increased	1 (<1)
Aspartate aminotransferase increased	1 (<1)
Blood alkaline phosphatase increased	4 (2)
Blood bilirubin increased	2 (1)
Gamma-glutamyltransferase increased	3 (2)
Hepatic enzyme increased	5 (3)
International normalised ratio increased	1 (<1)
Liver function test abnormal	2 (1)
Prothrombin time prolonged	2 (1)
Transaminases increased	2 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2)
Haemangioma of liver	2 (1)
Hepatic neoplasm malignant	1 (<1)
Hepatic neoplasm malignant recurrent	1 (<1)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Nervous system disorders	1 (<1)
Hepatic encephalopathy	1 (<1)
Skin and subcutaneous tissue disorders	3 (2)
Spider naevus	3 (2)

AE=adverse event; OCA=obcholic acid; SMQ=Standardized Medical Dictionary for Regulatory Activities query; TEAE=treatment-emergent adverse event

Percentages are based on the number of subjects assigned to each treatment group. Subjects reporting more than 1 AE within a special interest category, system organ class, or preferred term were counted only once per dose group.

A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of OCA. TEAEs are sorted alphabetically. Hepatic Disorders are events included in the Hepatic Disorders SMQ, excluding the following sub-SMQs: Congenital, familial, neonatal and genetic disorders of the liver; Hepatitis, non-infectious; Liver infections; and Pregnancy-related hepatic disorders.

* The event was considered by the Investigator to be serious in 4 subjects (747-301 LTSE CSR, Listing 16.2.7.7.3).

^b The event was considered by the Investigator to be serious in 1 subject (747-301 LTSE CSR, Listing 16.2.7.7.3).

Source: 747-301 LTSE CSR, Table 14.3.1.8.3

Serious Hepatic-Related Events

Eight (4.1%) subjects had a serious hepatic-related TEAE during the LTSE phase. Oesophageal varices haemorrhage (in 4 subjects) and varices oesophageal (in 2 subjects) were the only serious hepatic-related events that occurred in more than 1 subject. Other serious hepatic-related TEAEs were reported in a single subject each: hepatic failure, hepatic neoplasm malignant, ascites, and jaundice. In general, the types of serious hepatic-related TEAEs appeared to be consistent with progression of disease. All of the serious hepatic-related TEAEs were considered by the Investigator to be unlikely or not related to OCA. The majority of these subjects had prior medical history for which they would be contraindicated these per the new proposed SmPC. Of the below subjects, 3 received a liver transplant within 30 days of end of study.

--Subject 1 (Preferred Term: Hepatic failure)

Type of Event: Oesophageal variceal haemorrhage, hepatic failure, liver transplantation

Time of Event: Approximately 2 months after the start of the LTSE phase

A male subject with evidence of portal hypertension (low platelets) and synthetic liver function impairment (elevated international normalized ratio) at baseline. At inclusion into LTSE phase there was clear evidence of advanced chronic liver disease with portal hypertension and decreased liver function. Approximately 6 months after the start of the LTSE phase, the subject underwent evaluation for a liver transplant due to a Model for End-Stage Liver Disease (MELD) score of 15. He experienced jaundice with a bilirubin >3 mg/dL and portal hypertension manifested by ascites, lower extremity oedema, oesophageal varices, and hypersplenism. The subject began requiring regular paracentesis to treat recurrent ascites. The subject underwent variceal band ligation 3 times within the first year of participating in the LTSE. Approximately 1 year after the start of the LTSE phase of the study, the subject was admitted to the hospital with hematemesis, haematochezia, asthenia, and light-CHMP headedness. The subject underwent esophagogastroduodenoscopy with placement of 5 bands resulting in abatement of bleeding. The subject also underwent an intrahepatic portosystemic shunt procedure which achieved a reduction in the portosystemic gradient. The subject's MELD score was 20, and he eventually was transferred to the Transplant Surgical Service unit for liver transplant due to chronic hepatic failure. Approximately 2 weeks into hospitalization, the subject underwent orthotopic liver transplantation, and choledochcholedocostomy without complication. The subject had withdrawn OCA upon admission to the hospital and was subsequently discontinued from the study after undergoing liver transplant.

--Subject 2 (Preferred Term: Variceal bleed)

Type of Event: Oesophageal variceal haemorrhage

Time of Event: Approximately 4.5 years after the start of the LTSE phase

A female subject with evidence of advanced chronic liver disease with portal hypertension (splenomegaly and thrombocytopenia) at baseline was hospitalized with an oesophageal variceal bleed after experiencing haematochezia for a few days. An esophagogastroduodenoscopy (EGD) showed Grade 2 oesophageal varices, hiatal hernia, and portal hypertensive gastropathy. The subject underwent variceal banding and additionally received 1 unit of blood, as well as tranexamic acid, terlipressin, and carvedilol. The subject was discharged approximately 2 weeks later and was referred for liver transplant assessment. In response to the event, OCA was withdrawn and the subject was subsequently discontinued from study follow-up 2 months later.

--Subject 3 (Preferred Term: Oesophageal variceal haemorrhage)

Type of Event: Oesophageal variceal haemorrhage

Time of Event: Approximately 2 years and 3 months after the start of the LTSE phase

A male subject with a relevant medical history of splenomegaly with decreased platelets and stage three distortion of the hepatic architecture with numerous fibrous septa at baseline was admitted to the hospital due to oesophageal variceal bleeding. The subject presented to the emergency room with complaints of weakness, dizziness, general malaise, and a 3-day history of black stool. He experienced hematemesis while in the waiting room. During hospitalization, the subject was treated with 2 units of blood, sodium chloride, pantoprazole, octreotide, and ceftriaxone. An EGD showed circumferential large varices that were not bleeding but were banded and evidence of moderate portal hypertensive gastropathy. The subject underwent paracentesis due to ascites and was discharged approximately a week after being admitted. OCA was interrupted during hospitalization. Treatment was restarted the day after event resolution and the subject continued investigational product for approximately 2 years and 8 months until study completion.

--Subject 4 (Preferred Term: Hepatocellular carcinoma)

Type of Event: Hepatic neoplasm malignant, hepatic neoplasm malignant recurrent

Time of Event: Approximately 2 years and 11 months after the start of the LTSE phase

A female subject was diagnosed with hepatocellular carcinoma in liver segment 7 after a magnetic resonance imaging (MRI) revealed lesions suspicious for hepatocellular carcinoma. The subject showed evidence of cirrhosis with portal hypertension at inclusion into the LTSE phase. She was hospitalized and underwent laparoscopic biopsy and radiofrequency ablation of the lesion in segment 7. Biopsy showed a CK-19 negative hepatocellular carcinoma, confirmed with carcinoembryonic antigen antibody staining. The subject was discharged the next day. Approximately 8 months later, an MRI showed recurrent hepatocellular carcinoma in segment 7. The subject was hospitalized for an elective transarterial chemoembolization. A few months later, approximately 3 years and 8 months after the start of the LTSE phase, the subject underwent liver transplantation. The subject was subsequently discontinued from the study.

--Subject 5 (Preferred Term: Oesophageal variceal haemorrhage)

Type of Event: Oesophageal variceal haemorrhage

Time of Event Approximately 11 months after the start of the LTSE phase

A female subject with relevant past medical history of oesophageal varices and thrombocytopenia. She presented to the hospital after several episodes of haematemesis; was hypotensive and was admitted for further evaluation. Treatment included intravenous octreotide and pantoprazole. An upper endoscopy showed Grade 3 varices in the lower third of the oesophagus and severe portal gastropathy. Varices were banded due to high risk of bleeding. The subject was discharged 3 days later in stable condition. No action was taken with OCA in response to the event. The subject continued in the study on investigational product for approximately 2 years and 3 months when she was discontinued from the study due to Investigator decision.

--Subject 6 (Preferred Term: Ascites)

Type of Event: Ascites

Time of Event: Approximately 2 years after the start of the LTSE phase

A female subject who had previously, in the double-blind phase, been hospitalized due to life-threatening upper gastrointestinal haemorrhage due to Grade 3 oesophageal varices. The subject was hospitalized due to ascites. The subject was admitted to a local hospital with complaints of a bloated abdomen, fever, ascites, and abdominal pain in the right upper quadrant. She was treated with spironolactone and furosemide. Several days later, the subject underwent paracentesis; spontaneous bacterial peritonitis was ruled out when ascites analysis revealed low polymorphonuclear granulocytes. The subject was

discharged approximately a week after admission with only residual ascites remaining. No action was taken with OCA in response to the event. However, the subject experienced an episode of severe itching 20 days after discharge and the investigational product was subsequently ceased. She was listed for transplant 2 months later and underwent orthotopic liver transplantation the following month.

--Subject 7 (Preferred Term: Jaundice)

Type of Event Jaundice

See narrative in Section 2.1.3.3.1

--Subject 8 (Preferred Term: Varices oesophageal)

Type of Event: Oesophageal variceal haemorrhage

Time of Event: Approximately 11 months after the start of the LTSE phase

A female subject with relevant medical history of hepatosplenomegaly and thrombocytopenia at baseline was hospitalized due to hematemesis. An EGD showed 3 varices with no signs of recent bleeding. The next day, she was transferred to another hospital where she was admitted for oesophageal varices haemorrhage. She was treated with 1 unit of packed red blood cells. An EGD was performed for variceal ligation, but the subject did not tolerate the procedure and experienced vomiting with consequent bleeding varices. The varices were ligated and the subject was discharged the following day with diagnoses of digestive haemorrhage due to oesophageal varices, ligation of the varices, and advanced PBC. No action was taken with OCA in response to the event. The subject continued in the study on investigational product for approximately 4 years and 2 months until study completion.

Analysis of Hepatic Clinical Outcome Events

In addition to the assessment of the SMQ of Hepatic Disorders, the incidence and exposure-adjusted incidence rates of hepatic-related adverse events reflective of clinical outcomes (hepatic failure, hepatic cirrhosis, liver transplant and model for end-stage liver disease (MELD) ≥ 15) were also examined by baseline cirrhosis status.

One subject out of 193 experienced hepatic failure. This male subject assigned to the OCA titration group during the double-blind phase with cirrhosis at baseline was up-titrated to 10 mg and then 15 mg once daily during the LTSE phase prior to developing hepatic failure (Day 743). It was determined by the Investigator that the event was not related to OCA treatment.

Less than 10% of subjects had an increase in MELD ≥ 15 and there was no observed difference in EAIR.

Liver Transplantation

Three subjects underwent orthotopic liver transplantation during the LTSE phase of 747-301. Two of the subjects received placebo in the double-blind phase. At LTSE baseline all 3 subjects had progressed to cirrhosis with evidence of portal hypertension (exclusion per the proposed Summary of Product Characteristics [SmPC]). One subject was transplanted for recurrent multifocal hepatocellular carcinoma and intact synthetic liver function, the other 2 subjects had a gradual decline in synthetic liver function with recurrent episodes of decompensation event.

All 3 subjects showed evidence of advanced chronic liver disease at double-blind baseline: one each with: 1) decompensation and synthetic liver function impairment, 2) evidence of portal hypertension, and 3) evidence of portal hypertension and hepatocellular carcinoma. Per the proposed SmPC these subjects would be excluded from treatment.

LTSE – Dyslipidaemia Events

Dyslipidaemia TEAEs during the LTSE phase are summarized in Table 32. Overall, 19 (10%) subjects had an event. No subject had a serious TEAE related to dyslipidaemia.

Table 32: 747-301 LTSE – Dyslipidaemia Treatment-Emergent Adverse Events During the Long-Term Safety Extension Phase – Crude Incidence Rate: Safety Population (N=193)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Dyslipidaemia	19 (10)
Investigations	6 (3)
Blood cholesterol increased	2 (1)
Blood triglycerides increased	2 (1)
Lipids increased	1 (<1)
Low-density lipoprotein increased	4 (2)
Metabolism and nutrition disorders	13 (7)
Dyslipidaemia	4 (2)
Hypercholesterolaemia	8 (4)
Hyperlipidaemia	1 (<1)

AE=adverse event; OCA=obeticholic acid; SMQ=Standardized Medical Dictionary for Regulatory Activities query.

TEAE=treatment-emergent adverse event

Percentages are based on the number of subjects assigned to each treatment group. Subjects reporting more than 1 AE within a special interest category, system organ class, or preferred term were counted only once per dose group.

A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of OCA.

TEAEs are sorted alphabetically. Dyslipidaemia TEAEs are identified by using the Dyslipidaemia SMQ.

Source: 747-301 LTSE CSR, Table 14.3.1.8.3

747-301 LTSE – Cardiovascular Disorder Events

Cardiovascular disorder TEAEs during the LTSE phase are summarized in Table 33. Overall, 40 (21%) subjects experienced at least 1 cardiovascular disorder event.

Table 33: 747-301 LTSE – Cardiovascular Disorder Treatment-Emergent Adverse Events During the Long-Term Safety Extension Phase – Crude Incidence Rate: Safety Population (N=193)

Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Cardiovascular Disorders	40 (21)
Blood and lymphatic system disorders	1 (<1)
Splenic infarction	1 (<1)*
Cardiac disorders	33 (17)
Aortic valve incompetence	1 (<1)
Aortic valve stenosis	1 (<1)*
Arrhythmia	1 (<1)
Atrial fibrillation	7 (4)
Atrial flutter	1 (<1)
Atrioventricular block first degree	1 (<1)
Bradycardia	4 (2)
Bundle branch block right	2 (1)
Cardiac failure	2 (1) ^b
Cardiac failure congestive	2 (1) ^b
Cardiac flutter	2 (<1)
Cardiomyopathy	2 (1) ^b
Cyanosis	2 (1)
Extrasystoles	2 (1)
Heart valve incompetence	1 (<1)
Hypertrophic cardiomyopathy	1 (<1)
Left ventricular hypertrophy	1 (<1)
Mitral valve incompetence	4 (2)
Myocardial infarction	1 (<1)*
Palpitations	11 (6)
Tachycardia	2 (1)
Tricuspid valve incompetence	3 (2)
Ventricular extrasystoles	1 (<1)
Ventricular fibrillation	1 (<1)*
Special Interest Category System Organ Class Preferred Term, n (%)	Total OCA (N=193)
Eye disorders	1 (<1)
Ammaurosis fugax	1 (<1)
Gastrointestinal disorders	1 (<1)
Mesenteric vein thrombosis	1 (<1)
Investigations	2 (1)
Blood creatine phosphokinase increased	1 (<1)
Electrocardiogram ST segment abnormal	1 (<1)
Nervous system disorders	2 (1)
Ischaemic stroke	1 (<1)*
Transient ischaemic attack	1 (<1)*
Vascular disorders	2 (1)
Deep vein thrombosis	1 (<1)
Thrombophlebitis	1 (<1)

AE=adverse event; OCA=obedient acid; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; SMO=Standardized Medical Dictionary for Regulatory Activities query; TEAE=treatment-emergent adverse event
Percentages are based on the number of subjects assigned to each treatment group. Subjects reporting more than 1 AE within a special interest category, system organ class, or preferred term were counted only once per dose group.

A TEAE was defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of OCA. TEAEs are sorted alphabetically. Cardiac Disorders are any event in the MedDRA Cardiac Disorders SOC or the MedDRA SMOs of Embolic and thrombotic events or Ischaemic heart disease.

* The event was considered by the Investigator to be serious (747-301 LTSE CSR, Listing 16.2.7.7.5).

^b The event was considered by the Investigator to be serious in 1 subject (747-301 LTSE CSR, Listing 16.2.7.7.5).

Source: 747-301 LTSE CSR, Table 14.3.1.8.3

Eight (4%) subjects had a serious cardiovascular disorder TEAE during the LTSE phase, with atrial fibrillation (in 2 subjects) being the only event reported in more than 1 subject. Other serious cardiovascular disorder TEAEs were reported in a single subject each: myocardial infarction, cardiomyopathy, cardiac failure congestive, ischemic stroke, transient ischemic attack, and splenic infarction; a single subject experienced single events of aortic valve stenosis, ventricular fibrillation, and cardiac failure. Two subjects had a serious cardiovascular disorder TEAE considered by the Investigator to be possibly related to OCA (but unlikely related by the MAH): cardiac failure congestive and atrial fibrillation in 1 subject each).

--Subject ID: 1 (Preferred Terms: Atrial fibrillation, Myocardial infarction)

Type of Event: Atrial fibrillation

Time of Event: Approximately 2 years and 1 month after the start of the LTSE phase

A female subject with relevant medical history of hypertension and cardiac conduction abnormalities (AV block with bradycardia) at baseline was hospitalized for atrial fibrillation. She was admitted for electrophysiology study with ablation. The subject was successfully converted into sinus rhythm during the ablation procedure without complication. Additional treatment included dopamine, protamine, heparin, cefazolin, and mepivacaine. The subject was discharged in stable condition the next day. No action was taken with OCA in response to the event. The event was assessed as unlikely related to OCA by the Investigator and MAH. The subject continued in the study.

Type of Event: Myocardial infarction

Time of Event: Approximately 2 years and 5 months after the start of the LTSE phase

The subject presented to the hospital with chest pain and was hospitalized for possible myocardial infarction. Serum CK and troponin were elevated and a coronary angiogram did not show evidence of obstructive atherosclerotic coronary artery disease. The subject was also found to be in atrial flutter and had an episode of hypotension. Treatment included diltiazem, rivaroxaban, sublingual nitroglycerin, promethazine, paracetamol, alprazolam, temazepam, ondansetron, tramadol, morphine, ranitidine, atropine, lidocaine, heparin, and fentanyl. The subject was discharged the next day. No action was taken with OCA in response to the event. The event was assessed as unlikely related to OCA by the Investigator and MAH. The subject continued in the study.

--Subject 2 (Preferred Term: Non-ischemic cardiomyopathy)

Type of Event Cardiomyopathy

Time of Event: Approximately 3 years and 11 months after the start of the LTSE phase

A female subject with relevant medical history of hypertension and deep vein thrombosis at baseline was hospitalized with non-ischemic cardiomyopathy. She was re-admitted for elective implantation of an implantable cardioverter defibrillator after 3 months of attempted medical management of her cardiomyopathy. The procedure was completed without complication, and the subject was kept in the hospital overnight for observation. At the time of hospital discharge, telemetry demonstrated normal sinus rhythm without ectopy. No action was taken with OCA in response to the event. The event was assessed as not related to OCA by the Investigator and MAH. The subject continued in the study.

--Subject 3 (Preferred Term: Cardiac failure congestive)

Type of Event Congestive Cardiac Failure

Time of Event: Appr. 4 years and 9 months after the start of the LTSE phase

A female subject with a relevant medical history of antiphospholipid syndrome with previous deep vein thrombosis complicated by lung emboli at baseline was hospitalized for congestive cardiac failure.

Treatment during hospitalization included nadroparin. The subject was discharged 4 days later but re-admitted the following week due to worsening symptoms of congestive cardiac failure, as well as fever, elevated C-reactive protein, elevated troponin, and de novo atrial fibrillation. Treatment included acetylsalicylic acid, potassium chloride, oxycodone, furosemide, methylprednisolone, paracetamol, fondaparinux, amiodarone, immunoglobulin human normal, heparin, and dalteparin. The subject was discharged from the hospital approximately 10 days later with discharge diagnoses of multiple myocardial infarctions due to antiphospholipid syndrome exacerbation (not reported as separate TEAEs by the Investigator). No further details are available. No action was taken with OCA in response to the event. The event was assessed as possibly related to OCA by the Investigator and assessed as unlikely related to OCA by the MAH. The subject continued in the study.

--Subject 4 (Preferred Terms: Aortic valve stenosis, Ventricular fibrillation, Cardiac failure)

Type of Event: Aortic valve re-stenosis, ventricular fibrillation

Time of Event: Approximately 3 months after the start of the LTSE phase

A female subject with relevant medical history of previous aortic valve replacement, non-ischemic cardiomyopathy, implantable defibrillator due to ventricular tachycardias at baseline was admitted to the hospital for aortic restenosis requiring aortic valve replacement and also experienced ventricular fibrillation. The subject had complaints of shortness of breath since prior to starting the LTSE, and had undergone diagnostic testing, which had shown severe bioprosthetic aortic valve stenosis. On the day of admission, the subject underwent aortic valve replacement with aortic annuloplasty of the Manouagian variety. Ventricular fibrillation was noted during surgery and required cardioversion. The subject was also treated with furosemide for extreme hypervolemia post-surgery. She was discharged approximately 2 weeks later in good condition. OCA was interrupted during hospitalization and was eventually resumed approximately 5 months later. The events were assessed as not related to OCA by the Investigator and MAH. The subject continued in the study.

Type of Event: Cardiac failure

Time of Event: Approximately 1 year and 4 months after the start of the LTSE phase

The same subject was later admitted to the hospital for cardiac failure and renal failure. A right heart catheterization revealed moderately decreased cardiac output. A transthoracic echocardiogram revealed Grade 2 diastolic dysfunction suggestive of increased mean left atrial pressure, severe mitral and tricuspid regurgitation, properly functioning bioprosthetic valve in the aortic position and moderate pulmonary hypertension. The subject was transferred to another department for acute decompensated heart failure and for evaluation for mitral and tricuspid valve repair. Her hospitalization course was complicated by renal failure due to contrast induced nephropathy requiring ongoing haemodialysis. She was eventually discharged approximately 1 month later. OCA was interrupted for approximately 1 month as the subject ran out of medicine. It was resumed after discharge. The event was assessed as not related to OCA by the Investigator and MAH. The subject continued in the study.

--Subject 5 (Preferred Term: Ischaemic stroke)

Type of Event: Ischaemic Stroke

Time of Event: Approximately 3 years and 5 months after the start of the LTSE phase

A female subject with no relevant cardiovascular medical history at baseline was hospitalized with an ischemic stroke. The subject presented with left-sided weakness and was administered a tissue plasminogen activator. MRI of the brain without contrast showed multi-focal small acute infarcts in the right frontal and parietal parasagittal cortex. Head computed tomography (CT) showed no evidence for haemorrhagic transformation. OCA was interrupted during hospitalization but was resumed upon

discharge. The event was assessed as unlikely related to OCA by the Investigator and MAH. The subject continued in the study.

--Subject 6 (Preferred Term: Atrial fibrillation)

Type of Event: Atrial fibrillation

Time of Event: Approximately 4 years and 6 months after the start of the LTSE phase and approximately 2 weeks after the subject completed the study and initiated commercial Ocaliva.

A female subject with no relevant cardiovascular medical history at baseline was hospitalized due to paroxysmal atrial fibrillation. The subject reported acute onset of chest pain, spontaneous signs of exhaustion, and a 3-week history of numbness in the right hand and right foot, without signs of paralysis. She was treated with metoprolol and spontaneously converted to sinus rhythm overnight. The subject was discharged 2 days later. Action taken with OCA was not applicable as the subject had completed the study. The event was assessed as possibly related to OCA by the Investigator and assessed as unlikely related to OCA by the MAH.

--Subject 7 (Preferred Term: Transient ischaemic attack)

Type of Event Transient ischaemic attack

Time of Event Approximately 1 year and 9 months after the start of the LTSE phase

A female subject with no relevant cardiovascular medical history at baseline was hospitalized with a transient ischemic attack. She reported a short hemiparesis (1-minute duration) on the left side. CT and CT angiography showed no evidence of ischemia haemorrhage or significant hemodynamic stenosis. Treatment included acetylsalicylic acid; valsartan was discontinued. The subject was monitored for a few days, and eventually the diagnosis was confirmed as right hemispheric transient ischemic attack. The subject showed complete neurological recovery and was discharged 5 days after being admitted. No action was taken with OCA in response to the event. The event was assessed as not related to OCA by the Investigator and MAH. The subject continued in the study.

--Subject 8 (Preferred Term: Splenic infarction)

Type of Event Splenic Infarction (complication of Bacterial Endocarditis)

Time of Event Appr. 6 months after the start of the LTSE phase

See narrative in Section 2.1.3.3.1

LTSE – Relevant Clinical Laboratory Evaluations

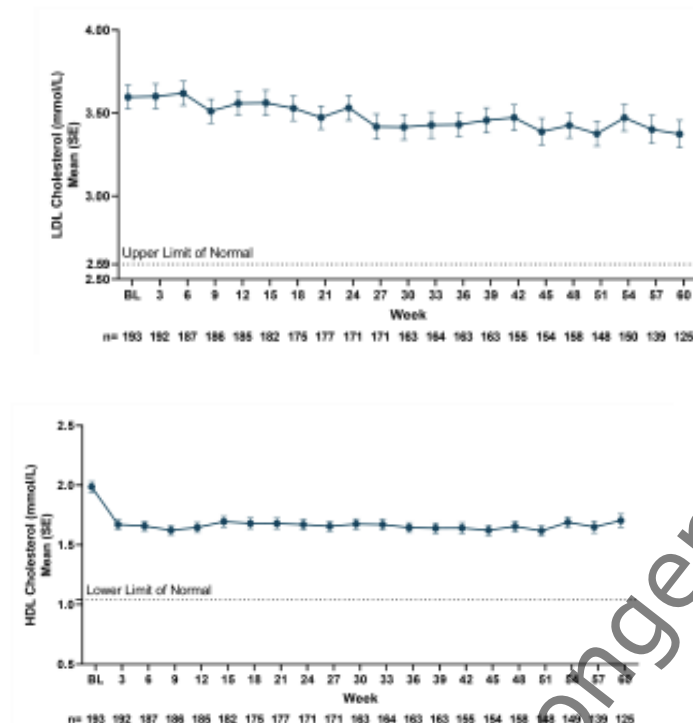
Renal Biochemistry Markers

Mean protein, blood urea nitrogen, and creatinine values were stable for the duration of the LTSE phase.

Serum Lipoproteins

As shown in Figure 24, lipid effects in the LTSE phase were consistent with the double-blind phase. With continued OCA treatment, there was no change from baseline in low density lipoprotein (LDL) while the modest decreases from baseline in high density lipoprotein (HDL) were sustained during the LTSE phase but remained within normal limits.

Figure 24: 747-301 - LTSE Mean (SE) LDL and HDL Concentrations Over Time



For subjects that received placebo in the double-blind phase, OCA baseline is the last assessment before the first OCA dose in LTSE. For subjects that received OCA in the double-blind phase, OCA baseline is the mean of all available evaluations before double-blind treatment.
Source: 747-301 LTSE CSR, Table 14.3.4.4.2

Serum Glucose

No meaningful changes in glucose were observed in the total OCA group from Month 3 through Month 72. One subject with no reported medical history of diabetes had Grade 2 serious TEAE of hypoglycaemia. There were no serious TEAEs of uncontrolled diabetes or hyperglycaemia.

747-301 - LTSE Safety Summary

Overall, administration of OCA was generally well tolerated over the 5-year LTSE phase in subjects with PBC; the safety profile during the LTSE phase was similar to that in the double-blind phase as well as the Phase 2 PBC studies with OCA, and no new safety signals were noted.

A total of 193 subjects received at least 1 dose of OCA during the LTSE. The median number of days on OCA was 1924.0 days (5.3 years) from initiation of OCA regardless of the double-blind or LTSE phases. The median weighted average daily OCA dose was 8.3 mg.

The most common TEAE was pruritus, which was mainly mild or moderate in severity. Pruritus frequency and severity remained steady after approximately 3 months of OCA treatment.

Overall, 61 (32%) subjects experienced a serious TEAE. There was no apparent pattern to the types of serious TEAEs. The majority of serious TEAEs were considered not related to OCA. Two (1%) deaths occurred during the LTSE (one was attributed to sepsis complications from a heart valve replacement and the other was due to jaundice associated with acute alcohol hepatitis); and both deaths were assessed as unrelated to OCA.

Cardiovascular-related safety was consistent with that reported in previous studies with OCA, and no new findings were noted following long-term treatment with OCA.

Hepatic-related safety was consistent with that reported in previous studies with OCA, and no new findings were noted following long-term treatment with OCA. Markers of hepatocellular injury and cholestasis improved with long-term OCA treatment. There is no evidence for an increased risk of hepatotoxicity in subjects receiving long-term treatment with OCA in the LTSE phase of pivotal study 747-301 with more than 7 subject-years of exposure.

- The majority of serious hepatic-related TEAEs appeared to be consistent with progression of disease and were all considered unlikely or not related to OCA. Most of these subjects had prior medical history for which they would be contraindicated per the new proposed SmPC.
- LDL remained unchanged with long-term OCA treatment and the decrease in HDL observed during the double-blind phase plateaued during the LTSE phase, with median values remaining above the LLN.

747-301 LTSE Conclusions

Of the 193 subjects enrolled in the LTSE phase of this study, 76% of the subjects completed the study protocol as specified over 6 years, demonstrating a high retention rate and adherence to OCA. Throughout the duration of treatment with OCA, up to 72 months, approximately 50% of subjects achieved the primary composite endpoint from the double-blind phase at every timepoint, indicating sustained and durable efficacy. This is of high clinical relevance given that PBC is a progressive liver disease and that most subjects had already failed first line treatment and are at higher risk of disease progression. Furthermore, subjects who had been randomized to placebo during the double-blind phase and transitioned on to OCA during the LTSE exhibited a nearly identical response to OCA as subjects who had been originally randomized into the OCA treatment groups.

Results from the LTSE phase demonstrated that OCA improved serum markers of cholestasis (ALP and GGT) and hepatocellular injury (AST and ALT) in subjects who had been randomized to placebo in the double-blind phase of the study, with sustained effects after long-term treatment for up to 72 months. Total bilirubin levels remained stable and within the normal range throughout the duration of the study. Importantly, total bilirubin levels which had risen in subjects randomized to placebo during the double-blind phase stabilized within the normal range throughout the LTSE after these subjects had initiated OCA. This is of important clinical significance as it has been shown that maintaining bilirubin levels at or below ULN is associated with improvement in liver related outcomes over time. Throughout the duration of the LTSE, no worsening was observed in non-invasive measures of fibrosis (enhanced liver fibrosis and TE), both of which have been associated with disease progression and clinical outcomes in subjects with PBC.

Several immune, inflammatory, and apoptotic markers (ie, immunoglobulin M, TNF- α , CRP, CK-18) showed improvement (ie, decreased levels) in the double-blind phase that continued to show a durable effect through the duration of the LTSE phase. Notably, a biopsy substudy demonstrated that 3 years of OCA treatment was generally associated with an improvement or stabilization of histologic fibrosis. Results of the post hoc reanalysis of the biopsy substudy were indicative that long-term OCA treatment in patients with PBC is associated with improvement or stabilization across a spectrum of histologic features of PBC. These data further support that OCA impacts multiple aspects of the PBC disease pathology.

Consistent with the known safety profile observed in the double-blind phase of Study 747-301 as well as the Phase 2 studies 747-201 and 747-202, OCA treatment was generally well tolerated in subjects with PBC, and there were no apparent new safety signals with long-term treatment. There were 2 deaths in the study that occurred during the LTSE, and both were deemed unrelated to OCA (see Section 2.1.3.3.1 for details on one additional death from the double-blind phase). As expected, mild-to-moderate pruritus was the most common TEAE in subjects treated with OCA. Pruritus frequency and

severity remained steady after approximately 3 months of OCA treatment. Ten percent of subjects withdrew from the LTSE due to pruritus or any other clinical or laboratory TEAE, and adherence in the study was high. Hepatic-related safety was consistent with that reported in previous studies with OCA, and no new findings were noted following long-term treatment with OCA.

Study 747-301 confirms the positive benefit:risk balance in patients with mild to moderate PBC treated for up to 6 years. This patient group is representative of what is expected in actual clinical target practice and consistent with the current and proposed SmPC.

Assessment of the MAH's response

Patients randomized to placebo in Study 747-301 crossed over to OCA treatment and all patients were followed for 5 additional years (747-301 LTSE). The Company was requested to provide a more comprehensive presentation of the relevant efficacy and safety results (focusing on SAEs and AESIs) from the LTSE of the pivotal study submitted at the time of the initial MA (Study 747-301).

The LTSE was interrupted prematurely due to Sponsor's decision, where all patients had a long-term follow-up of at least 72 months. A total of 193 subjects were included in the LTSE, of them 47 (24%) were discontinued prematurely, 20 (10%) due to AE and 12 (6%) due to patient's decision.

For subjects previously randomized to OCA and who continued treatment with OCA in the LTSE, the percentage of subjects achieving the primary composite endpoint at the end of the double-blind phase, i.e., Month 12 (47% for 5-10 mg OCA and 46% for 10 mg OCA), was sustained over the subsequent open-label period. The same pattern was seen for each biochemical parameters (ALP, BR, GGT, AST, ALT, and inflammatory markers) for subjects who stay in the study on continued treatment with OCA. A similar effect was reached after switching from placebo to OCA in the LTSE. By LTSE Month 60, nearly 50% of OCA-treated subjects saw a $\geq 40\%$ improvement in ALP, while BR tended to remain within normal values.

Long-term data show no significant progression of hepatic stiffness (as measured by elastography) in a subset of 106 subjects. The assessment of changes in histology was limited to 17 PBC subjects who provided biopsies at baseline and after 3 years on OCA treatment. The planned analysis showed improvement in histologic fibrosis in 7/17 subjects, stabilisation 6/17 subjects, and worsening in 4/17 subjects. A post hoc reanalysis of the biopsy substudy was conducted with a consensus read from 2 pathologists using the most modern histologic scoring system for PBC (Nakanuma Histologic Staging) and automated second harmonic generation imaging for collagen morphometry. The results were: 2/17 subjects showed improvements in histologic fibrosis, 10/17 showed stabilisation and 5/17 showed worsening.

Overall, the results in liver biochemical parameters, although might overestimate the actual rates of treatment responders over time given that these are estimated based on observed data at each time point and do not account for the significant rate of discontinuations (24%), overall support the maintenance of the effect in the long-term. The assessment of hepatic stiffness and histology also provided some supportive evidence, but numbers are limited to selected subsets of subjects and thus, a firm conclusion cannot be drawn.

Overall, 189 (98%) subjects had at least 1 **TEAE**. A total of 105 (54%) subjects had a severe TEAE (incidence largely driven by pruritus), 64 (33%) subjects had a moderate TEAE, 20 (10%) subjects had a mild TEAE, and 150 (78%) subjects had a treatment-related TEAE. Two (1%) subjects had a TEAE that led to death, but these were considered not treatment related; 61 (32%) subjects had at least 1 serious TEAE; and 25 (13%) subjects had a TEAE that led to discontinuation.

The AE profile in the LTSE phase was consistent with that reported in the double-blind phase, with no new findings noted. The most common TEAE by PT was pruritus (132 [68%] subjects), followed by UTI

(24%), nasopharyngitis (23%), and gastrointestinal disorders (nausea (16%), diarrhoea (15%). Overall, 61 (32%) subjects had a serious TEAE. Three subjects died across both phases of the study, 2 in the LTSE phase and 1 in the double-blind phase. Two subjects died during the LTSE, and both deaths were considered not related to OCA by the Investigator and the MAH. The above described in the LTSE and double-blind phases deaths were unexpected and unrelated to the subjects' underlying liver disease. All subjects had stable synthetic liver function and no evidence of decompensation at baseline. The only serious TEAEs reported in more than 1 subject were osteoarthritis (in 6 subjects), oesophageal varices haemorrhage (in 4 subjects), radius fracture and pneumonia (in 3 subjects each), and pancreatitis, procedural pain, atrial fibrillation, and anaemia (in 2 subjects each). Two of the serious TEAEs (atrial fibrillation and cardiac failure congestive) were considered by the Investigator to be possibly related to OCA; all other serious TEAEs were considered not related or unlikely related. All serious TEAEs resolved with or without sequelae except for the 2 deaths in the LTSE phase and the serious TEAEs of chronic myeloid leukaemia and breast cancer, which were ongoing at the end of the study.

Overall, 26 (13%) subjects had a TEAE that led to discontinuation. The only TEAEs that led to discontinuation reported in more than 1 subject were pruritus (in 14 subjects) and oesophageal varices haemorrhage and fatigue (in 2 subjects each). Several of the TEAEs that led to discontinuation were considered by the Investigator to be possibly or probably related to OCA.

Pruritus was the most reported TEAE, also during the LTSE. Overall, 151 (78%) subjects had an event. No subject had a serious TEAE of pruritus. Pruritus TEAEs that led to discontinuation were reported in 14 subjects. Throughout treatment, more pruritus days were mild than moderate or severe. Pruritus frequency and severity remained steady after approximately 3 months of OCA treatment.

Despite being a relatively mild PBC population, 47 (24%) subjects (Total OCA) had a hepatic-related event during the LTSE. The most common events were oesophageal varices in 11 (6%), ascites in 10 (5%), and hepatic cirrhosis in 7 (4%) subjects, which generally reflected disease progression. Of them, only 8 (4.1%) subjects had a serious hepatic-related TEAE during the LTSE phase. Oesophageal varices haemorrhage (in 4 subjects) and varices oesophageal (in 2 subjects) were the only serious hepatic-related events that occurred in more than 1 subject. Other serious hepatic-related TEAEs were reported in a single subject each: hepatic failure, hepatic neoplasm malignant, ascites, and jaundice. In general, the types of serious hepatic-related TEAEs appeared to be consistent with progression of disease. If this is the normal course of the disease or if OCA treatment is modifying the course, in any sense, cannot be ascertain in the absence of a comparator arm. It is agreed with the Company that most of the subjects having a serious hepatic event had prior medical history for which they would be contraindicated these per the new proposed SmPC, which is reassuring.

With respect to dyslipemia/ CV events, a total of 19 (10%) subjects had a dyslipemia event, consistent with those seen in the double blind: with continued OCA treatment, there was no change from baseline in low density lipoprotein (LDL) while the decreases from baseline in high density lipoprotein (HDL) were sustained during the LTSE phase but remained within normal limits. Overall, 40 (21%) subjects experienced at least 1 cardiovascular disorder event. Eight (4%) subjects had a serious cardiovascular disorder TEAE during the LTSE phase, with atrial fibrillation (in 2 subjects) being the only event reported in more than 1 subject. A specific pattern of CV events could not be determined, and most patients had personal history of cardiac events/risk factors.

In conclusion, the MAH has presented the requested detailed information from the LTSE of Study 747-301, the pivotal trial supporting the initial MAA. Overall, long term efficacy data support the maintenance of the effect of OCA treatment in liver biochemical and inflammatory parameters. A high proportion of patients had a severe TEAE (54%), and SAEs (32%), though the overall rate of treatment discontinuation was relatively low (13%). The safety profile remains unchanged, with

pruritus being the most common bothersome TEAEs, largely responsible for the severe TEAEs. CV (21%) and hepatic events (24%) were commonly reported during the trial, though the incidence of serious CV and hepatic events was relatively low (around 4% both), and most of these cases occurred in patients with underlying conditions or in whom treatment with OCA is currently contraindicated. Overall, these data do not raise major concerns, although the absence of a control arm does not allow drawing firm conclusions on the actual role of OCA in the incidence of these events.

This **issue is** considered **solved**. The information requested has been provided.

Study 747-401

Question 4

The MAH is invited to present the safety results for this study in more detail and tabulated, including details of the nature of severe, serious TEAEs and AESIs, those leading to discontinuation and to death.

Summary of the MAH's response

Background

747-401 was a Phase 4, 48-week study designed to characterize the pharmacokinetics and safety of obeticholic acid (OCA) in subjects with primary biliary cholangitis (PBC) with moderate to severe hepatic impairment as this population was not evaluated in the initial submission. It was one of the 2 Specific Obligations, and an imposed Post Authorisation Efficacy Study, associated with the Conditional Marketing Authorisation.

This study was conducted based on results from previous Phase 1 and 2 studies that showed doses of OCA administered to subjects with moderate or severe hepatic impairment should be lower than those for subjects with normal hepatic function to achieve similar hepatic exposure. To evaluate this, the study was designed such that all subjects initiated investigational product once weekly with OCA 5 mg or matching placebo. At Week 12, if the investigational product was tolerated and laboratory assessments did not indicate a safety concern, the subject could be up titrated to OCA 5 mg twice weekly.

The study was planned to recruit approximately 50 patients and approximately 35 study sites globally. By 2020, the majority of targeted sites (41/45) had been activated and almost half of the targeted number of subjects (22/50) had been enrolled. In response to Data Monitoring Committee recommendation and the COVID-19 pandemic, the MAH temporarily halted screening, randomization, and site activation. The study was terminated upon the submission of the European Union (EU) Summary of Product Characteristics (SmPC) Variation in 2021, with last-subject-last-visit on 09 Jul 2021. Twenty-two subjects were enrolled (21 assessed as Child Pugh [CP]-B and 1 subject assessed as CP-C).

Following Ocaliva approval, it became clear that patients with CP-B or CP-cirrhosis were not appropriate for Ocaliva treatment due to the increased risk of hepatic failure/decompensation events, including fatal cases observed in clinical trials and post-marketing experience. In 2021, regional labelling and the Company Core Data Sheet (CCDS) were revised to contraindicate this patient population:

- The United States Prescribing Information (USPI) was revised to contraindicate use of OCA in patients with decompensated cirrhosis or a prior decompensation event and those with compensated cirrhosis with evidence of portal hypertension.
- The SmPC was updated to contraindicate Ocaliva in patients with decompensated cirrhosis (including CP-B or CP-C) or has had a prior decompensation.

Notably, all subjects who were enrolled in Study 747-401 would meet the revised contraindicated criteria of both the USPI and SmPC.

Safety findings from Study 747-401, as well as the safety findings in more advanced disease patients in Study 747-302 (see Question 10) reinforce that the contraindications are appropriate to ensure a positive benefit:risk with the proposed SmPC indicated population (i.e., patients without cirrhosis or compensated cirrhosis who had not experienced clinically significant portal hypertension or a previous decompensation event prior to initiation of Ocaliva).

Subject Characteristics

Per the study design, baseline characteristics were consistent with a population of PBC subjects with moderate to advanced cirrhosis. Key baseline laboratory variables indicative of intrahepatic cholestasis and synthetic hepatic function are summarized in Table 34.

Table 34: Study 747-401 – Baseline Liver Biochemistries and Other Baseline Characteristics (ITT Population)

	Placebo (N=12) n (%)	OCA (N=10) n (%)	Overall (N=22) n (%)
Baseline Child-Pugh Score			
n	12	10	22
Mean (SD)	7.9 (0.90)	7.7 (0.67)	7.8 (0.80)
SE	0.26	0.21	0.17
Median (Q1, Q3)	8.0 (7.0, 8.0)	8.0 (7.0, 8.0)	8.0 (7.0, 8.0)
Min, Max	7, 10	7, 9	7, 10
Baseline Child-Pugh Class, n (%)			
B	11 (91.7)	10 (100.0)	21 (95.5)
C	1 (8.3)	0	1 (4.5)
Baseline MELD Score			
n	12	10	22
Mean (SD)	12.4 (2.97)	12.7 (3.47)	12.5 (3.13)
SE	0.86	1.10	0.67
Median (Q1, Q3)	12.0 (11.0, 14.0)	13.0 (10.0, 16.0)	12.5 (11.0, 15.0)
Min, Max	6, 18	7, 17	6, 18
Baseline Alkaline Phosphate (U/L)			
n	12	10	22
Mean (SD)	236.2 (115.27)	271.7 (131.70)	252.3 (121.33)
SE	33.27	41.65	25.87
Median (Q1, Q3)	216.0 (144.5, 290.0)	267.5 (151.0, 381.0)	232.5 (151.0, 367.0)
Min, Max	94, 491	91, 487	91, 491
Baseline Total Bilirubin (μmol/L)			
n	12	10	22
Mean (SD)	46.813 (22.917)	60.664 (46.483)	53.109 (35.369)
SE	6.616	14.699	7.541
Median (Q1, Q3)	45.375 (34.568, 55.788)	41.500 (19.000, 106.875)	45.375 (23.370, 79.515)
Min, Max	9.500, 92.000	15.390, 126.000	9.500, 126.000
Baseline INR (RATIO)			
n	12	10	22
Mean (SD)	1.157 (0.145)	1.200 (0.122)	1.176 (0.134)
SE	0.042	0.039	0.028
Median (Q1, Q3)	1.150 (1.100, 1.200)	1.225 (1.100, 1.300)	1.175 (1.100, 1.250)
Min, Max	0.90, 1.50	1.00, 1.40	0.90, 1.50
Baseline Platelets (10⁹/L)			
n	11	9	20
Mean (SD)	137.05 (75.452)	125.67 (38.901)	131.93 (60.558)

	Placebo (N=12) n (%)	OCA (N=10) n (%)	Overall (N=22) n (%)
SE	22.750	12.967	13.541
Median (Q1, Q3)	141.50 (80.00, 160.50)	132.50 (84.50, 158.50)	134.25 (80.25, 160.25)
Min, Max	65.0, 323.0	76.5, 177.0	65.0, 323.0
Baseline Albumin (g/L)			
n	12	10	22
Mean (SD)	35.58 (4.284)	33.37 (4.710)	34.58 (4.516)
SE	1.237	1.489	0.963
Median (Q1, Q3)	34.50 (33.00, 36.75)	33.00 (30.00, 36.50)	34.00 (32.00, 36.50)
Min, Max	32.0, 48.0	26.0, 41.5	26.0, 48.0

INR=international normalized ratio; ITT=Intent-to-Treat; Max=maximum; MELD=Model for End-Stage Liver Disease; Min=minimum; OCA=obeticholic acid; Q=quartile; SD=standard deviation; SE=standard error
Normal ranges: ALP=35 U/L to 130 U/L; total bilirubin=3.42 µmol/L to 20.52 µmol/L; platelets=130 x10⁹/L to 394 x10⁹/L; and albumin=33 g/L to 46 g/L

Note: Percentages are based on number of subjects in the ITT Population within each treatment group and overall.
Source: 747-401 CSR, Table 14.1.3.1.1

Extent of Exposure

In the double-blind phase and double-blind extension phase, the overall mean duration of exposure to study treatment was 296.5 days in the OCA and 233.4 days in the placebo groups.

Summary of Adverse Events

All 10 (100.0%) subjects in the OCA and 12 (100.0%) subjects in the placebo groups reported at least 1 treatment-emergent adverse event (TEAE) during the double-blind phase and double-blind extension phase of the study. Treatment-related TEAEs occurred in 4 (40.0%) subjects in the OCA group and 6 (50.0%) subjects in the placebo group. Nine (90.0%) subjects in the OCA group and 9 (75.0%) subjects in the placebo group experienced TEAEs of special interest. Six (60.0%) subjects in the OCA group and 7 (58.3%) subjects in the placebo group experienced severe TEAEs. Overall, study treatment or study discontinuations occurred in 5 (50.0%) subjects in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) subjects in the OCA and 4 (33.3%) subjects in the placebo groups. A total of 7 (70.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced serious adverse events (SAEs). Five subjects died during the study. One of the deaths (clear cell renal cell carcinoma; placebo group) occurred within the study period; however, was reported after database lock. All 5 cases are described in Section 2.2.4.

Table 36: Study 747-401 – Treatment-Emergent Adverse Events in the Double-Blind and Double-Blind Extension Phases (Safety Population)

	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Any TEAEs	12 (100.0) [98]	10 (100.0) [110]
Serious TEAEs	9 (75.0) [16]	7 (70.0) [12]
Severe TEAEs	7 (58.3) [11]	6 (60.0) [10]
Treatment-Related TEAEs	6 (50.0) [10]	4 (40.0) [11]
TEAEs of Special Interest	9 (75.0) [26]	9 (90.0) [29]
TEAEs Leading to Discontinuation	5 (41.7) [5]	5 (50.0) [5]
Treatment-Related TEAEs Leading to Discontinuation	1 (8.3) [1]	2 (20.0) [2]
TEAEs Leading to Death*	2 (16.7) [2]	2 (20.0) [2]
COVID-19 TEAEs	0	1 (10.0) [1]

n=number of events; eCRF=electronic case report form; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

* One case of death (226001, clear cell renal cell carcinoma) in the placebo group occurred within study period, however, was reported after database lock and is not included in this table.

Notes: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

TEAEs with missing severity are considered severe. TEAEs with a missing relationship are considered related.

Discontinuation includes either 'Drug Withdraw' or 'Patient Discontinued from Study' on the eCRF.

Summaries are presented as n (%) [e]: number of subjects (percentage of subjects) [number of events].

For each row category, a subject with two or more adverse events in that category is counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within each treatment group.

Source: 747-401 CSR, Table 14.3.1.1, 14.3.1.16

Most Common Adverse Events by Preferred Term

The most common TEAEs were ascites, oesophageal varices haemorrhage, pneumonia, urinary tract infection, pruritus, and anaemia in the OCA group.

Table 37: Study 747-401 – Summary of Treatment-Emergent Adverse Events ≥ 2 Subjects in Any Treatment Group by Preferred Term in the Double-Blind and Double-Blind Extension Phases (Safety Population)

Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Ascites	4 (33.3) [5]	6 (60.0) [6]
Oesophageal varices haemorrhage	0	3 (30.0) [3]
Pneumonia	0	3 (30.0) [3]
Urinary tract infection	2 (16.7) [2]	3 (30.0) [3]
Pruritus	2 (16.7) [4]	3 (30.0) [4]
Anaemia	1 (8.3) [1]	3 (30.0) [3]
Abdominal distension	3 (25.0) [3]	2 (20.0) [2]
Abdominal pain	2 (16.7) [3]	2 (20.0) [3]
Diarrhoea	1 (8.3) [2]	2 (20.0) [3]
Nausea	2 (16.7) [3]	2 (20.0) [3]
Vomiting	1 (8.3) [1]	2 (20.0) [4]
Fatigue	1 (8.3) [1]	2 (20.0) [3]
Dizziness	1 (8.3) [1]	2 (20.0) [2]
Portal vein thrombosis	1 (8.3) [1]	2 (20.0) [2]
Pain in extremity	0	2 (20.0) [3]
Epistaxis	0	2 (20.0) [2]
Acute kidney injury	2 (16.7) [4]	2 (20.0) [3]
Oedema peripheral	4 (33.3) [4]	1 (10.0) [1]
Hepatic encephalopathy	2 (16.7) [5]	1 (10.0) [1]
Arthralgia	2 (16.7) [3]	1 (10.0) [2]
Tooth fracture	2 (16.7) [2]	1 (10.0) [1]
Constipation	2 (16.7) [2]	0
Pyrexia	2 (16.7) [5]	0
Iron deficiency anaemia	2 (16.7) [2]	0
Joint injury	2 (16.7) [2]	0

e=number of events; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

Adverse events are coded using MedDRA Version 24.0.

Summaries are presented as n (%) [e]: number of subjects (percentage of subjects) [number of events].

For each row category, a subject with two or more adverse events in that category is counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within each treatment group.

Source: 747-401 CSR, Table 14.3.1.2.

Adverse Events by Maximum Severity

In the double-blind phase and double-blind extension phase, the majority of reported TEAEs were mild (Grade 1) or moderate (Grade 2) in severity. A total of 6 (60.0%) subjects in the OCA and 7 (58.3%) subjects in the placebo groups experienced severe (Grade 3) TEAEs (Table 39). Related Grade 3 TEAEs included upper gastrointestinal haemorrhage, hepatic failure, pyrexia, and hepatic function abnormal. Of the Grade 3 TEAEs, 4 subjects experienced a TEAE (multiple organ dysfunction syndrome, cardiac arrest, hepatic encephalopathy, and aortic aneurysm rupture, respectively) that resulted in a fatal outcome, which were all not related or unlikely related to the study treatment, were reported before database lock, and are further described in Section 2.2.4.

Table 39: Study 747-401 – Summary of Treatment-Emergent Adverse Events Grade 3 in Severity by Preferred Term in the Double-Blind and Double-Blind Extension Phases (Safety Population)

Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Subjects with at least 1 severe TEAE	7 (58.3) [11]	6 (60.0) [10]
Liver transplant	1 (8.3) [1]	0
Hepatic failure	0	1 (10.0) [1]
Hepatic function abnormal	1 (8.3) [1]	0
Hepatic encephalopathy	2 (16.7) [5]	0
Oesophageal varices haemorrhage	0	3 (30.0) [3]
Ascites	1 (8.3) [1]	0
Pancytopenia	1 (8.3) [1]	0
Upper gastrointestinal haemorrhage	0	1 (10.0) [2]
Pneumonia	0	1 (10.0) [1]
Multiple organ dysfunction syndrome	0	1 (10.0) [1]
Aortic aneurysm rupture	1 (8.3) [1]	0
Cardiac arrest	0	1 (10.0) [1]
Rhabdomyolysis	0	1 (10.0) [1]
Pyrexia	1 (8.3) [1]	0

e=number of events; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; TEAE=treatment-emergent adverse event

Note: Severity of adverse events are determined as Severe: causing inability to carry out usual activities; the subject may experience intolerable discomfort or pain.

TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

Adverse events are coded using MedDRA Version 24.0.

Summaries are presented as n (%) [e]: number of subjects (percentage of subjects) [number of events].

For each row category, a subject with two or more adverse events in that category is counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within each treatment group.

Source: 747-401 CSR, Table 14.3.1.4 and Table 14.3.1.17.2

Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment or Study Discontinuation

Overall, in the double-blind phase and double-blind extension phase, TEAEs leading to study treatment withdrawal or study discontinuation occurred in 5 (50.0%) subjects in the OCA and 5 (41.7%) subjects in the placebo groups (Table 40). Four subjects (3 OCA-treated and 1 placebo-treated) experienced a TEAE (upper gastrointestinal haemorrhage, COVID-19, cardiac arrest, and hydrothorax, respectively) that led to both study drug withdrawal and study discontinuation. One OCA-treated subject experienced a TEAE of multiple organ dysfunction syndrome, which led to study drug withdrawal and was fatal.

Table 40: Study 747-401 – Treatment-Emergent Adverse Events Leading to Study Drug Withdrawal or Study Discontinuation by System Organ Class and Preferred Term in the Double-Blind and Double-Blind Extension Phases (Safety Population)

System Organ Class Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Subjects with at least 1 TEAE	5 (41.7) [5]	5 (50.0) [5]
Cardiac disorders	0	1 (10.0) [1]
Cardiac arrest	0	1 (10.0) [1]
Gastrointestinal disorders	1 (8.3) [1]	1 (10.0) [1]
Upper gastrointestinal haemorrhage	0	1 (10.0) [1]
Ascites	1 (8.3) [1]	0
General disorders and administration site conditions	0	1 (10.0) [1]
Multiple organ dysfunction syndrome	0	1 (10.0) [1]
Hepatobiliary disorders	0	1 (10.0) [1]
Hepatic failure	0	1 (10.0) [1]
Infections and infestations	0	1 (10.0) [1]
COVID-19	0	1 (10.0) [1]
Nervous system disorders	1 (8.3) [1]	0
Hepatic encephalopathy	1 (8.3) [1]	0
Respiratory, thoracic and mediastinal disorders	1 (8.3) [1]	0
Hydrothorax	1 (8.3) [1]	0
Surgical and medical procedures	1 (8.3) [1]	0
Liver transplant	1 (8.3) [1]	0
Vascular disorders	1 (8.3) [1]	0
Aortic aneurysm rupture	1 (8.3) [1]	0

Treatment-Emergent Adverse Events Leading to Study Drug Interruption

Overall, in the double-blind phase and double-blind extension phase, TEAEs leading to study treatment interruption occurred in 5 (50%) subjects in the OCA and 4 (33.3%) subjects in the placebo groups. The most common TEAE leading to study treatment interruption in subjects within the double-blind phase and double-blind extension phase was ascites (2 [20.0%] subjects in OCA and 1 [8.3%] in placebo groups).

Table 41: Study 747-401 - Treatment-Emergent Adverse Events Leading to Study Drug Interruption in the Double-Blind and Double-Blind Extension Phases (Randomized Population)

Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Subjects with at least 1 TEAE leading to study drug interruption	4 (33.3) [6]	5 (50.0) [10]
Hepatic encephalopathy	1 (8.3) [3]	1 (10.0) [1]
Oesophageal varices haemorrhage	0	1 (10.0) [1]
Ascites	1 (8.33) [1]	2 (20.0) [2]
Pancytopenia	1 (10.0) [1]	0
Coronary artery disease	0	1 (10.0) [1]
Upper gastrointestinal haemorrhage	0	1 (10.0) [1]
Haematemesis	0	1 (10.0) [1]
Peritonitis bacterial	0	1 (10.0) [1]
Blood bilirubin increased	0	1 (10.0) [1]
Hyperbilirubinaemia	0	1 (10.0) [1]
Acute kidney injury	1 (10.0) [1]	0

e=number of events; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

Adverse events are coded using MedDRA Version 24.0.

Source: 747-401 CSR, Listing 16.2.7.1

Deaths

There were 5 deaths in the study (3 in placebo-treated subjects: hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal cell carcinoma; and 2 in OCA-treated subjects: multiple organ dysfunction syndrome and cardiac arrest). All were assessed by the Investigator as not related or unlikely related to the study treatment. The death from clear cell renal cell carcinoma occurred within the study period, however, was reported after database lock.

--Subject 1

Cause of Death: Multiple organ dysfunction syndrome

Time of Death: Approximately 2 years, 2 months, 3 weeks and 1 day after the subject initiated the study drug, and 1 day after the subject's second OCA 10 mg twice weekly dose on Day 813 (Week 69) of the double-blind extension phase. A male subject was hospitalized following an incidence of collapse. He had multiple organ failure. On Day 821, the subject died, predominantly due to acute kidney injury, which was on a background of chronic kidney disease, decompensated cirrhosis, and cardiogenic shock. An autopsy was not performed. Per the death certificate, the chain of events that caused the death of this subject included acute liver failure and acute congestive heart failure exacerbation; significant conditions contributing to death included acute kidney failure and PBC. The SAE of multiple organ dysfunction syndrome was considered by the Investigator and the MAH as not related to OCA.

--Subject ID 2

Cause of Death: Hepatic encephalopathy

Time of Death: Approximately 13 days after the initiation of placebo once weekly, and 6 days since the last dose prior to the event during the double-blind phase. A female subject presented with hepatic encephalopathy and was hospitalized. On Day 19, the subject died from hepatic encephalopathy, which was considered unlikely related to placebo by the Investigator and the MAH. The subject had a medical history of intermittent confusion, aortic stenosis, left breast cancer, lower bilateral extremity oedema, cirrhosis, ascites, and decompensated liver disease.

--Subject 3

Cause of Death Clear cell renal cell carcinoma

Time of Death Approximately 1 year, 3 months and 22 days after the initiation of placebo

The female subject experienced worsening of pruritus during an interruption of investigational product. The subject's CP score was Class B and MELD score was 17 at that time. The Investigator site noted that the subject was not on study medication, thus considered the increased pruritus to be related to disease progression (considered an SAE) assessed as an important medical event. Ten months and 5 days after the last administered dose (Day 176) of study treatment (placebo once weekly), the subject was diagnosed with clear cell renal cell carcinoma. Approximately 1 month and 5 days after removal of the subject's right kidney tumour, the subject died from clear cell renal cell carcinoma (Grade 1), which was considered not related to placebo by the Investigator and the MAH.

--Subject 4

Cause of Death: Aortic aneurysm rupture

Time of Death: Approximately 3 weeks and 5 days after the initiation of placebo, and 3 days after the subject's last dose of placebo once weekly during the double-blind phase. A male subject died from a ruptured abdominal aortic aneurysm, which was considered not related to placebo by the Investigator and the MAH. The subject had a known history of aortic aneurysm prior to the start of the study.

--Subject 5

Cause of Death: Cardiac arrest

Time of Death: Approximately 1 month and 4 days after the subject initiated the study drug, and 6 days after the subject's dose of OCA 5 mg once weekly during the double-blind phase. A male subject was hospitalized due to gastrointestinal bleeding from oesophageal varices. During the endoscopy procedure, the subject experienced cardiac arrest, which was fatal. The cardiac arrest was considered a consequence of the bleeding from gastroesophageal varices and was assessed as not related to OCA by the Investigator and the MAH.

Other Serious Adverse Events

Overall, in the double-blind phase and double-blind extension phase, a total of 7 (70.0%) subjects in the OCA group and 9 (75.0%) subjects in the placebo group experienced SAEs (Table 42). Notable SAEs of upper gastrointestinal haemorrhage and hepatic failure are described below.

- A female subject experienced 2 events of upper gastrointestinal haemorrhage in the OCA group, which were deemed by the Investigator as possibly related to the study treatment. The MAH assessed both events of upper gastrointestinal haemorrhage as unlikely related to the study treatment. The subject had advanced hepatic disease as evidenced by a history of cirrhosis with hepatomegaly, oesophageal varices (as observed on esophagogastroduodenoscopy), gastropathy, and portal hypertensive gastropathy. The episodes of upper gastrointestinal haemorrhage in this subject were likely related to the subject's established advanced chronic liver disease and the pre-existing oesophageal varices.

- A female subject experienced 1 event of hepatic failure in the OCA group, which was deemed by the Investigator as probably related to the study treatment. Approximately 2 months after the initiation of investigational product, the subject was hospitalized due to an important medical event of liver decompensation (preferred term: hepatic failure; considered a serious AE). The MAH assessed the event of hepatic failure as possibly related to the study treatment. PBC is a progressive disease that can be complicated by hepatic failure after many years and development of advanced disease. However, there is insufficient information to assess the relatedness with any degree of certainty, and therefore, it is possible that study treatment may have contributed to the onset of the event.

Table 42: Study 747-401 - Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in the Double-Blind and Double-Blind Extension Phases (Safety Population)

System Organ Class Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Subjects with at least one Serious TEAE	9 (75.0) [16]	7 (70.0) [12]
Hepatobiliary disorders	1 (8.3) [1]	1 (10.0) [1]
Hepatic failure	0	1 (10.0) [1]
Hepatic function abnormal	1 (8.3) [1]	0
Blood and lymphatic system disorders	1 (8.3) [1]	0
Pancytopenia	1 (8.3) [1]	0
Gastrointestinal disorders	2 (16.7) [3]	4 (40.0) [5]
Oesophageal varices haemorrhage	0	3 (30.0) [3]
Upper gastrointestinal haemorrhage	0	1 (10.0) [2]
Abdominal pain	2 (16.7) [2]	0
Ascites	1 (8.3) [1]	0
Cardiac disorders	0	2 (20.0) [2]
Acute myocardial infarction	0	1 (10.0) [1]
Cardiac arrest	0	1 (10.0) [1]
General disorders and administration site conditions	1 (8.3) [1]	1 (10.0) [1]
Multiple organ dysfunction syndrome	0	1 (10.0) [1]
Pyrexia	1 (8.3) [1]	0
Infections and infestations	0	1 (10.0) [1]
COVID-19	0	1 (10.0) [1]
Pneumonia	0	1 (10.0) [1]
Respiratory, thoracic and mediastinal disorders	1 (8.3) [2]	1 (10.0) [1]
Pneumonia aspiration	0	1 (10.0) [1]
Hydrothorax	1 (8.3) [2]	0
Nervous system disorders	2 (16.7) [5]	0
System Organ Class Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Hepatic encephalopathy	2 (16.7) [5]	0
Renal and urinary disorders	1 (8.3) [1]	0
Acute kidney injury	1 (8.3) [1]	0
Surgical and medical procedures	1 (8.3) [1]	0
Liver transplant	1 (8.3) [1]	0
Vascular disorders	1 (8.3) [1]	0
Aortic aneurysm rupture	1 (8.3) [1]	0

e=number of events; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

Adverse events are coded using MedDRA Version 24.0.

Summaries are presented as n (%) [e]: number of subjects (percentage of subjects) [number of events].

For each row category, a subject with two or more adverse events in that category is counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within each treatment group.

Source: 747-401 CSR, Table 14.3.1.7

Treatment-Emergent Adverse Events of Special Interest

Overall, in the double-blind phase and double-blind extension phase, a total of 9 (90.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced adverse events of special interest (AESIs) (Table 43).

Table 43: Study 747-401 - Summary of Treatment-Emergent Adverse Events of Special Interest by Preferred Term in the Double-Blind and Double-Blind Extension Phases (Safety Population)

Preferred Term	Placebo (N=12) n (%) [e]	OCA (N=10) n (%) [e]
Subjects with at least 1 TEAE of Special Interest	9 (75.0) [26]	9 (90.0) [29]
Hepatic	8 (66.7) [15]	9 (90.0) [14]
Ascites	4 (33.3) [5]	6 (60.0) [6]
Oesophageal varices haemorrhage	0	3 (30.0) [3]
Blood alkaline phosphatase increased	0	1 (10.0) [1]
Blood bilirubin increased	1 (8.3) [1]	1 (10.0) [1]
Hepatic encephalopathy	2 (16.7) [5]	1 (10.0) [1]
Hepatic failure	0	1 (10.0) [1]
Hyperbilirubinaemia	0	1 (10.0) [1]
Hepatic function abnormal	1 (8.3) [1]	0
Liver transplant	1 (8.3) [1]	0
Portal hypertensive gastropathy	1 (8.3) [1]	0
Cardiovascular	1 (8.3) [1]	3 (30.0) [5]
Portal vein thrombosis	1 (8.3) [1]	2 (20.0) [2]
Acute myocardial infarction	0	1 (10.0) [1]
Angina pectoris	0	1 (10.0) [1]
Coronary artery disease	0	1 (10.0) [1]
Pruritus	2 (16.7) [4]	3 (30.0) [4]
Pruritus	2 (16.7) [4]	3 (30.0) [4]
Renal	3 (25.0) [6]	3 (30.0) [6]
Acute kidney injury	2 (16.7) [4]	2 (20.0) [3]
Blood urea increased	0	1 (10.0) [1]
Encephalopathy	1 (8.3) [1]	1 (10.0) [1]
Hyperkalaemia	1 (8.3) [1]	1 (10.0) [1]

e=number of events; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; TEAE=treatment-emergent adverse event

Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product.

Adverse events are coded using MedDRA Version 24.0.

Summaries are presented as n (%) [e]: number of subjects (percentage of subjects) [number of events].

For each row category, a subject with two or more adverse events in that category is counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within each treatment group.

Source: 747-401 CSR, Table 14.3.1.16

Hepatic AESIs

Overall, in the double-blind phase and double-blind extension phase, 9 (90.0%) subjects in the OCA and 8 (66.7%) subjects in the placebo groups had a hepatic-related AESI (Table 43). Nine subjects (OCA: 4 [40.0%] subjects; placebo: 5 [41.7%] subjects) had a severe (Grade 3) hepatic-related AESI. Nine subjects (OCA: 4 [40.0%] subjects; placebo: 5 [41.7%] subjects) had experienced at least 1 SAE. Three subjects (OCA: 1 [10.0%] subject; placebo: 2 [16.7%] subjects) had hepatic-related AESIs (hepatic failure, hepatic encephalopathy, and liver transplant, respectively) leading to study treatment or study discontinuation. Of the 29 reported AESIs, 6 were mild (Grade 1) in severity, 11 were moderate (Grade 2) in severity, and 12 were severe (Grade 3) in severity. A total of 24 were considered not related or unlikely related to study treatment, and 5 were considered possibly or probably related to study treatment.

Assessment for Potential Liver Injury

Potential liver injury cases were identified by predefined triggers and assessed according to the Hepatic Safety Committee Charter. Two of 22 cases (in 20 subjects) sent for adjudication were assessed as possibly related to study treatment (1 placebo, 1 OCA).

Eighty-six triggers for potential liver injury were identified from 20 unique subjects. Of these triggers, 16 had no evidence of liver injury. The remaining 70 triggers were assessed as potential liver injury and were grouped into 22 cases that were sent for blinded adjudication. Twenty (90.9%) of these 22 cases were assessed as unlikely related to study treatment. The remaining 2 cases, 1 in the placebo arm and 1 in the OCA arm, were assessed as possibly related to study treatment. Comments from the Hepatic Safety Committee panel are summarized below:

-A male subject (placebo once weekly; possibly related): Shortly after starting study drug, the subject developed encephalopathy. This subject had a history of cirrhosis at entry and the encephalopathy could have been related to study drug, which the subject improved following discontinuation of study drug.

-A female subject (OCA 5 mg once weekly; possibly related): This subject had elevated bilirubin at baseline with >1.5x baseline increase occurring 2 months after start of study drug, at which time the study drug was stopped. No changes from baseline in ALT, AST, GGT, or ALP were noted. The subject had a history of oesophageal varices since 2016 and developed pruritus 3 days after start of study drug. Relatedness to the study drug cannot be excluded with the limited data provided.

Cholelithiasis/Cholecystectomy AESIs

No TEAEs of cholelithiasis or cholecystectomy were reported during the study.

Cardiovascular AESIs

Overall, in the double-blind phase and double-blind extension phase, 3 (30.0%) subjects in the OCA and 1 (8.3%) subject in the placebo groups had a cardiovascular-related AESI (Table 43). No subjects had a severe (Grade 3) cardiovascular-related AESI. One subject in the OCA group had an SAE of acute myocardial infarction, which was moderate (Grade 2) in severity and was not related to study treatment (747-401 CSR, Listing 16.2.7.1).

One male subject had Grade 2 (moderate) coronary artery disease, which resulted in a coronary stent placement, and a Grade 2 SAE of acute myocardial infarction, from which the subject had recovered. The subject continued in the study without further cardiac issues, however, later experienced a fatal TEAE of multiple organ dysfunction syndrome (Section 2.2.4). This subject had a relevant medical history of hypertension and type 2 diabetes mellitus. Another subject who had Grade 1 (mild) angina pectoris, recovered, and continued in the study without further cardiac issues, however, later discontinued the study due to a TEAE of upper gastrointestinal haemorrhage. No cardiovascular-related AESIs leading to study treatment or study discontinuation were reported. Of the 6 reported AESIs, 2 were mild (Grade 1) in severity, 4 were moderate (Grade 2) in severity, all were considered not related to study treatment.

Renal AESIs

Overall, in the double-blind phase and double-blind extension phase, 3 (30.0%) subjects in the OCA and 3 (25.0%) subjects in the placebo groups had a renal-related AESI (Table 43). No subjects had a severe (Grade 3) renal-related AESI. One subject in the placebo group had an SAE of acute kidney injury, which was moderate (Grade 2) in severity, resulted in drug interruption, and was assessed as possibly related to study treatment. No renal-related AESIs led to study treatment or study discontinuation were reported. Of the 12 reported AESIs, 5 were mild (Grade 1) in severity, 7 were moderate (Grade 2) in severity, 8 were not related to study treatment, and 4 were considered possibly or probably related to study treatment.

Pruritus AESIs

Overall, in the double-blind phase and double-blind extension phase, 3 (30.0%) subjects in the OCA and 2 (16.7%) subjects in the placebo had a pruritus-related AESI (Table 43). Time to onset of first TEAE of pruritus was 4 to 84 days in the OCA group versus 22 to 56 days in the placebo group. No subjects had a severe (Grade 3) or serious TEAE of pruritus. No pruritus-related AESIs leading to study treatment or

study discontinuation were reported. Of the 8 reported AESIs, all were mild (Grade 1) in severity, 7 were considered not related or unlikely related to study treatment, and 1 was considered probably related to study treatment (OCA).

Summary and Conclusion of Study 747-401:

At the time of Ocaliva approval in 2016, there were limited clinical data available for OCA treatment in patients with PBC suffering from more advanced liver disease. Results from previous Phase 1 and 2 studies showed doses of OCA administered to patients with moderate or severe hepatic impairment should be lower than those for patients with normal hepatic function to achieve similar hepatic exposure. Thus, the initial labelling included a weekly dosing regimen for PBC patients with moderate (CP-B) and severe (CP-C) hepatic impairment of 5 mg twice weekly (at least 3 days apart between doses) and subsequently to 10 mg twice weekly (at least three days apart between doses) depending on response and tolerability.

Subject recruitment and retention in Study 747-401 were challenging given the availability of marketed Ocaliva was a significant disincentive to subjects with progressive liver disease to take part in a placebo-controlled study.

Following Ocaliva approval, it became clear that patients with CP-B or CP-C cirrhosis were not appropriate for Ocaliva treatment due to the increased risk of hepatic failure/decompensation events, including fatal cases observed in clinical trials and post-marketing experience. In 2021, regional labelling and the CCDS were revised to contraindicate this patient population:

- The USPI was revised to contraindicate use of OCA in patients with decompensated cirrhosis or a prior decompensation event and those with compensated cirrhosis with evidence of portal hypertension.

- The SmPC was updated to contraindicate Ocaliva in patients with decompensated cirrhosis (including CP-B or CP-C) or has had a prior decompensation.

Notably, all subjects who were enrolled in Study 747-401 would meet the revised contraindicated criteria of both the USPI and SmPC.

Safety findings from Study 747-401, as well as the safety findings in more advanced disease subjects in Study 747-302 (see Question 10) reinforce that the contraindications are appropriate to ensure a positive benefit:risk with the proposed SmPC indicated population (i.e., patients without cirrhosis or compensated cirrhosis who had not experienced clinically significant portal hypertension or a previous decompensation event prior to initiation of Ocaliva).

Assessment of the MAH's response

Study 747-401 was a one of the agreed SOB at the time of granting the CMA. This was a RCT, placebo controlled study conducted in PBC subjects with moderate to severe hepatic impairment to assess PK and safety. The study only included a total 22 subjects, out of to the initially planned 50 subjects, due to retention difficulties and its premature interruption once the new SmPC contraindications were included.

Despite testing a reduced dose of OCA (5mg once a week, titrated to 5mg twice a week), treatment was poorly tolerated in both treatment arms. All 22 (100.0%) subjects reported at least 1 treatment-emergent adverse event (TEAE). The most common TEAEs were ascites, oesophageal varices haemorrhage, pneumonia, all of them reported most in OCA treated arm. Treatment-related TEAEs occurred in 4 (40.0%) subjects in the OCA group and 6 (50.0%) subjects in the placebo group. Nine (90.0%) subjects in the OCA group and 9 (75.0%) subjects in the placebo group experienced TEAEs of special interest. Six (60.0%) subjects in the OCA group and 7 (58.3%) subjects in the placebo group experienced severe (Grade 3) TEAEs. Related Grade 3 TEAEs included upper gastrointestinal

haemorrhage, hepatic failure, pyrexia, and hepatic function abnormal. Of the Grade 3 TEAEs, 4 subjects experienced a TEAE (multiple organ dysfunction syndrome, cardiac arrest, hepatic encephalopathy, and aortic aneurysm rupture, respectively) that resulted in a fatal outcome, which were all not related or unlikely related to the study treatment. Overall, study treatment or study discontinuations occurred in 5 (50.0%) subjects in the OCA and 5 (41.7%) in the placebo groups and study treatment interruptions occurred in 5 (50.0%) subjects in the OCA and 4 (33.3%) subjects in the placebo groups. Four subjects (3 OCA-treated and 1 placebo-treated) experienced a TEAE of upper gastrointestinal haemorrhage, cardiac arrest secondary to bleeding from oesophageal varices, hepatobiliary disorder, and ascites, respectively) that led to both study drug withdrawal and study discontinuation. A total of 7 (70.0%) subjects in the OCA and 9 (75.0%) subjects in the placebo groups experienced serious adverse events (SAEs). Six out of the 7 subjects in OCA reported SAEs of bleeding of oesophageal varices/upper GI haemorrhage (4 cases) or cardiac arrest/MI (2) vs no subjects in placebo. Five subjects died during the study (3 in placebo-treated subjects: hepatic encephalopathy, aortic aneurysm rupture, and clear cell renal cell carcinoma; and 2 in OCA-treated subjects: multiple organ dysfunction syndrome and cardiac arrest).

Overall, no relevant differences were observed between treatment arms in the incidences of TEAEs, G3 TEAEs, SAEs TEAEs, and those noted can be explained by the low number of subjects in each treatment arm. Indeed, the low number of subjects included and premature study interruption, do not allow reaching sound conclusions on the actual safety profile of OCA in PBC with an advanced liver disease. Nevertheless, a numerical difference between treatment arms, disfavours OCA treatment, is systematically observed for hepatic AESI (9 patients (14 events) OCA vs 8 patients (11 events) placebo), cardiac AESIs (3 patients 5 events in OCA vs 1 subject/event placebo), pruritus (3 OCA vs 1 placebo), and bleeding GI events (both G3 and SAEs were reported in OCA patients while no such cases were reported in placebo [4 in OCA: 3 events of bleeding of oesophageal varices +1 upper GI haemorrhage OCA treated groups]), which should be noted and support the current contraindication in the SmPC.

Issue partially solved, but not further pursued within this procedure. The information requested has been provided. The study results point towards a higher toxicity in patients with advanced PBC. Treatment with OCA is currently contraindicated in this PBC patients, however inconsistent recommendations are included in Section 4.4. A revised proposal to monitor disease progression and interrupt treatment with OCA in patients who progress to advanced PBC stages with OCA should be included.

Question 5

OCA treatment is contraindicated in "Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see section 4.4)", due to the increased risk of hepatic failure/decompensation events, including fatal cases. Measures have been put in place to minimise this risk, i.e. a contraindication in section 4.3 and precautionary wording in section 4.4 of the SmPC to include new information about hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, occurring with obeticholic acid treatment in patients with PBC with cirrhosis, either compensated or decompensated. Section 4.8 ('Undesirable effects') was also updated to include hepatobiliary disorders in the tabulated list of adverse reactions. It is uncertain if these measures are currently (effectively) in place in clinical practice and sufficient to minimise these risks, but probably it is too early to know. The MAH is invited to comment, and should commit to monitor the actual effectiveness of this RMM in clinical practice.

Summary of the MAH's response

Following the termination of study 747-401, the MAH has implemented risk minimization measures (RMMs) in June/July 2022 i.e., updated European Union (EU) Summary of Product Characteristics (SmPC) and "Dear Health Care Professional communication" (DHPC) to emphasize the risks related to hepatic adverse events following initiation of treatment with Ocaliva (obeticholic acid [OCA]).

The MAH has conducted a cumulative review until 15 May 2023 of the available data to assess the effectiveness of the actual RMMs, and the result of this review is presented in the section below (Effectiveness check of implemented RMMs).

This review has shown a decrease in frequency/trend of hepatic events suggesting a positive trend post implementation of RMMs. The MAH commits to assessing the effectiveness of the implemented and newly proposed RMMs going forward. In the future, the MAH proposes to perform a 6-monthly effectiveness check and any significant negative impact/no impact will be submitted.

Effectiveness Check of Implemented RMM

Background:

OCA was first approved in the United States (US) on 27 May 2016. Conditional approval in the EU was granted on 12 Dec 2016. Approvals were granted under the tradename Ocaliva for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

According to the initially approved SmPC, Ocaliva was contraindicated in patients with complete biliary obstruction and there was a specific warning pertaining to liver-related adverse events (AEs) (elevations in ALT and AST, and clinical signs and symptoms of hepatic decompensation) and severe pruritus. In 2018, the US Food and Drug Administration (FDA) published a Drug Safety Communication clarifying hepatic decompensation and failure occurred in patients with decompensated and Child Pugh (CP)-B and CP-C cirrhosis who were dosed more frequently than recommended in patients treated with OCA.

The EU SmPC was subsequently updated highlighting the recommended dosing in patients with decompensated or CP-B or CP-C cirrhosis in Sections 4.2 and 4.4. The updated SmPC was endorsed by Committee for Medicinal Products for Human Use (CHMP) and approved by the EU Commission on 23 Mar 2018. In addition, reinforced differential dosing recommendations for Ocaliva in PBC patients with decompensated or CP-B or CP-C cirrhosis were communicated via a DHPC as agreed with Pharmacovigilance Risk Assessment Committee in 2018.

Following termination of Study 747-401, hepatic updates to the EU SmPC were submitted to CHMP on 01 Jul 2021 updating Section 4.3 to include contraindication in patients with decompensated cirrhosis (CP-B or CP-C) or a prior decompensation event, and Section 4.4 to include new warning on monitoring and management of patients for possible progression of PBC and other hepatic AEs and was approved in Jul 2022.

As a part of this assessment, CHMP had also requested the MAH to distribute a second DHPC related to contraindication in patients with decompensated cirrhosis (CP-B or CP-C) or a prior decompensation event, also to sensitize the health care providers on monitoring and management of patients for possible progression of PBC and other hepatic adverse events in Ocaliva (OCA) treated patients. The same was disseminated in June 2022.

The product was Conditionally Approved in the EU in the context of successful closure of Studies 747-302 (Efficacy and Safety) and 747-401 (Pharmacokinetics and Safety). However, these studies were prematurely closed after informing Health Authorities. Study reports were submitted in Dec 2022 as a Type II Variation. As part of the assessment of the shared study data, the MAH received the above query related to effectiveness of the implemented RMMs.

The MAH is committed to assessing the effectiveness of the implemented RMMs. This document presents the first assessment the MAH has conducted based on the cumulative data until 15 May 2023. Going forward the MAH will update this assessment on a 6-monthly basis.

A search was conducted in the Global Safety Database for OCA and the post-marketing data captured are from the date of approval until 15 May 2023. Out of the cumulative data, the MAH has evaluated post-marketing datasets from EU, United Kingdom and Rest of the World (excluding US) to identify hepatic AEs which are included in the Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries (SMQ): "Hepatic Disorders SMQ (broad), excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders." as per MedDRA version 26.0.

This search retrieved 726 case reports which included 1151 Hepatic AEs. Of these 726 case reports, 237 were serious (32.65 %), and 489 were non-serious case reports (67.34 %). Out of 1151 Hepatic AEs reported, 338 were serious (29.37%) and 814 were non-serious AEs (70.72%).

Out of these 726 unique case reports, there were:

- 11 reports where the patient had a history of compensated liver disease
- 20 reports where the patient had a history of decompensated liver disease at the time of OCA treatment initiation
- 45 case reports where the patient experienced hepatic decompensation post initiation of treatment with OCA
- 25 case reports mentioning indication of PBC with CP-B and in 6 case reports mentioning indication of PBC with CP-C

The MAH has followed 2 approaches to conduct the analysis:

Quantitative analysis:

The analysis was performed based on the number of AEs from the Hepatic SMQ: "Drug-related hepatic disorders - comprehensive search" in comparison with "per 100 patients-years exposed" to OCA in the regions where MAH holds an active license.

Estimations of post-marketing exposure data are based on sales distribution in EU, United Kingdom, and Rest of the World (excluding US). Each unit (bottle) of OCA contains 30 tablets. As per the SmPC, recommended dose is one tablet daily. Based on the response, the strength can be increased, however frequency remains 1 tablet daily. Hence one unit can signify one patient for 30 days.

The number of patients exposed to OCA has been calculated based on patient treatment years (PTY) using the formula mentioned below, where total number of units sold is equivalent of number of bottles sold, since each bottle contains 30 tablets covering 30 days (number of tablets sold is equal to sold units*30).

One unit=one patient for 30 days treatment

Total number of patient exposure in terms of PTY:

$$PTY = \frac{\text{Total number of units} \times 30}{365.25}$$

To calculate frequency of hepatic AEs for the relevant time period, the following formula was further used:

$$\text{Frequency of AEs per 100 PTY} = \frac{\text{Number of AEs in year} \times 100}{\text{Patient exposure for year}}$$

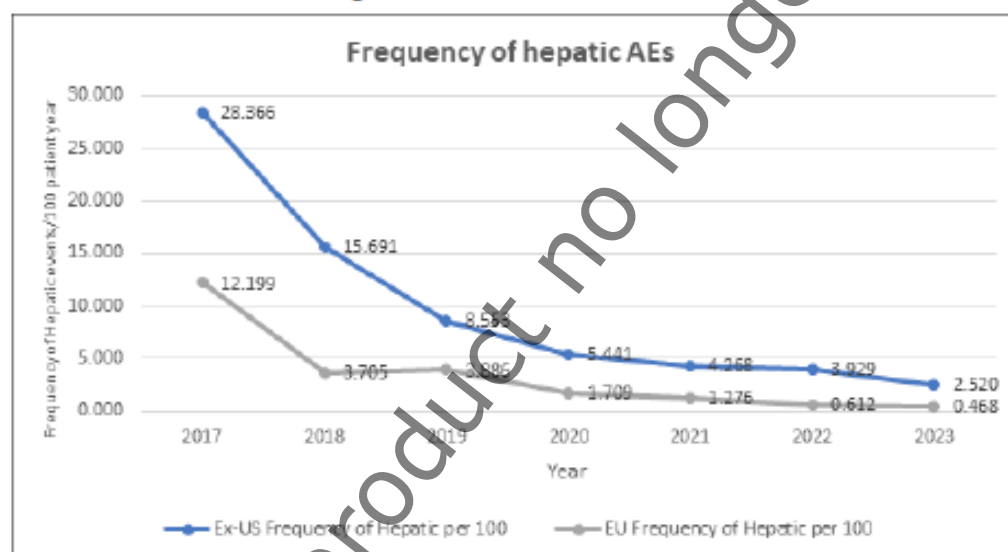
Table 45: Number and Frequency of Hepatic Adverse Events

Year	EU, UK and ROW (Excluding US)			EU		
	Patient-years-exposure	Hepatic AEs	Frequency per 100 patients/year	Patient-years-exposure	Hepatic AEs	Frequency per 100 patients/year
2017	360	102	28.366	328	40	12.199
2018	1332	209	15.691	1161	43	3.705
2019	2537	217	8.553	2161	84	3.886
2020	3437	187	5.441	2867	49	1.709
2021	4264	182	4.268	3526	45	1.276
2022	4963	195	3.929	4084	25	0.612
2023*	2341	59	2.520	1921	9	0.468

AE=adverse event; EU=European Union; ROW=rest of the world; UK=United Kingdom; US=United States

* Date of data cut-off 15-May-2023

Figure 26: Frequency of Hepatic Adverse Events “per 100-patient years” in EU and in EU, United Kingdom and Rest of the World



AE=adverse event; EU=European Union

According to data presented in Table 45 and Figure 26, there is a continuous downward trend in the reporting rate of hepatic AEs from 2017 until 2023. This trend can further be correlated with various milestones in the lifecycle of OCA since approval. The trend shows a clear decline in hepatic AEs from:

- 2017 to 2018, indicating a better understanding of the drug and its usage by healthcare professionals
- 2018 to 2019, a slight increase of liver AE frequency, followed by a decrease from 2019 to 2021 which is aligned with the RMM measure of the DHPC dissemination in 2018 and adoption by healthcare professionals over the time
- 2021 to 2023, post implementation of RMM of SmPC update and rolling out another DHPC in 2022

In the EU specifically, the frequency has further declined from 0.612 to 0.468 post implementation of RMMs.

Qualitative Analysis:

A search was conducted in the Global Safety Database for OCA and the data captured were from the date of approval until 15 May 2023. Out of the cumulative data, the MAH has evaluated post-marketing dataset from the EU, United Kingdom, and Rest of the World excluding US to identify hepatic AEs which are included in the SMQ: "Drug-related hepatic disorders - comprehensive search" as per MedDRA version 26.0. This search retrieved 726 case reports which included 1151 hepatic AEs.

MAH has reviewed all the 726 case reports including 1151 hepatic AEs, irrespective of outcome of the AEs, and analysis is as provided below:

- Out of 726 case reports related to hepatic events, 337 had minimal information to conclude any meaningful causal relationship with OCA.
- Three hundred eighty reports described other confounding information to conclude any meaningful causal relationship with OCA.
- Nine cases were assessed with probable causal relationship based on temporal relationship and positive de-challenge. In these cases, reported hepatic AEs were assessed as listed in line with EU SmPC. No new relevant safety information was identified in these cases.

The MAH concluded no new relevant safety information was identified during the qualitative analysis.

Analysis of Fatal Case Reports

Out of 726 case reports, there were 31 with a fatal outcome. Of these 31 reports, in 20 cases fatal outcome was associated with hepatic AEs and in remaining 11 reports fatal outcome was associated with other causes (scleroderma, transplantation complication, renal disorder, breast cancer metastatic, upper gastrointestinal haemorrhage, lung disorder, pneumonia and sepsis or unknown cause of death).

A decrease in the number of fatal hepatic AEs has also been observed. Twenty reports having hepatic AEs with a fatal outcome were identified between 2017-2023. In the year 2017, 1 fatal hepatic AE was reported, 3 were reported in 2018, 6 cases in 2019, 4 cases each 2020 and 2021, and 1 case in 2022 and 2023 up to date.

Table 46: Number of Hepatic Reports with a Fatal Outcome Since 2017 until 2023*

Year	Number of fatal reports due to Hepatic AEs (n)
2017	1
2018	3
2019	6
2020	4
2021	4
2022	1
2023*	1

AE=adverse event

In 20 cases with fatal outcome (associated with hepatic AEs), a total of 23 hepatic AEs were identified. The summary is provided below:

A female patient with medical history of PBC, multiple sclerosis, and allergies to tetracycline, Bactrim (sulfamethoxazole, trimethoprim), sulpha drugs, Tylenol (acetaminophen), methoxazole, and Flagyl (metronidazole) received Ocaliva 5 mg orally daily for PBC and 7 months after drug initiation, she experienced fatal event of liver failure. CP-C was reported at some point during the treatment. Ocaliva was discontinued several weeks before the time of the patient's death.

MAH Comment: The death has been assessed as unlikely related to OCA in line with the progressive nature of patient's underlying medical conditions (PBC and multiple sclerosis) and patient's advancing age.

A patient of unknown age and sex on Ocaliva therapy for PBC experienced fatal liver failure. The physician noted that the patient used Ocaliva too late. No further information was reported.

MAH Comment: The death has been assessed as unlikely related to OCA due to limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, details about medical history and concomitant medications.

A patient of unknown age and sex on Ocaliva via unknown dose, frequency, and route for PBC experienced fatal liver failure. The physician noted that he used Ocaliva too late.

MAH Comment: The death has been assessed as unlikely related to OCA due to limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, details about medical history and concomitant medications.

An adult patient of unspecified age and sex with PBC died due to cirrhosis of liver while on Ocaliva initiated at an unspecified date, dose, and frequency via oral route.

MAH Comment: The death has been assessed as unlikely related to OCA due to limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, details about medical history and concomitant medications.

An adult patient of unspecified age and sex with PBC experienced bleeding oesophageal varices after an unknown duration while on Ocaliva initiated at an unspecified date, dose, and frequency.

MAH Comment: The death has been assessed as unlikely related to OCA due to limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, details about medical history and concomitant medications.

A female patient with medical history of PBC and CP-C was unresponsive to UDCA and bezafibrate. The patient was treated with Ocaliva (5 mg oral weekly) for PBC and experienced the fatal events of "advanced PBC" and "decompensated cirrhosis" on an unknown date. After approximately 4 months, Ocaliva was discontinued due to the patient's continued deterioration and 1 month later developed decompensated cirrhosis. The patient died due to advanced PBC and decompensated cirrhosis.

MAH Comment: The death has been assessed as unlikely related to OCA. Fatality in this case is confounded by advanced stage of underlying medical condition PBC Child Pugh class C, with a likely poor prognosis, prior to initiation of OCA.

A female patient on Ocaliva 5 mg daily for PBC experienced a fatal event of decompensated liver failure and serious hepatic events of hepatorenal syndrome and ischemic hepatopathy requiring hospitalization. Patient's medical history included PBC, CP-A, cirrhosis, chronic obstructive pulmonary disease, dyslipidaemia, peripheral vascular disease, transient ischemic attack, bilateral kidney stones, chronic pain syndrome, cholecystectomy, total knee replacement, low haemoglobin, low potassium, excess weight loss, anaemia, drug allergies to Aspirin and codeine. Concomitant medications included UDCA, hydromorphone (hydromorphone hydrochloride), gabapentin, Dilaudid (hydromorphone hydrochloride), Plavix (clopidogrel bisulfate), Pantoloc (pantoprazole), Crestor (rosuvastatin calcium), risedronate, and ergocalciferol.

MAH Comment: The death has been assessed as unlikely related to OCA. Further, the co-morbid diseases (peripheral vascular disease, anaemia, and cachexia) were considered contributory to sepsis, liver failure, and death. Hydromorphone Contin (hydromorphone hydrochloride) and Dilaudid (hydromorphone hydrochloride) were considered co-suspect medications.

A female patient on Ocaliva 5 mg orally weekly for PBC experienced hepatic events of hepatic failure, ascites, and blood bilirubin increased. The patient's medical history included PBC, anaemia, cholelithiasis, haemolytic anaemia with an increased risk of gallstones, cysts on her ovaries, low platelets, eyes sometimes get yellow, bladder cysts, and CP score of 11. Approximately 3 months after Ocaliva initiation the patient was hospitalized for ascites. She also experienced complications stemming from renal failure. The patient died from sepsis related to cirrhosis and liver failure. Ocaliva was continued until the time of death.

MAH Comment: The death has been assessed as unlikely related to OCA. This patient had significantly elevated bilirubin prior to starting OCA along with confounding comorbidity (haemolytic anaemia and gallstones).

A female patient was on Ocaliva for PBC (dose of 5 mg, daily orally) with concomitant medication ursodeoxycholic acid. Approximately 3 years and 8 months after starting Ocaliva the patient died due to liver related disorder.

MAH Comment: The event liver disorder was assessed as possibly related to OCA, in view of plausible temporal association, however the underlying condition of PBC confounded the causal assessment.

A female patient died of liver failure (liver failure), following treatment with Ocaliva 5 mg once daily for PBC (initiated on 30 Jul 2018). The patient's concomitant medication included Ursodiol 2 g/day. The patient had been in hospital for about a month and she died on 16 Jan 2023 due to liver failure in the hospital.

MAH Comment: The event hepatic failure was assessed as possibly related to OCA, in view of plausible temporal association, however the underlying condition of PBC confounded the causal assessment.

A female patient of unknown age on Ocaliva 5 mg for PBC experienced the fatal event of progression of PBC while awaiting a transplant for an unknown duration after Ocaliva was initiated.

MAH Comment: The death has been assessed as not related to OCA. However, limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, medical history, concomitant medications preclude relatedness assessment in this case.

An adult patient of unspecified age and sex with PBC experienced hepatocellular carcinoma after an unknown duration of receiving an unknown dose of Ocaliva.

MAH Comment: The death has been assessed as unlikely related to OCA. Limited information regarding drug start date, drug dosing details, event onset date, action taken with OCA, medical history, and concomitant medications precludes relatedness assessment in this case.

A male patient with product used for unknown indication experienced fatal hepatorenal syndrome derived from decompensated cirrhosis while on Ocaliva at a dose of 5 mg, daily. On an unspecified date, the patient died due to hepatorenal syndrome derived from decompensated cirrhosis.

MAH Comment: The death has been assessed as unlikely related to OCA. Limited information regarding drug start date, drug dosing details, indication, event onset date, action taken with OCA, medical history, concomitant medications preclude relatedness assessment in this case.

A female patient with PBC was on Ocaliva (5 mg daily) which was decreased to 5 mg once weekly on an unknown date due to decompensated cirrhosis. Current conditions included PBC, sulfonamide allergy, hepatic cancer, and CP-B. After the initiation of Ocaliva, MELD score increased, and CP score progressed to CP-C. On an unspecified date, the patient developed multifocal hepatocellular carcinoma (hepatocellular carcinoma) that was deemed too advanced for treatment. The patient died due to decompensated cirrhosis and hepatocellular carcinoma.

MAH Comment: The death has been assessed as unlikely related to OCA. Fatality in this case is confounded by progressive nature of patient's underlying condition of PBC, with a Child-Pugh score of B and hepatic cancer.

A female patient was receiving Ocaliva (dose of 5 mg) for 6 months for PBC. Ocaliva was titrated to 10 mg based on liver function test values. Current conditions included PBC, CP-A, cirrhosis liver, and hypertension. Patient had no history of decompensating events, and good synthetic function. Patient was hospitalised (on 27 Jan 2020) due to community acquired bilateral pneumonia and treated with antibiotics. She died on 05 Feb 2020. Patient's primary cause of death was pneumonia and secondary causes were heart failure (heart failure), liver cirrhosis (liver cirrhosis), and PBC (primary biliary cirrhosis).

MAH Comment: The death has been assessed as not related to OCA. Pneumonia was considered as the primary cause of death while secondary causes were heart failure (heart failure), liver cirrhosis (liver cirrhosis), and PBC (primary biliary cirrhosis).

A female patient with PBC experienced gastrointestinal bleeding, liver cirrhosis, hepatic encephalopathy, international normalized ratio increased, prothrombin time increased and died due to hepatic decompensation while on Ocaliva. Past medical history included gallbladder polyp; current conditions included PBC, CP-B (score 7), depression, hypothyroidism, diabetes, vitamin B12 deficiency, hepatic decompensation, ascitic decompensation, impaired renal function, and hepatic cirrhosis. Procedures included liver biopsy and cholecystectomy for vesicular polyp. The patient was on multiple concomitant medications.

MAH Comment: The death has been assessed as unlikely related to OCA. Fatality in this case is confounded by progressive nature of patient's underlying condition of PBC, with a CP-B classification.

A female patient on Ocaliva (5 mg once a week) for PBC experienced hepatic events blood bilirubin increased, hepatomegaly, hepatic function abnormal, cholestasis, jaundice, ascites, drug-induced liver injury, and hepatic failure. Medical history included PBC, probable overlap connective tissue disorder, positive antinuclear antibody rheumatoid factor, anti-Ro and anti-RNP with hypergammaglobulinaemia, rheumatoid arthritis, hypothyroidism, mixed connective tissue disorder, eating disorder (anorexia), bronchiectasis, osteoporosis, alcoholic liver disease, alcohol abuse, ankle swelling, and a designation of CP-B (score 7) and a MELD score of 6. The patient was on multiple concomitant medications. The patient had an inadequate response to UDCA with a CP Score of B7. The patient began Ocaliva on 28 May 2018 and stopped Ocaliva when she felt unwell and then restarted it herself. On 10 Oct 2018, Ocaliva was discontinued but restarted again on 11 Oct 2018 until Jan 2019 at a dose of 10 mg per week. On 16 Feb 2019, the patient remained febrile and further developed worsening hypoxia and ongoing fevers that did not respond to intravenous antibiotics. High-dose steroid treatment for possible interstitial lung disease, respiratory support, and other symptomatic support was considered, however the patient died.

MAH Comment: The cause of death was considered as bronchopneumonia which was unlikely related to OCA. Further the relationship of OCA to the events of drug-induced liver injury, jaundice, bilirubin increased, and hepatic failure was reported as possibly related based on temporal association, however it could be confounded by the underlying condition of PBC with a CP-B classification.

A female patient on Ocaliva (5 mg orally once weekly) for PBC experienced serious hepatic events of ascites, blood alkaline phosphatase increased, blood bilirubin increased, and hepatic failure. Child-Pugh classification at the start of Ocaliva was "C" and at start of event was also "C" with score of 12. Medical history included PBC, itchiness, fluid retention associated with cortisone, and an allergy to codeine. Concomitant medications included UDCA, spironolactone, fluoxetine, and Vitamin D3 (colecalciferol). Approximately 6 months after Ocaliva initiation, the patient was hospitalized. Additionally, on an unknown date in 2019 she developed kidney stones and an unspecified infectious disease.

Ursodeoxycholic acid was discontinued on an unspecified date in Oct 2019. The patient was hospitalized due to worsening liver disease (hepatic decompensation) on an unknown date in 2019. On 17 Dec 2019, the event of "liver disease worsened" was fatal.

MAH Comment: The worsening of liver disease has been assessed as not related to OCA. Fatality in this case is confounded by the progressive nature of patient's underlying PBC with CP Class C prior to OCA initiation.

A male patient with PBC experienced advanced liver failure and death while receiving Ocaliva (5 mg, an unknown date in 2017). Medical conditions included PBC, portal hypertension, ascites, and CP-B. Concomitant medications taken at the time of the event included spironolactone, UDCA, rifaximin, and venlafaxine. At the end of 2018, the patient was added to the transplant list. In Jun 2019, the patient developed advanced liver failure and Ocaliva was discontinued. On an unknown date, the patient restarted a new Ocaliva dose of 5 mg, orally, twice a week. On 19 Jun 2019, the patient was admitted to the hospital for palliative care. On 25 Nov 2019, the patient died due to advanced liver failure. Ocaliva was ongoing at the time of death.

MAH Comment: The death has been assessed as unlikely related to OCA. Fatality in this case is confounded by patient's medical conditions suggestive of progression of PBC (of Child-Pugh B class) namely portal hypertension and ascites.

A female patient with PBC experienced hepatic events: chronic hepatic failure, international normalised ratio abnormal, alanine aminotransferase abnormal, aspartate aminotransferase abnormal, and hepatic encephalopathy. Current conditions included primary biliary cholangitis, drug allergy (opioids), cholestasis, fatigue, pulmonary hypertension, CREST syndrome, arthritis, iron deficiency anaemia, chronic obstructive lung disease, hypothyroidism, depression, hypertension, decompensated cirrhosis, blood creatinine abnormal, CP-B, portal hypertension, and chronic kidney disease. The patient was on multiple concomitant medications. Ocaliva was initiated on 10 Mar 2019 at a dose of 5 mg, once a week orally for PBC-related cirrhosis. On 19 Jul 2019, the dose was uptitrated to 5 mg twice weekly orally. In 2019, the patient experienced progressive end-stage liver disease and mild hepatic encephalopathy (hepatic encephalopathy) for which patient was treated with lactulose. On 30 Jan 2020, the patient died from chronic end stage liver disease secondary to PBC.

MAH Comment: The death has been assessed as unlikely related to OCA. Fatality in this case is confounded by patient's multiple medical histories as well as by progressive nature of underlying PBC (of Child Pugh class B).

Among the 20 cases with a fatal outcome, no cases were identified with any strong association between the events and OCA. The causal association was unlikely in most of the case reports, possible in 2 and not related on 3 case reports. Furthermore, it was identified that in 9 of these cases, the CP classification was mentioned as (or score correlated with) CP-B or -C, which is a contraindication for the use of OCA. No new relevant safety information was identified.

Conclusion:

Based on the quantitative and qualitative analyses, the MAH concluded that the benefit:risk profile of OCA remains positive for appropriate patients with PBC. It is further concluded that the implemented RMMs, i.e., SmPC updates and distribution of DHPC, appear to be effective.

The MAH will continue to monitor the effectiveness of the implemented RMMs on a 6-monthly basis. The trend analysis will be performed on cumulative data and during the period. Any significant negative impact/no impact will be submitted along with the PBRER as annexure.

Assessment of the MAH's response

The MAH conducted a search in the Global Safety Database for OCA and the post-marketing data captured from the date of approval until 15 May 2023. Out of the cumulative data, the MAH has evaluated post-marketing datasets from EU, United Kingdom and Rest of the World (excluding US) to identify "Hepatic Disorders SMQ (broad), excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders." Based on the quantitative analysis conducted considering sales data, the data presented shows a continuous downward trend in the reporting rate of hepatic AEs from 2017 until 2023, including fatal cases, although the correlation with relevant RMM milestones is not that obvious as claimed by the MAH. However, the decrease in reporting might be explained by a continuous descent of clinical trials as the main source of data, such that over the last years spontaneous reporting might be the main (or even the only) source of evidence, with the inherent risk of under notification that worsens with prolonged time in the market. Furthermore, the low rates of under notification might be particularly aggravated in this case, given that these hepatic events would be expected by the progression of the underlying condition. Thus, the quantitative data provided, even if somewhat reassuring, do not allow concluding that the proposed RMM have been duly implemented and are effective. To this aim, a drug utilisation study or other tools that allow collecting data on the actual uses of OCA in clinical practice, not only at the time of prescribing but in the long-term, such that treatment is interrupted once the disease progress, would be needed together with measures to estimate the actual incidence of these hepatic events.

The issue is **considered solved**. Further discussion on the need for further RMM and proposals to assess the effectiveness may be needed, but would need to be addressed in an appropriate procedure reviewing the B/R of the product.

Study 747-302

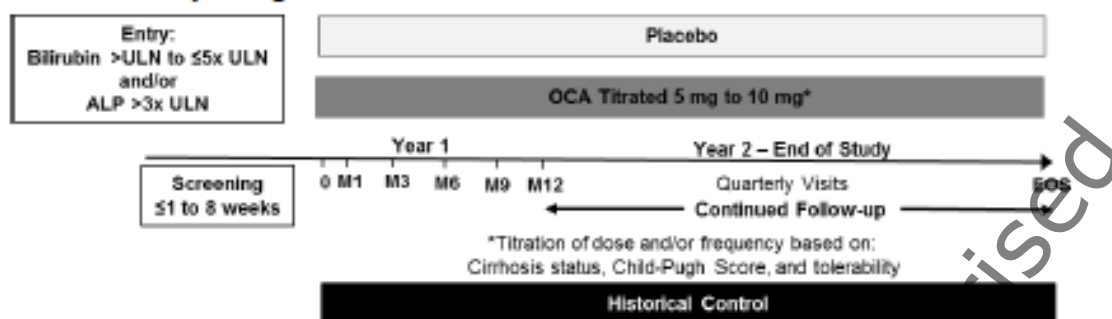
Question 6

The MAH should provide the baseline characteristics of the patients excluded from the overall safety analysis of Study 747-302, and confirm that these patients fulfil criteria for contraindication for OCA treatment according to the EU SmPC.

Summary of the MAH's response

Study 747-302 was carried out as part of one of the two Specific Obligations (SoBs) of the imposed Post-Authorisation Efficacy Studies (PAES) in the European Union (EU) to confirm the efficacy and safety of OCA. Study 747-302 is a confirmatory double-blind, randomized, placebo-controlled, multicentre study in a predominantly advanced primary biliary cholangitis (PBC) population. Most subjects enrolled into Study 747-302 had more advanced disease stage (i.e., higher risk for liver-related clinical complications) compared to previous studies and only a subpopulation of subjects is reflective of the current Summary of Product Characteristics (SmPC) indicated population. The rationale for this SoB was to confirm the clinical benefit of OCA in subjects with PBC by investigating its effect on clinical outcomes (see Figure 27) below.

Figure 27: Study Design (747-302)



CP-B=Child-Pugh Class B cirrhosis; CP-C=Child-Pugh Class C cirrhosis; EOS=end of study; M=month; OCA=obeticholic acid
 * Initial dose titration of investigational product should have occurred at the Month 3 visit, or any study visit thereafter for subjects on all dosing regimens, based on tolerability and biochemical response (Up-titration should have been considered when ALP and/or total bilirubin were >ULN). Subsequent dose titration(s) for subjects classified as CP-B or CP-C and following a modified dosing schedule may have occurred no earlier than 6 weeks after the previous dose titration

Source: 747-302, Figure 1

Following update to the United States Prescribing Information (USPI) label in May 2021, patients with decompensated cirrhosis, or with a prior decompensation event, or with compensated cirrhosis with evidence of portal hypertension at baseline stopped being eligible for enrolment in 747-302 in the US only. The EU SmPC was updated accordingly only in June 2022 (i.e., 7 months after the study was terminated on 03 Nov 2021). For this reason, it did not affect the EU subjects eligible for enrolment in the study.

Notwithstanding the change in the inclusion/exclusion criteria, per the pre-specified statistical analysis plan (SAP), the safety population included all 334 randomized subjects who receive any amount of investigational product (OCA or placebo). The safety population was the primary population used for safety analyses and treatment assignment was based on the treatment received. Given the USPI label changes in May 2021, the 747-302 SAP also prespecified subgroup analyses based on baseline disease stage severity (Figure 28, Table 47). The first subgroup category was based on baseline cirrhosis status, which is reflective of the current SmPC. An additional subgroup category was also analysed, which is more restrictive and excludes patients with clinical evidence of portal hypertension. This latter baseline subgroup category is reflective of the proposed SmPC labelling. Both subgroup categories include all subjects in the Study 747-302 intent-to-treat (ITT) and safety populations (both N=334).

21% of subjects who entered into Study 747-302 had decompensated cirrhosis or had a prior decompensation event at baseline and thus met the criteria of contraindicated per current SmPC. In contrast, 55% of subjects who entered into Study 747-302 met the criteria for the proposed SmPC contraindicated population, which is more restrictive and excludes all subjects with clinical evidence of portal hypertension.

Figure 28: Subgroup Analyses Based on Baseline Disease Severity (Study 747-302, N=334)

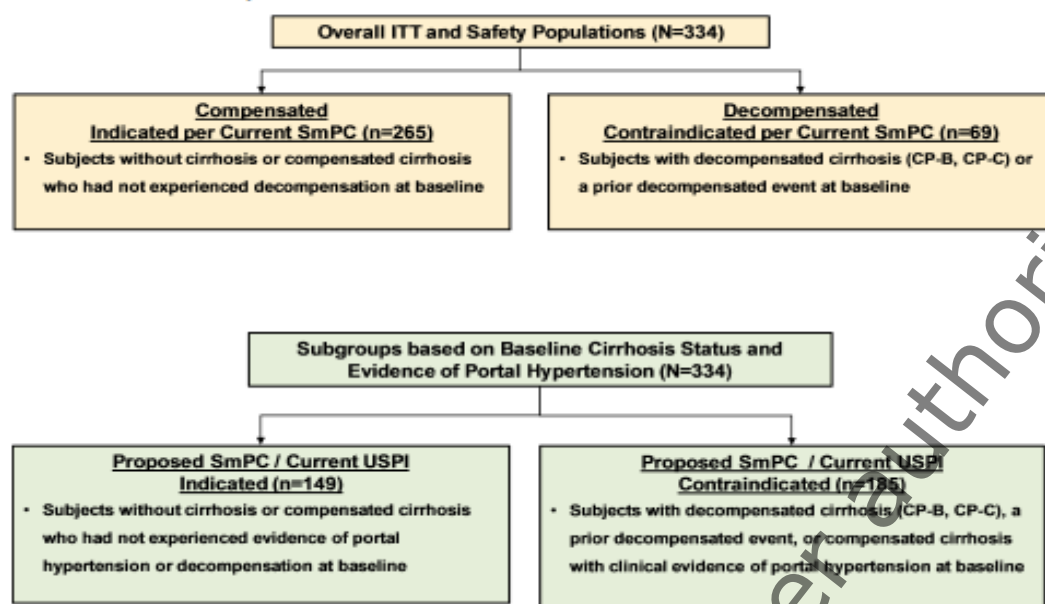


Table 47: Study 747-302 - PBC Baseline Disease Severity (ITT Population [N=334])

	Placebo N=166 n (%)	OCA N=168 n (%)	Overall N=334 n (%)
Current SmPC^a, n (%)			
Compensated (Indicated)	129 (77.7)	136 (81.0)	265 (79.3)
Decompensated (Contraindicated)	37 (22.3)	32 (19.0)	69 (20.7)
Proposed SmPC/Current USPI^b, n (%)			
Indicated	68 (41.0)	81 (48.2)	149 (44.6)
Contraindicated	98 (59.0)	87 (51.8)	185 (55.4)

OCA=obeticholic acid; PBC=primary biliary cholangitis; SmPC=Summary of Product Characteristics, USPI=United States Packaging Information

^a Current SmPC:

- Compensated (indicated) is defined as subjects without cirrhosis or with compensated cirrhosis who had not experienced decompensation at baseline.
- Decompensated (contraindicated) is defined as subjects with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event at baseline.

^b Proposed SmPC (Current indicated and contraindicated definitions):

- Indicated is defined as subjects without cirrhosis or compensated cirrhosis who did not have clinical evidence of portal hypertension or decompensation at baseline.
- Contraindicated is defined as subjects with decompensated cirrhosis (CP-B, CP-C), a prior decompensated event, or with compensated cirrhosis who had clinical evidence of portal hypertension at baseline.

Source: 747-302 CSR, Table 14.1.3.1.1

Study 747-302 Baseline Characteristics

Baseline characteristics for subjects by baseline disease severity based on the current SmPC, as well as the MAH's proposed SmPC are summarized in Table 48. As noted in Major Objection 1, the 747-302 subject population is not reflective of the current and proposed SmPC. 747-302 included a more advanced liver disease population.

Subjects recruited into Study 747-301 were more representative of the patients treated in real-world clinical practice.

Table 48: Study 747-302 - PBC Baseline Disease Severity and Key Laboratory Parameters by Baseline Disease Severity (ITT Population [N=334])

	Overall	Current SmPC				Proposed SmPC			
		Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
		PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Rotterdam Criteria^a, n (%)									
Early	106 (31.7)	0	2 (6.3)	51 (39.5)	53 (39.0)	40 (58.8)	45 (55.6)	11 (11.2)	10 (11.5)
Moderate	206 (61.7)	30 (81.1)	22 (68.8)	74 (57.4)	80 (58.8)	28 (41.2)	35 (43.2)	76 (77.6)	67 (77.0)
Advanced	22 (6.6)	7 (18.9)	8 (25.0)	4 (3.1)	3 (2.2)	0	1 (1.2)	11 (11.2)	10 (11.5)
Child-Pugh Class, n (%)									
CP-B	55 (16.5)	31 (83.8)	24 (75.0)	0	0	0	0	31 (31.6)	24 (27.6)
MELD Score	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	8.50 (6.90, 9.80)	11.00 (10.30, 11.50)	10.40 (9.90, 11.30)	7.90 (6.60, 9.10)	7.90 (6.40, 8.85)	7.20 (6.40, 8.35)	7.10 (6.40, 8.60)	9.60 (8.20, 11.00)	9.10 (8.20, 10.50)
MELD-Na Score	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	8.80 (7.20, 10.50)	12.10 (11.10, 12.90)	10.90 (10.30, 11.85)	8.40 (7.10, 9.60)	8.15 (6.85, 9.65)	7.40 (6.40, 9.00)	7.50 (6.40, 8.90)	10.05 (8.60, 11.90)	10.10 (8.40, 11.20)
Baseline ALP (U/L)	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	434.0 (262.0, 652.0)	332.0 (205.0, 512.0)	318.5 (202.5, 536.5)	447.0 (299.0, 719.0)	476.0 (293.5, 641.5)	587.5 (410.0, 781.5)	531.0 (378.0, 669.0)	360.0 (213.0, 526.0)	343.0 (202.0, 626.0)
Baseline GGT (U/L)	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	306.0 (175.0, 533.0)	212.0 (104.0, 412.0)	199.5 (111.5, 411.5)	373.0 (191.0, 582.0)	341.5 (203.0, 542.0)	414.0 (236.5, 612.0)	392.0 (227.0, 580.0)	253.0 (128.0, 482.0)	269.0 (148.0, 490.0)
Baseline Total Bilirubin (mg/dL)	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87

	Overall	Current SmPC				Proposed SmPC			
		Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
		PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Median (Q1, Q3)	1.50 (1.00, 2.00)	2.80 (2.00, 3.20)	2.40 (1.00, 3.10)	1.40 (0.90, 1.70)	1.40 (0.80, 1.80)	1.15 (0.70, 1.50)	1.10 (0.60, 1.60)	1.80 (1.40, 2.50)	1.80 (1.50, 2.40)
>ULN, n (%)	235 (70.4)	37 (100.0)	31 (96.9)	80 (62.0)	87 (64.0)	28 (41.2)	39 (48.1)	89 (90.8)	79 (90.8)
Baseline Creatinine (mg/dL)	n=298	n=31	n=28	n=118	n=121	n=66	n=74	n=83	n=75
Median (Q1, Q3)	0.670 (0.600, 0.790)	0.680 (0.570, 0.800)	0.680 (0.590, 0.740)	0.670 (0.600, 0.790)	0.670 (0.610, 0.800)	0.680 (0.620, 0.790)	0.680 (0.610, 0.820)	0.670 (0.570, 0.800)	0.660 (0.600, 0.750)
Baseline INR (RATIO)	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	1.00 (0.90, 1.00)	1.10 (1.00, 1.20)	1.05 (1.00, 1.10)	0.90 (0.90, 1.00)	0.90 (0.90, 1.00)	0.90 (0.90, 1.00)	0.90 (0.90, 1.00)	1.00 (0.90, 1.10)	1.00 (0.90, 1.10)
Baseline Platelets (10⁹/L)	n=334	n=36	n=32	n=127	n=136	n=66	n=81	n=97	n=87
Median (Q1, Q3)	201.0 (120.0, 273.0)	130.0 (86.5, 186.5)	103.0 (70.5, 189.5)	201.0 (142.0, 272.0)	219.5 (153.0, 291.5)	235.5 (201.0, 310.0)	271.0 (213.0, 312.0)	142.0 (93.0, 199.0)	139.0 (80.0, 207.0)
Baseline Albumin (g/L)	n=334	n=37	n=32	n=129	n=136	n=68	n=81	n=98	n=87
Median (Q1, Q3)	40.30 (37.70, 42.70)	36.00 (33.30, 40.30)	35.80 (33.00, 38.40)	40.80 (38.30, 42.70)	41.15 (39.00, 43.30)	42.30 (40.70, 43.50)	42.00 (39.80, 43.70)	38.00 (35.00, 41.00)	38.70 (36.30, 41.30)

CP=Child-Pugh; INR=international normalized ratio; ITT=Intent-to-Treat; MELD=model of end-stage liver disease; OCA=obeticholic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics

Note: Percentages are based on number of subjects in the ITT Population within each treatment group and overall.

ALP ULN=135 U/L (Female) and 131 U/L (Male)

GGT ULN=61 U/L (Female) and 50 U/L (Male)

Total Bilirubin ULN=1.2 mg/dL (Female and Male)

Creatinine ULN=0.95 mg/dL (Female) and 1.17 mg/dL (Male)

INR normal range=0.8 to 1.2 (Female and Male)

Platelets 10⁹/L LLN=130 (Female and Male)

Albumin g/dL=46 to 49 (Female and Male)

As shown in Table 49, the 747-302 cohort had higher ALP values at baseline, than the 747-301 population and European cohorts (Median (U/L) [IQR]: 244.0 [204.0, 361.0] in Spain, 259.0 [203.0, 391.0] in Italy and 343.4 [250.7, 469.4] in the UK PBC).

Table 49: PBC Baseline Key Laboratory Parameters and Disease Severity for 747-301, 747-302, and Real-World Cohorts

	747-301	747-302	RECAPITULATE Italy	Iberian cohort Spain	UK PBC
	N=216	N=334	N=441	N=120	N=349
Child-Pugh Class, n (%)					
Cirrhosis	36 (16.7)	NA	152 (34.5)	26 (21.7)	57 (16.5)
CP-B	NA	55 (16.5)	3 (2.0)	5 (20.0)	12 (3.4)
Not evaluated / Missing	NA	6 (1.8)	38 (25.0)		
Baseline ALP (U/L)	n=216	n=334	n=441	n=120	n=349
Median (Q1, Q3)	286.6 [143.8, 811.0] ^c	434.0 (262.0, 652.0)	259.0 (203.0, 391.0)	244.0 (204.0, 361.0)	343.4 (250.7, 469.4)
Baseline GGT (U/L)	n=70 ^a	n=334	n=431		
Median (Q1, Q3)	196.85 [48.2, 1084.0] ^c	306.0 (175.0, 533.0)	184.0 (107.0, 297.0)	NA	NA
Baseline ALT (U/L)	n=70 ^a	n=168 ^b	n=434	n=120	
Median (Q1, Q3)	45.20 [16.3, 240.2] ^c	71.0 (40.5, 103.5)	44.0 (32.0, 68.0)	47.0 (34.0, 74.9)	NA
Baseline AST (U/L)	n=70 ^a	n=168 ^b	n=433	n=120	
Median (Q1, Q3)	42.73 [23.3, 186.5] ^c	74.0 (50.5, 107.0)	41.0 (31.0, 58.0)	44.0 (33.0, 64.0)	NA
Baseline Total Bilirubin (mg/dL)	n=216	n=334	n=432	n=120	n=349
Median (Q1, Q3)	0.54 [0.09, 2.30] ^d	1.50 (1.00, 2.00)	0.7 (0.5, 1.0)	0.7 (0.5, 1.1)	0.55 (0.35, 0.90)
>ULN, n (%)	18 (8.3)	235 (70.4)	NA	NA	NA
Baseline Platelets (10⁹/L)	n=215	n=331	n=309	n=120	n=336
Median (Q1, Q3)	229.0 [56.0, 553.0] ^c	201.0 (120.0, 273.0)	227.0 (159.0, 294.0)	228.5 (164.0, 300.8)	262.0 (206.0, 321.0)
Baseline Albumin (g/L)	n=216	n=334	n=251	n=120	n=349
Median (Q1, Q3)	43.40 [32.5, 50.5] ^c	40.3 (37.7, 42.7)	40.0 (37.0, 43.0)	4.2 (4.0, 4.4)	41.0 (37.0, 45.0)
LSM (e.g., Fibroscan®), n (%)	n=35 ^a	n=122 ^b	n=307	n=120	n=349
Median (Q1, Q3)	6.80 [1.1, 38.6] ^c	12.55 (8.30, 22.00)	7.9 (6.0, 11.9)	7.9 (6.5, 11.3)	9.50 (7.05, 14.0)

	747-301	747-302	RECAPITULATE Italy	Iberian cohort Spain	UK PBC
	N=216	N=334	N=441	N=120	N=349
Portal Hypertension, n (%)	-	185 (55.4)	-	-	-
Non-bleeding varices, n (%)	-	69 (20.7)	42 (9.5)	13 (10.8)	-
OGD not performed, n (%)	-	-	6 (1.4)	-	-
Splenomegaly, n (%)	-	54 (16.2)	-	-	58 (30.7)
Decompensated at baseline, n (%)	-	69 (20.7)	6 (1.4)	-	-

^a OCA titration arm only

^b OCA arm only.

^c values are expressed in median [Min;Max]

^d $\mu\text{mol/L}$ values converted using $1 \mu\text{mol/L} = 0.05847953 \text{ mg/dL}$

Source 747-301: Table 14.1.5.1, Table 14.2.14.1, data on file (cirrhosis status), Table 14.2.9.1.10.

Source 747-302: Table 14.1.3.1.1, Table 14.1.3.2.1, Table 14.2.3.1, Table 14.2.5.1, Table 14.1.3.3.1, Table 14.1.3.1.1.2

Source UK PBC: Abbas 2023, data on file for ALP

Source RECAPITULATE: Data on file

Source Iberian cohort: Gomez 2020.

Assessment of the MAH's response

The Company has presented the information requested. These data confirm that 747-302 included a more advanced liver disease population, based on Rotterdam criteria of severity, Child-Pugh Class, MELD Score, baseline ALP, GGT, creatinine, INR, platelets, albumin, and total BR values at baseline, than that included in Study 747-301. Given the differences in the restrictions applied in the SmPC between US and EU, in addition to the overall safety analysis based on the safety population that included all 334 randomized subjects who receive any amount of investigational product (OCA or placebo), which was the primary population used for safety analyses, the 747-302 SAP also prespecified subgroup analyses based on baseline disease stage of severity. The first subgroup category was based on baseline cirrhosis status, which is reflective of the current SmPC (this excluded 21% of subjects who entered into Study 747-302 but had decompensated cirrhosis or had a prior decompensation event at baseline and thus met the criteria of contraindicated per current EU SmPC). An additional subgroup category was also analysed, which is more restrictive and excludes patients with clinical evidence of portal hypertension. This latter baseline subgroup category was not pre-specified and reflects the newly proposed restricted

indication that excludes 55% of subjects who entered Study 747-302. Whether this truly represent a portion of the PBC population where a favourable benefit/risk balance can be concluded with certainty is a matter of assessment within an appropriate procedure.

This issue is considered clarified.

Question 7

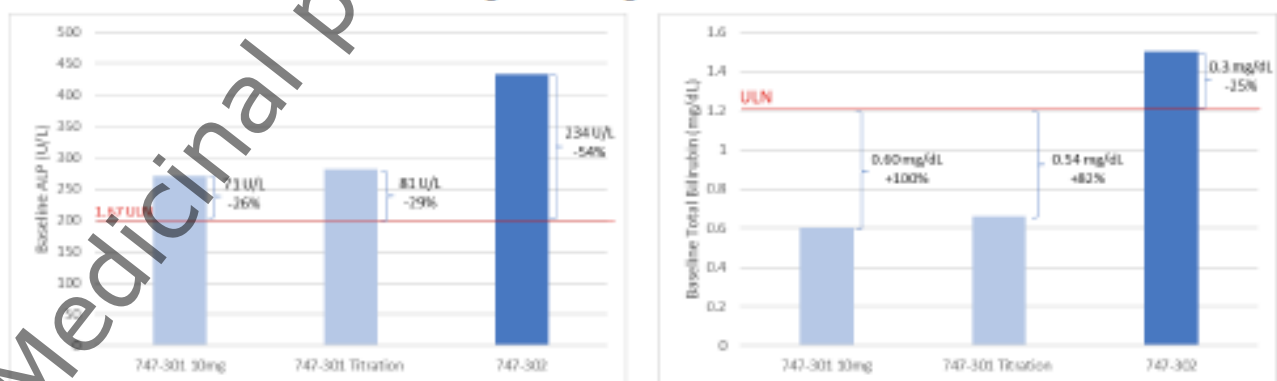
Secondary endpoint analyses show that only a total of 21 (6.3%) of patients enrolled in Study 747-302 met the primary endpoint as defined in the pivotal Phase 3 Study 747-301 of an ALP $<1.67\times$ ULN and total bilirubin $\leq$ ULN and ALP decrease from baseline of $\geq 15\%$. Indeed, the rate of responders was substantially lower compared to that previously reported and this was the case in both treatment arms, but rather noticeable in the OCA treated group (OCA 10.1% vs 2.4% placebo in Study 747-302 vs OCA 34.0% vs 7% placebo in Study 747-301). No statistically significant differences were reported, adding even further uncertainties to the actual efficacy of OCA in the treatment of PBC. The MAH should present a detailed description of changes in relevant liver biochemical parameters and explain the observed differences, considering that Study 747-302 included a more advanced liver disease population likely representative of the actual target in clinical practice.

Summary of the MAH's response

Subjects recruited into Study 747-301 had milder disease at an earlier stage and are representative of patients with PBC currently treated in routine clinical practice. Study 747-302 recruited subjects with more advanced disease to enhance accrual of clinical events. This is supportive by significant differences in baseline disease characteristics, the magnitude of change required to achieve biochemical thresholds of the primary response criteria in Study 747-301, the time course of ALP and total bilirubin, and real-world clinical practice patient characteristics.

As shown in Figure 4 and Figure 5, median baseline ALP and total bilirubin values were substantially higher in Study 747-302 versus 747-301. Figure 4 also shows that the percent reduction from baseline required to achieve the target ALP ($\leq 1.67\times$ ULN) or total bilirubin ($< \text{ULN}$) thresholds from the primary response criteria of Study 747-301 were significantly different between studies.

Figure 4: Reduction from Median Baseline ALP and Total Bilirubin Required to Achieve 747-301 Endpoint (Responder)

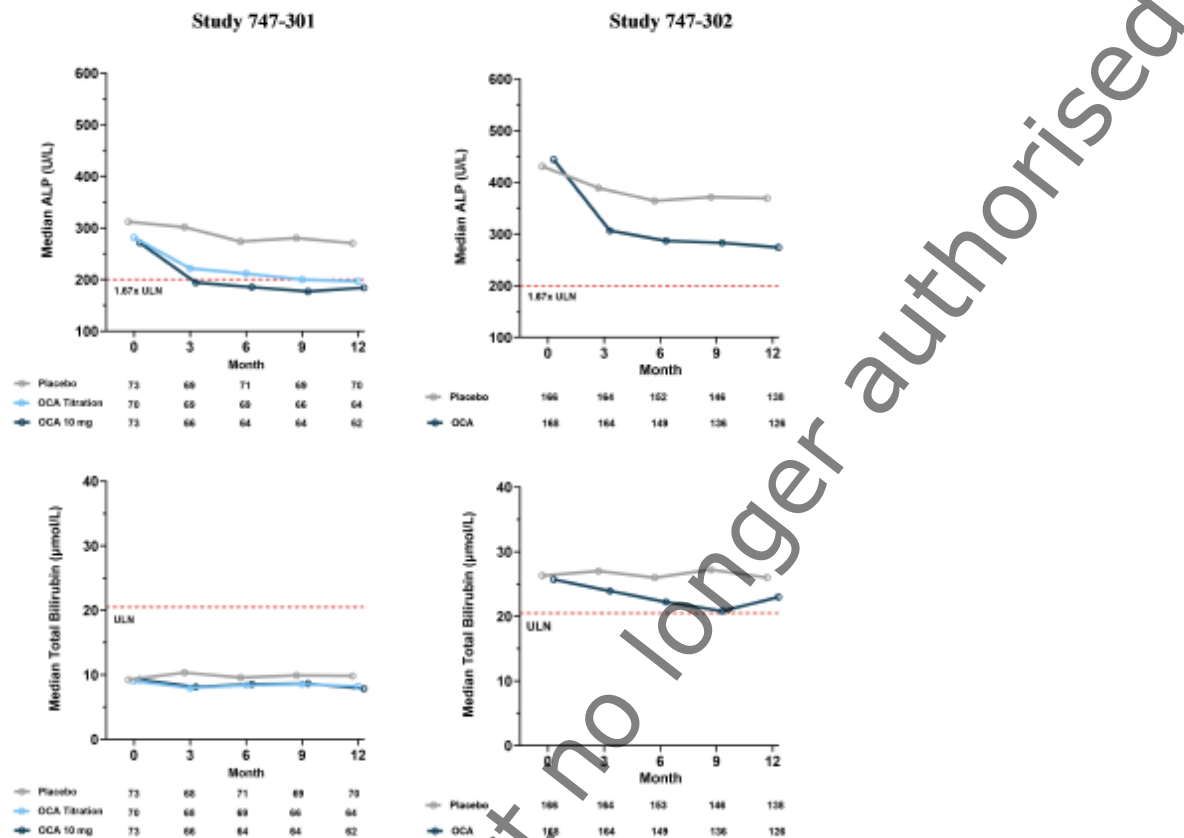


Represented the same Figure 4 as above for easy reference

Despite differences in baseline ALP and total bilirubin, clinically meaningful improvements in ALP and total bilirubin were observed in the OCA group compared to the placebo group in both studies (Figure 5). The magnitude of improvements in ALP were consistent for the OCA group for both studies, while a

greater reduction in total bilirubin was observed for the OCA group in Study 747-302 compared to Study 747-301 (Table 1).

Figure 5: Median ALP (U/L) and Total Bilirubin (μmol/L) Over Time for Studies 747-301 and 747-302



Source: 747-301 CSR, 14.2.9.1.1; 747-302 CSR, Table 14.2.3.1
Represented the same Figure 5 as above for easy reference

Table 1: Studies 747-301 and 747-302 - ALP and Total Bilirubin at Baseline and Month 12

	Study 747-301				Study 747-302	
	OCA Titration		OCA 10 mg		OCA	
	n	Median	n	Median	n	Median
ALP (U/L)						
Baseline	70	281.3	73	271.3	168	444.0
Month 12	64	196.6	62	184.2	126	274.0
Absolute Change		-85.5		-99.4		-99.0
Total Bilirubin (μmol/L)						
Baseline	70	9.1	73	9.2	168	25.7
Month 12	64	8.2	62	7.9	126	23.0
Absolute Change		-0.3		-0.4		-1.2

OCA=obeticholic acid

Source: 747-301 CSR, 14.2.9.1.1; 747-302 CSR, Table 14.2.3.1

Represented the same Table 1 as above for easy reference

As shown in Table 2 patient characteristics from European PBC and OCA registries provide supportive evidence that the Study 747-301 subject population is more representative of the patient population treated with Ocaliva in real-world clinical practice than the Study 747-302 population. The median ALP levels of patients initiating Ocaliva in cohorts from Spain, Italy and the UK are similar to or lower than baseline ALP levels in Study 747-301.

Table 2: Median (IQR) ALP (U/L) in MAH Registrational Trials and European Registries of Patients Treated with OCA

	Randomized, Double-blind, Placebo-controlled Studies		European Registries OCA-treated Patients		
	747-301 N=216	747-302 N=334	Iberian Cohort Spain N=120	RECAPITULATE Italy N=441	UK-PBC N=349
ALP (U/L) Median (IQR)	286.6 (143.8, 811.0)	434.0 (262.0, 652.0)	244.0 (204.0, 361.0)	259.0 (203.0, 391.0)	343.4 (250.7, 469.4)
Total Bilirubin (mg/dL) Median (IQR)	0.54 (0.09, 2.30)	1.50 (1.00, 2.00)	0.7 (0.5, 1.1)	0.7 (0.5, 1.0)	0.55 (0.35, 0.90)

IQR=25th and 75th interquartile ranges ; OCA=obeticholic acid

Source: 747-301 CSR Table 14.1.5.1.1; 747-302 CSR Table 14.1.3.1.1; Gomez 2020 (Iberian Cohort Spain); data on file (RECAPITULATE); Abbas 2023 (UK-PBC, total bilirubin), data on file (UK-PBC, ALP)

Represented the same Table 2 as above for easy reference

Biochemical Response Predicts Clinical Outcomes

Because of the high rate of treatment cross-over in Study 747-302, an analysis of biochemical response and correlation with clinical outcomes was conducted, independent of initial randomization status. As shown Table 3, irrespective of treatment group, there was an association between biochemical response (based on the Study 747-301 primary endpoint) and improved clinical outcomes (based on the Study 747-302 primary outcomes endpoint). This demonstrates that changes in biochemistries, specifically reductions in abnormal values of ALP and total bilirubin, which are known to reflect ongoing damage in progressive cholestatic disease, are predictive of improved clinical outcomes. The HR of 0.23 indicates a substantial reduction in the risk of liver transplant or death in subjects who achieve the biochemical response as initially described in Study 747-301.

Table 3: Time to the Event by Biochemical Response at Month 12: 747-301 Primary Endpoint Responder Criteria (ITT Population)

Statistics	Biochemical Responder*			Non-Biochemical Responder		
	Placebo	OCA	Total	Placebo	OCA	Total
Responder Definition: ALP $\leq 1.67 \times$ ULN and Total Bilirubin $\leq$ULN and ALP Decrease from Baseline of $\geq 15\%$ at Month 12						
Number of Responders, N	4	17	21	162	151	313
Number of Subjects with the 747-302 Primary Endpoint Event, n (%)	1 (25.0)	2 (11.8)	3 (14.3)	79 (48.8)	69 (45.7)	148 (47.3)
Number of Subjects Censored, n (%)	3 (75.0)	15 (88.2)	18 (85.7)	83 (51.2)	82 (54.3)	165 (52.7)
Log Rank p-value ^b	0.006					
Hazard Ratio (95% CI) ^c	0.23 (0.07, 0.72)					

ALP=alkaline phosphatase, CI=confidence interval, ITT=intent to treat, OCA=obeticholic acid, ULN=upper limit of normal

* A biochemical responder is defined as a subject who attains an ALP < 1.67 times the ULN and total bilirubin $\leq$ ULN and an ALP decrease of $\geq 15\%$ from Baseline at Month 12 visit. Subjects missing values at Month 12 are considered non-responders.

^b Log-Rank p-value was based on log-rank test stratified by the treatment group.

^c Hazard ratio was estimated using stratified Cox's proportional hazards model with responder as an independent variable and the treatment group as strata. The results represent the ratio of Responder to Non-responder. A hazard ratio < 1 indicates an advantage for Responder.

Source: 747-302 CSR, Table 14.2.9.1

Represented the same Table 3 as above for easy reference

As shown in Table 50, this outcome benefit was observed across various established biochemical

responder criteria.

Table 50: Time to the Event by Biochemical Response at Month 12: ALP ≤ 2 x ULN and Total Bilirubin < 1 x ULN (ITT Population)

Statistics	Biochemical Responder*			Non-Biochemical Responder		
	Placebo	OCA	Total	Placebo	OCA	Total
Responder Definition: ALP ≤ 2 x ULN at Month 12						
Number of Responders, N	35	54	89	131	114	245
Number of Subjects with the 747-302 Primary Endpoint Event, n (%)	21 (60.0)	16 (29.6)	37 (41.6)	59 (45.0)	55 (48.2)	114 (46.5)
Number of Subjects Censored, n (%)	14 (40.0)	38 (70.4)	52 (58.4)	72 (55.0)	59 (51.8)	131 (53.5)
Log Rank p-value ^a	0.270					
Hazard Ratio (95% CI) ^b	0.81 (0.55, 1.18)					

Statistics	Biochemical Responder*			Non-Biochemical Responder		
	Placebo	OCA	Total	Placebo	OCA	Total
Responder Definition: Total Bilirubin < 1 x ULN at Month 12						
Number of Responders, N	46	57	103	120	111	231
Number of Subjects with the 747-302 Primary Endpoint Event, n (%)	7 (15.2)	9 (15.8)	16 (15.5)	73 (60.8)	62 (55.9)	135 (58.4)
Number of Subjects Censored, n (%)	39 (84.8)	48 (84.2)	87 (84.5)	47 (39.2)	49 (44.1)	96 (41.6)
Log Rank p-value ^a	< 0.001					
Hazard Ratio (95% CI) ^b	0.17 (0.10, 0.28)					

ALP=alkaline phosphatase, CI=confidence interval, ITT=intent to treat, OCA=obeticholic acid, ULN=upper limit of normal

^a A biochemical responder is defined as a subject who attains an ALP ≤ 2.0 times the ULN and total bilirubin < 1.0 times ULN at Month 12 visit. Subjects missing values at Month 12 are considered non-responders.

^b Log-Rank p-value was based on log-rank test stratified by the treatment group.

^c Hazard ratio was estimated using stratified Cox's proportional hazards model with responder as an independent variable and the treatment group as strata. The results represent the ratio of Responder to Non-responder. A hazard ratio < 1 indicates an advantage for Responder.

Source: 747-302 CSR, Table 14.2.9.2, Table 14.2.9.3

Assessment of the MAH's response

In response to this question, the MAH argues that the actual target population in clinical practice is more like that included in Study 747-301, based on the comparison of baseline disease characteristics of subjects from European PBC and OCA registries, and much less severe than that included in Study 747-302; this is agreed based on the data presented, but it is not known if these data truly represents the actual treated population in clinical practice or rather a selected subset of patients within those actually treated.

It is also argued that subjects with higher values at baseline, representative of a more severe condition, might unlikely reach normal (or near normal) biochemical ALP/BR values, and that similar absolute changes in ALP values are expected. However, the actual meaning of the observed quantitative reductions of ALP/BR values, in the absence of concurrent changes in histological progression, is highly uncertain and of doubtful clinical relevance. Indeed, the predictive value of the changes in biochemical parameters with respect to relevant clinical outcomes in PBC has not been established definitively. Available literature appears to indicate that for UDCA, ALP reductions to normal (or near normal) values might be associated to lower liver outcomes. But available evidence shows contradictory findings.

The analyses conducted by the MAH aimed to correlate biochemical responses with clinical outcomes in Study 747-302, cannot be taken as demonstrative of a correlation as this should be formally demonstrated by the outside evidence.

In conclusion, OCA treatment has demonstrated to reduce ALP (and BR) levels, though the effect is of

modest magnitude and the actual clinical meaning is uncertain. The confirmatory trial has failed to demonstrate the benefit of OCA treatment in clinical outcomes.

Issue solved, given that the requested information has been provided. The efficacy of OCA treatment is further discussed under MO1.

Question 8

The MAH justifies the need for the EC group by stating that the validity of ITT analyses depends on successfully balancing randomisation and maintaining treatment and placebo allocation throughout the trial. Additional arguments are based on the claim that the reported results in Study 747-302 were underpowered and potentially biased for a list of reasons discussed below. These arguments cannot be accepted. Overall, the observed differences in the estimation of the treatment effect for the primary endpoint using the primary randomisation and the IPCW, demonstrate the high risk of bias associated to the reported analyses based on the weighting procedure, as compared to the results of Study 747-302. All results based on the EC are considered to have the same problem of bias. Furthermore, in addition to all the issues discussed above, the analyses resulting from the comparisons with EC should be understood in the context of a pivotal trial in which the primary analysis failed, leaving no alpha for confirmatory testing. As a result, any further analyses should be considered exploratory only. The MAH is invited to further justify the validity of these analyses considering the CHMP arguments.

Summary of the MAH's response

Study 747-302 Primary Endpoint Definitions

Two separate primary objectives were analyzed in Study 747-302 based on discussions with the FDA and EMA regarding the feasibility of assessing the long-term efficacy in subjects in Study 747-302. The EMA requested that the Sponsor retain the original primary composite endpoint as defined in Table 51, while the FDA, following the May 2021 USPI update, agreed to an expanded primary composite endpoint as defined Table 52.

Table 51: Protocol Version 6 Composite Endpoint (747-302; EMA Primary)

All Subjects
• Death (all-cause) • Liver transplant • MELD score ≥ 15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥ 2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

This endpoint is considered primary for the EMA and as a secondary endpoint for FDA.

To support the primary objective, based on recommendation from the FDA, the primary efficacy endpoint was expanded beyond what was outlined in Protocol Version 6. The primary objective based on this expanded endpoint was to compare the effect of OCA to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with PBC as measured by time to first occurrence of the following adjudicated events, derived as an expanded composite event endpoint (including all Group 1 to Group 3 events described in Table 52. This efficacy endpoint is referred to as primary for the FDA and secondary for the EMA.

Table 52: Expanded Composite Endpoint (747-302; FDA Primary)

Group 1 (applies to all subjects)
• Death (all-cause) • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of $>250/\text{mm}^3$ polymorph leukocyte [PMNs] in the ascitic fluid), or bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid) • Uncontrolled or refractory ascites (requiring large volume paracentesis) • Portal hypertension syndromes (hepatorenal syndrome as defined by International Ascites Club [Angeli 2019], portopulmonary syndrome, or hepatopulmonary syndrome) • MELD-Na score ≥ 15 if MELD-Na < 12 at baseline • MELD score ≥ 15 if MELD-Na ≥ 12 at baseline
Group 2 (applies to subjects without decompensation at Baseline)
Progression to decompensated liver disease (for subjects without decompensation at baseline), prioritized as follows: • New onset of hepatic hydrothorax, variceal bleeding, or ascites requiring treatment with sodium restriction, diet modification, or diuretics • Hepatic encephalopathy requiring lactulose and/or rifaximin • New onset of Child-Pugh ≥ 7 or total bilirubin $> 3 \text{ mg/dL}$
Group 3 (applies to subjects without decompensation or clinical evidence of portal hypertension at Baseline)
Progression to clinical evidence of portal hypertension without decompensation (for subjects without decompensation or clinical evidence of portal hypertension at baseline) • Endoscopic evidence of portal hypertension without bleeding (i.e., gastroesophageal varices [requiring banding or progression to large varices if no or small varices were observed at baseline] or portal hypertensive gastropathy) • Platelets $< 150 \times 10^9/\text{L}$ with splenomegaly and/or with transient elastography $> 15 \text{ kPa}$

The Committee for Medicinal Products for Human Use (CHMP) raises an important point, which itself highlights the bias in Study 747-302.

CHMP appears to be referencing Table 30 from the 747-302 clinical study report (CSR) (as shown in Table 53). For the primary composite endpoint in Protocol Version 6, there were 48 events in the OCA-treated group and 48 events in the placebo group. The primary analysis produced a hazard ratio of 1.01 (95% CI 0.68, 1.51). When inverse probability of censoring weighting (IPCW) was applied, the hazard ratio decreased to 0.82 (95% CI 0.53, 1.27).

Table 53: Study 747-302 - Time to the First Occurrence of Primary Clinical Outcome Event (ITT Population [N=334])

Statistics	Primary Composite Endpoint			
	Protocol Version 6 Endpoint (EMA Primary)		Expanded Endpoint (FDA Primary)	
	Placebo (N=166)	OCA (N=168)	Placebo (N=166)	OCA (N=168)
Number of Subjects with Clinical Event, n (%)	48 (28.9)	48 (28.6)	80 (48.2)	71 (42.3)
Log Rank p-value*	0.954		0.304	
Hazard Ratio (95% CI)*	1.01 (0.68, 1.51)		0.84 (0.61, 1.16)	
IPCW Hazard Ratio (95% CI)*	0.82 (0.53, 1.27)		0.80 (0.58, 1.12)	

EMA=European Medicines Agency; FDA=Food and Drug Administration; IPCW=inverse probability of censoring weighting; ITT=Intent-to-Treat; IWRS=interactive web response system; OCA=obeticholic acid

Note: Percentages are based on number of subjects in the ITT Population within each treatment group.

* Log-Rank p-value was based on log-rank test stratified by the randomization stratification factor.

* Hazard ratio was estimated using stratified Cox's proportional hazards model with treatment group as an independent variable and the randomization stratification factors as entered in the IWRS as strata. The results represent the ratio of OCA to placebo. A hazard ratio < 1 indicates an advantage for OCA.

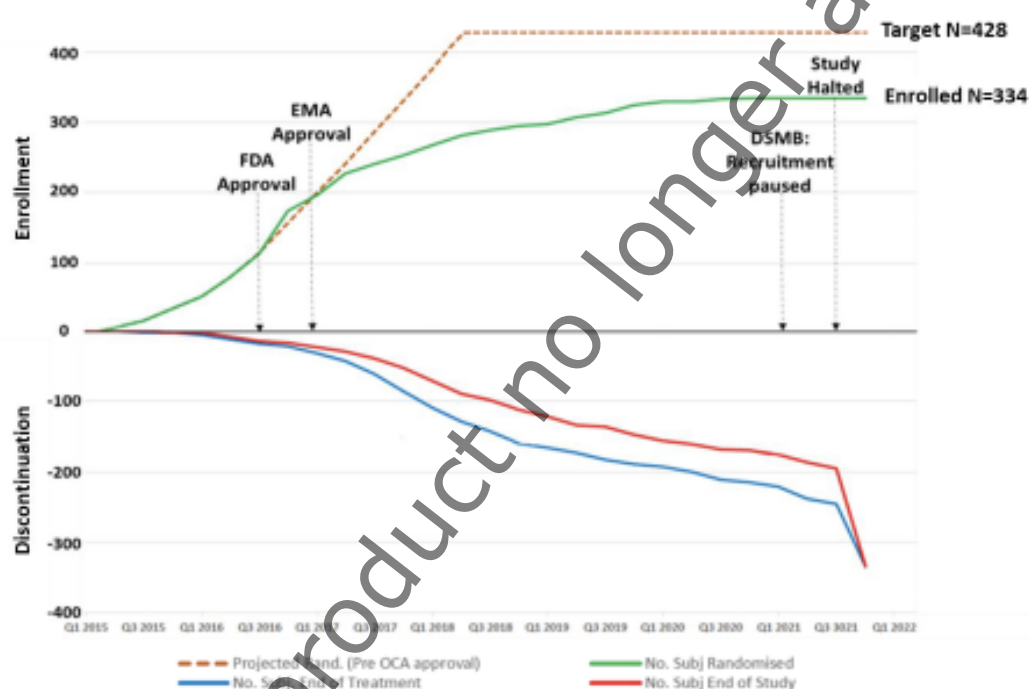
* IPCW hazard ratio and corresponding 95% CI were estimated using a Sandwich estimator with a weighted Cox's proportional hazards model with treatment group as an independent variable. The results represent the ratio of OCA to placebo. A hazard ratio < 1 indicates an advantage for OCA.

Source: 747-302 CSR, Table 14.2.1.1.1, Table 14.2.2.1.1

It is important to note that the number of subjects (N=334) and number of Protocol Version 6 endpoint events (48 in each treatment arm) leave the analysis of the Protocol Version 6 endpoint significantly under-powered. As shown in Figure 29, recruitment was on track to enrol 428 subjects (dashed brown line) until Ocaliva received approval and became commercially available in the United States (US) and

European Union (EU). At that point, recruitment slowed dramatically (solid green line), while investigational product discontinuation (solid blue line) and study discontinuation (solid red line) accelerated. In 2019, the Marketing Authorisation Holder (MAH) discussed recruitment/retention concerns with CHMP and agreed to initiate study sites in additional countries. With the advent of the COVID-19 pandemic in early 2020, healthcare restrictions made such site initiation impossible. At the time the MAH, US Food and Drug Administration (FDA), and European Medicines Agency (EMA) agreed to stop the study for lack of feasibility in 2021, only 334 subjects were enrolled (78% of the target number of subjects) and 96 of the targeted 127 adjudicated endpoints (76%) were observed. Assuming a true hazard ratio (HR) of 0.8, which would match the IPCW HR point estimate as well as the expanded endpoint point estimate, the analysis of the EMA endpoint was significantly underpowered ($1-\beta=0.192$). As such, the HR point estimate is inherently unstable, with a wide confidence interval. The HRs of the unweighted and IPCW analyses are well within each other's 95% CIs and cannot be viewed as meaningfully different.

Figure 29: Study 747-302: Recruitment and Retention Over Time



DSMB=Data Safety Monitoring Board; EMA=European Medicines Agency; FDA=Food and Drug Administration; No.=number; OCA=obeticholic acid; Q=quarter; Rand.=randomized; Subj.=subject

With 151 events, the expanded (FDA) endpoint analysis is also underpowered assuming an HR of 0.8 ($1-\beta=0.28$). Here the unweighted and IPCW hazard ratios are very similar, and very similar to the IPCW Protocol Version 6 endpoint analysis, though here again all 95% CIs are widely overlapping. Taken together, the outlier HR in these analyses is the unadjusted Protocol Version 6 endpoint analysis, which CHMP correctly points out is compelling evidence of the censoring bias in that analysis.

The post hoc analyses performed by the MAH go further, demonstrating that the censoring was not random but was informative, pointing to functional unblinding and the use of rescue therapy in the placebo group.

The key sources of bias in the primary 747-302 study are as follows:

- Subjects in the placebo group with high ALP levels discontinued placebo (Figure 1)
- Subjects in the placebo group disproportionately initiated commercial PBC treatments (i.e., OCA,

fibrates, or UDCA if not on UDCA at baseline, Figure 2)

- Subjects in the placebo group who initiated commercial PBC treatments showed large decreases in ALP (Figure 3)

Taken together, placebo subjects with more severe disease (based on high ALP levels) either dropped out of the study or discontinued placebo in favour of commercial PBC treatments, which substantially lowered ALP levels. Supporting this observation, the MAH was told directly by several Investigators that they felt it was unethical to maintain patients with high ALP levels on study drug when effective commercial treatment was available. Lower ALP has been shown to be associated with fewer deaths and liver transplants (Lammers 2014, Carbone 2013). Thus, the event rates in the placebo group do not reflect non-treatment. The positive effects of informative censoring and active treatment meaningfully reduced ALP levels, and thus reduced the number of clinical events in the placebo group. These effects were not observed to the same degree in the OCA-treated group.

- Among subjects randomized to OCA treatment, 65% of events occurred in patients who discontinued OCA a median of 9 months prior to an event.

The MAH believes that the events rates in the OCA-treated group do not fully reflect the clinical benefits of OCA treatment. The majority of events in the OCA-treated group happened in patients who discontinued investigational product, and for a sufficiently long period that treatment benefit would no longer be observed.

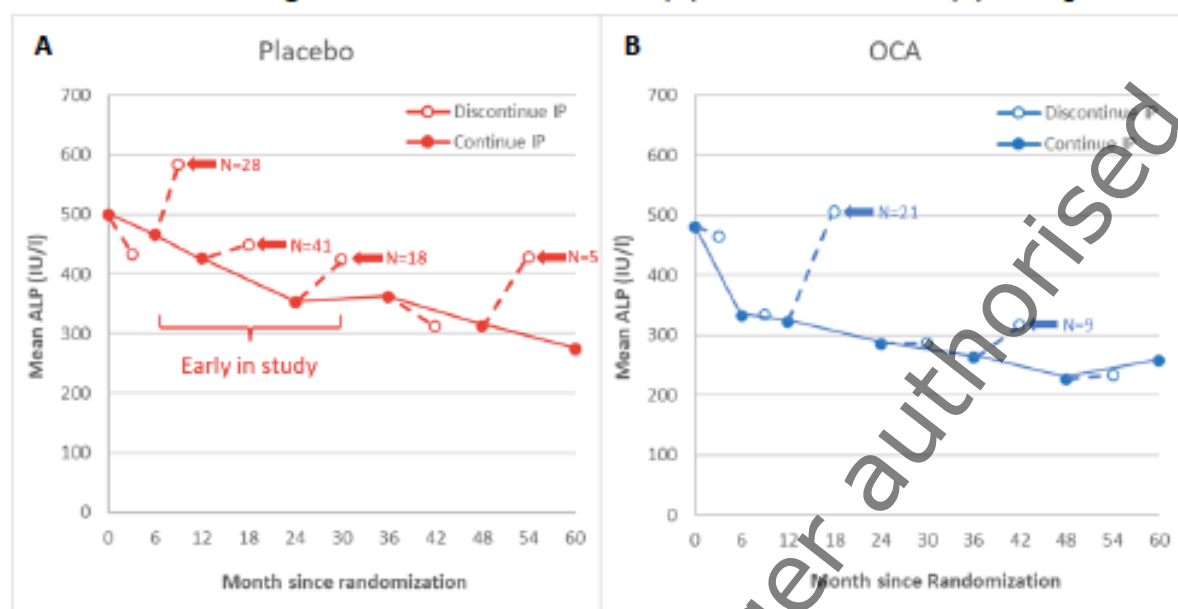
The substantial treatment crossover in both placebo- and OCA-treated groups are not accounted for in the ITT analyses, which maintains subjects in the group to which they were randomized, not allowing for reassignment based upon actual treatment. As CHMP correctly points out, the IPCW analysis begins to account for this, and changes the HR from indicating no benefit ($HR=1.01$) to moderate benefit ($HR=0.82$).

A detailed review of each of these analyses is provided below.

Figure 1 shows the mean ALP levels of the placebo-treated subjects who continued placebo treatment (solid red line and circles). PBC is a slowly progressive disease marked by rising ALP levels over time. The steady decrease in ALP in placebo subjects is counter to the natural history of disease and was not observed in the Phase 2 double-blind 3-month studies evaluating OCA in PBC (Hirshfield 2015, Kowdley 2018) and the 12-month double-blind phase of Study 747-301 (Nevens 2016) nor in other placebo-controlled, double-blind studies in PBC including a 24-month study of bezafibrate in addition to ursodeoxycholic acid (Corpechot 2018) and a 3-months study of seledapar (Jones 2017). As shown in the red open circles and dashed lines, the patients who discontinued placebo had substantially higher ALP levels than those who continued investigational product. As those patients either dropped out of the study all together or initiated commercial PBC treatments (see Figure 1), the decrease in ALP levels in the placebo group reflect both informative censoring and the effects of active treatment, not a true placebo ALP. This predominantly occurred in the first 2 years after randomization, in which 87 placebo subjects with high mean ALP levels discontinued placebo.

In the OCA-treated group, the ALP levels of subjects who discontinued investigational product were generally similar to those who stayed on investigational product. Only the group of 21 subjects who discontinued OCA in Months 12 to 18 had substantially higher mean ALP levels than those that stayed on investigational product.

Figure 1: Study 747-302: ALP Levels in Subjects Continuing and Discontinuing Investigational Product on Placebo (A) and OCA-treated (B) Groups



IP=investigational product; OCA=obeticholic acid

Note: Mean serum ALP levels in subjects remaining on investigational product (solid dots and line; red for placebo and blue for OCA) and the mean ALP levels in subjects before investigational product discontinuation prior to an endpoint event (open dots and dashed lines; red for placebo and blue for OCA).

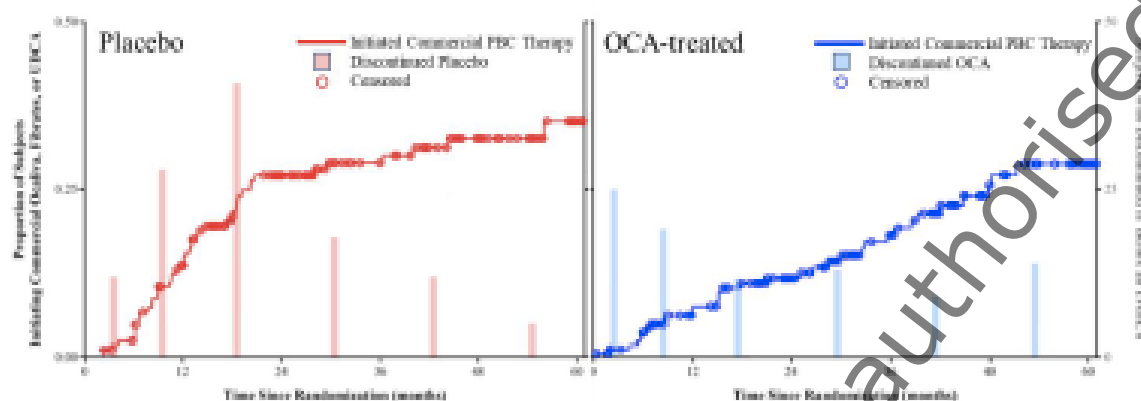
Represented the same Figure 1 as above for easy reference

Figure 2 examines investigational product discontinuation in the context of initiating commercial PBC therapies over time by treatment group. The solid lines show the proportion of subjects initiating commercial PBC treatments (OCA, fibrates, or UDCA if not taking UDCA at baseline) in the placebo arm (red line) and OCA-treated arm (blue line). This is overlaid on a bar graph showing absolute number of patients in the placebo- (pink bars) and OCA-treated (light blue bars) arms discontinuing study drug.

In the OCA-treated arm, peak discontinuation happened in the first 6 months ($n=25$, 14.8%) and declined afterwards. The primary reason for discontinuation through Month 6 was pruritus (10 of 25, 40% for OCA-treated versus none in placebo). There was minimal initiation of non-investigational product therapies in the first 6 months for either group. For OCA-treated subjects, initiation of commercial treatments was generally linear from baseline to Month 60.

In the placebo group, discontinuation of investigational product increased from baseline and peaked between Months 12 and 24. The rise in subjects initiating commercial treatment closely mirrors the rise in discontinuations, thus as placebo subjects discontinued investigational product, they disproportionately initiated commercial therapies. As discussed above, subjects discontinuing placebo had higher ALP levels. Over the entire study period, placebo subjects were significantly more likely to initiate non-investigational product therapy compared to OCA-treated subjects (HR 1.59; 95% CI 1.02 to 2.50; $p<0.05$).

Figure 2: Study 747-302: Initiation of Commercial PBC Treatments (OCA, Fibrates or UDCA if Not Taking UDCA at Baseline) versus Discontinuation of Investigational Product by Treatment Group over Time

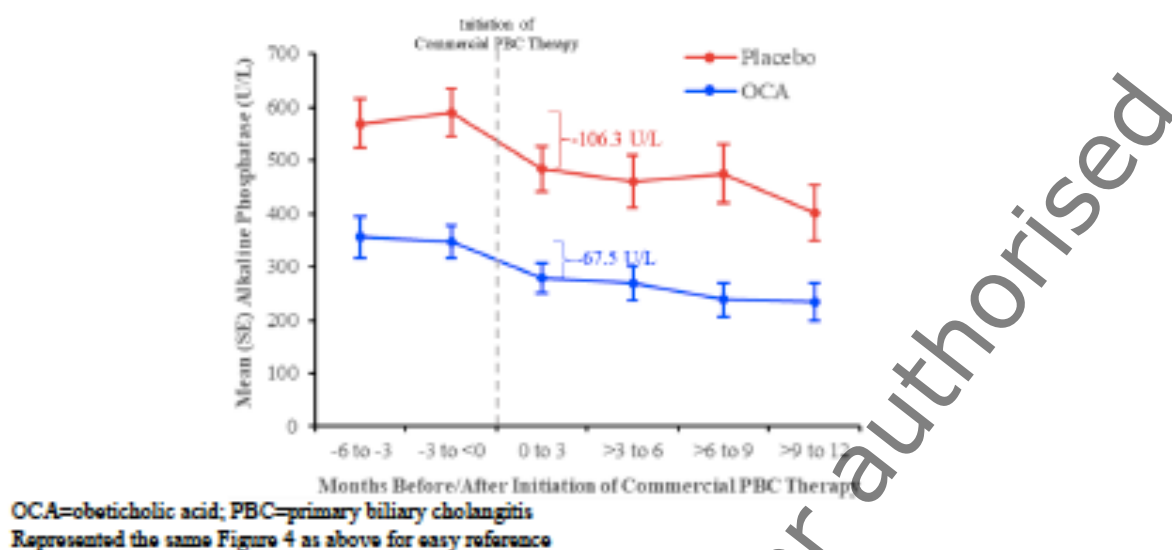


IP=investigational product; OCA=obeticholic acid; PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid
 Note: Kaplan-Meier plot of initiation of PBC rescue therapy and a bar graph of the proportion of subjects discontinuing study treatment before experiencing a clinical endpoint event (red for placebo; blue for OCA).
 Represented the same Figure 2 as above for easy reference

Figure 3 shows the impact of initiation of commercially available PBC therapies on mean ALP. The two cohorts of subjects had similar mean baseline ALP values (493 U/L, placebo; 481 U/L OCA). However, before initiating commercial therapies, the mean ALP in the placebo group was 590 U/L (red line) versus 347 U/L in the OCA-treat group (blue line). These substantial differences strongly suggest functional unblinding in the placebo group. Significant subject and provider education regarding the strong correlation of persistent high levels of ALP with increased risk of negative clinical outcomes, including progression to liver transplant and death, made conduct of a fully blinded clinical study unfeasible. Investigators were not prevented from reviewing real-time ALP values for their subjects, nor from sharing those values and the implications for disease progression with their patients.

In the first 3 months after initiating commercial treatments, placebo subjects had a mean ALP of 484 U/L compared to a mean ALP of 590 U/L in the 3 months prior to initiating commercial treatment, a difference of 106.3 U/L. Subjects in the OCA-treated group who initiated commercial therapies had a mean ALP of 280 U/L in the 3 months after initiating commercial treatment compared to a mean ALP of 347 U/L in the 3 months prior to initiating commercial treatment, a difference of 67.5 U/L. Commercial PBC therapies were effective in reducing ALP in both groups during the first 36 months following randomization.

Figure 3: Change in ALP Before and After Initiation of Commercial PBC Therapy by Treatment Group Over Time



In summary, there was significant crossover of subjects in the placebo group to commercial PBC treatments, leading to substantial ALP improvement. This was driven, in part, by higher ALP levels, suggesting functional unblinding occurred. Given the known association between reduction in ALP and improved outcomes (Lammers 2014, Carbone 2013), this significantly reduced clinical events in the placebo group.

The discontinuation of investigational product in patients with high ALP, and initiation of commercial treatments, was not observed in the OCA treatment group to the same degree and did not occur early in treatment. In addition, the OCA-treated group also showed significant treatment crossover: 65% of endpoint events occurred in subjects who had discontinued OCA, a median of 9 months before the event occurred. This resulted in an increase in clinical events in the OCA-treated group.

This degree of bias cannot be overcome, and the primary ITT analyses of the Protocol Version 6 endpoint cannot be considered valid, though IPCW can mitigate that bias to a degree.

CHMP then validly asks: if the primary study is biased in a way that cannot be mitigated analytically, can an external control adequately address these issues?

First, the informative discontinuation of investigational product and crossover to commercial PBC treatments disproportionately affected the placebo group. The primary issue for the OCA-treated group was discontinuation of treatment before an event. By taking an as-treated approach to the external control analyses, patients in the non-OCA-treated control group are censored when they discontinue investigational product and/or start rescue therapy, and the patients OCA-treated group are censored 90 days after discontinuation of OCA (the period an expert panel of hepatologists advised would be the maximal extension of treatment benefit after discontinuation). Thus, the HRs reflect the effect of actual treatment versus non-treatment on outcomes.

Table 54 shows unweighted and weighted sample sizes, events, and hazard ratios (95% CIs) for the external control analyses of the 747-302 study. Here, we see the effect of weighting (in this case standardized morbidity ratios) on the hazard ratios is negligible. In part, this is because the external control balance took place in 2 phases. In the first phase, subjects were selected who met 747-302 eligibility criteria (modified to accommodate data availability, e.g., excluding MELD score), and thus were similar before weighting. Second, propensity scores and standardized morbidity ratio weights were applied. The samples were well balanced at baseline. The consistency of the weighted and unweighted effect size estimates should help mitigate CHMP concerns regarding the effects of weighting on the

results.

Table 54: Analyses Comparing OCA-treated Subjects from 747-302 to External Controls on Time to First Occurrence of Protocol Version 6 Composite Endpoint and Expanded (FDA) Composite Endpoint: Unweighted and Weighted

	Primary Composite Endpoint			
	Protocol Version 6 Endpoint (EMA Primary)		Expanded Endpoint (FDA Primary)	
	External Control	OCA	External Control	OCA
Unweighted N	1232	168	1232	168
Weighted N	165	168	165	168
Unweighted # of Subjects with Event, n (%)	275 (22.3)	17 (10.1)	294 (28.0)	28 (16.7)
Weighted # of Subjects with Event, n (%)	35 (21.5)	17 (10.1)	46 (27.6)	28 (16.7)
Unweighted Hazard Ratio (95% CI)	0.33 (0.20, 0.53)		0.43 (0.29, 0.63)	
Weighted Hazard Ratio (95% CI)	0.39 (0.22, 0.69)		0.48 (0.30, 0.77)	

FDA=Food and Drug Administration; EMA=European Medicines Agency; OCA=obeticolic acid

Note: Detailed definitions for the primary composite endpoints are summarized in Table 51 (Protocol Version 6 Endpoint) and Table 52 (Expanded Endpoint).

747-302 EC CSR, Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.5, and Table 14.2.1.6

In summary, the MAH agrees with CHMP that the differences between the unweighted and IPCW analysis of the primary EMA endpoint, while they fall well within each other's 95% CIs, suggest bias in the primary study. Importantly, in 2021 FDA strongly recommended that the primary endpoint for Study 747-302 be expanded while the study remained ongoing in an effort to increase study power. Analysis of the more adequately powered expanded (FDA) endpoint demonstrated an HR that was consistent with the IPCW analysis.

Post hoc analyses revealed that the censoring was not random but informative as detected by the IPCW. Patients in the placebo group with higher ALP levels discontinued study drug, with the majority either discontinuing the study all together or disproportionately initiating commercial PBC treatments. As a result, the ALP levels in the placebo group improved, lowering event rates in this group. OCA-treated patients discontinued therapy sufficiently before events that those events do not reflect the effect of treatment, i.e., events were increased in the OCA-treated group.

The external control as-treated analyses addressed these issues by censoring control patients who initiated commercial PBC treatments, and censoring OCA-treated patients 90-days after discontinuing treatment. Groups were well balanced before and after the application of SMR weights, and results of unweighted and weighted analyses showed very similar and clinically meaningful reduction in events. The MAH believes this should mitigate some of the concerns CHMP expressed regarding the application of weights in these analyses.

Assessment of the MAH's response

The MAH argues that there was a high rate of study treatment discontinuation in both treatment arms with cross-over to treatment options available during the conduct of the pivotal study, and that this happened in a different degree in both treatment arms and at a different time during the trial; being due to lack of efficacy in ALP reductions in the placebo arm, that were subsequently crossed over to receive an effective treatment, which might have reduced the incidence of clinical events in placebo. The actual rates and timing of treatment discontinuations, the reasons behind and the treatments received after stopping study treatment, have not been clearly detailed for any treated groups; in fact, in some cases is difficult to disentangle the results from the double-blinding and the extension phases. In fact, the overall number (%) of placebo and OCA patients who (a) discontinued treatment was 51

(30.7%) and 65 (38.7%), (b) discontinued study visits was 61 (36.7%) and 72 (42.9%), and (c) discontinued the study was 83 (50%) and 88 (52.4%); notably, these figures do not suggest an overall higher rate in the placebo group, but quite the opposite. This is an important piece of information because there are not too many effective treatments available for patients with PBC who do not respond to UDCA, and if the Applicant is suggesting a potential effect of these treatments, this may have affected both arms. Furthermore, if this happened truly during the conduct of the study, it is simply not possible to estimate with fair the actual rate of events during treatment with either placebo or OCA. Because of this bias in the estimation, neither of the analyses conducted (pre-planned or post-hoc) are valid to reach conclusions. In essence, the primary analysis was clearly negative (HR [95%CI]: 1.01 [0.68, 1.51]) under a strategy for dealing with intercurrent events that closely resembles the treatment policy strategy, which more closely resembles the expected treatment effect under pragmatic conditions in clinical practice. These results are not only inconsistent with the expected HR in the pre-specified sample size (i.e. HR of 0.60), but also with a smaller but still relevant effect in the studied trial population.

In addition, even if the estimation of the OCA treatment effect were deemed a valid one, the post-hoc external cohort comparison to rescue a failed primary analysis of the trial is not considered reliable and acceptable to reach conclusions given the anticipated difficulties in ensuring the due comparability in this condition, which cannot be sorted out by simply applying the CI inclusion/exclusion criteria + the IPDW analysis.

This **issue is not considered solved**.

Question 9

A high proportion of subjects in both treatment groups required dose adjustments at least once, dose interruptions/discontinuations, but this information is only presented for CP-B or CP-C patients at any time during the study. The MAH is invited to provide this information of the overall safety population, and for both the subset of compensated vs decompensated patients at baseline.

Summary of the MAH's response

Study 747-302 was initiated prior to approval of obeticholic acid (OCA). Dosing regimen for all subjects in the initial protocol was OCA 5 mg once daily with titration to OCA 10 mg once daily at 6 months, if tolerated. Based on data from Study 747-301, the initial approved dosing regimens for OCA for the treatment of subjects with PBC were 5 mg and 10 mg once daily for non-cirrhotic and Child-Pugh (CP) Class A cirrhosis subjects. Considering the risk for liver-related adverse reactions in subjects with higher OCA hepatic exposure, the initial labelling recommended a modified, lower dosing frequency (once or twice weekly) for advanced PBC subjects (e.g., moderate to severe hepatic impairment).

Following approval of OCA, the 747-302 protocol (Version 3) was amended and dosing adjustments (dose, frequency, titration, titration criteria) were made based on cirrhosis status and CP scoring as described in Table 55:

Table 55: Study 747-302 - Planned Dosing Regimen by Cirrhosis and Child-Pugh Score (747-302 Protocol Version 3.0 and Beyond)

	Planned Dosing Regimen	
	Noncirrhotic/CP-A	CP-B or CP-C
Starting Dose ^a (Day 0)	5 mg daily	5 mg once weekly
Titration 1 ^{b,c} (≥Month 3)	10 mg daily	5 mg twice weekly
Titration 2 ^{b,c} (≥6 weeks after Titration 1)	NA	10 mg twice weekly
Titration 3 ^{b,d} (≥6 weeks after Titration 2)	NA	5 mg daily (CP-B only)

CP=Child-Pugh; NA=not applicable

^a Starting dose based on subject's cirrhosis status and CP Score at Screening.

^b Planned titration regimen is shown; however, the titration of dose and/or frequency was dependent on subject tolerability, biochemical response, and/or changes in cirrhosis status

^c Dosing per the twice weekly schedule must have been at least 3 days apart.

^d Titration 3 was no longer applicable to the study after Protocol Version 3.0 (04 Jan 2018).

A summary of dosing is provided in Table 56 for the overall safety population and by the following baseline stages: decompensated (contraindicated per the current SmPC), compensated (indicated per the current SmPC), proposed SmPC indicated population (i.e., subjects who had not experienced evidence of portal hypertension or decompensation at baseline), and proposed SmPC contraindicated population (i.e., subjects who had experienced portal hypertension and/or decompensation at baseline).

- Across all populations and treatment groups, a similar proportion of subjects in both treatment groups (87.3% of placebo subjects to 81.5% of OCA subjects) had any dose change. This high percentage is not unexpected given the protocol-specified dosing titration regimen (Table 55)
- Across treatment groups, a similar proportion of subjects (34.3% of placebo subjects to 36.9% of OCA subjects) had any drug holiday. However, higher proportion of OCA-treated subjects with hepatic decompensation, now contraindicated in the SmPC, had a drug holiday (56.3%) compared to placebo-treated subjects (32.4%). The MAH acknowledges this difference, and believes this difference further supports the decision to exclude these patients from OCA treatment.
- More subjects in the placebo group discontinued product >30 days prior to an event than OCA-treated patients in both the compensated subgroup (55.8% vs 44.1%) and proposed SmPC subgroup (57.4% vs 44.4%). The issue of functional unblinding and informative discontinuation of placebo based on high ALP levels was discussed extensively in Major Objection 1 and is further reflected in these data.

Table 56: Study 747-302 – Summary of Dose Change or Investigational Product Interruption/Discontinuation by Overall and Baseline Disease Stage Severity (Safety Population [N=334])

Dose Change/Interruption, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Any Dose Change	145 (87.3)	137 (81.5)	29 (78.4)	27 (84.4)	116 (89.9)	110 (80.9)	58 (85.3)	67 (82.7)	87 (88.8)	70 (80.5)
Any Drug Holiday	57 (34.3)	62 (36.9)	12 (32.4)	18 (56.3)	45 (34.9)	44 (32.4)	22 (32.4)	30 (37.0)	35 (35.7)	32 (36.8)
Any Discontinuation of Investigational Product >30 Days Prior to an Endpoint Event	90 (54.2)	79 (47.0)	18 (48.6)	19 (59.4)	72 (55.8)	60 (44.1)	39 (57.4)	36 (44.4)	51 (52.0)	43 (49.4)

AE=adverse events of special interest; OCA=obeticholic acid; PBO=placebo PH=portal hypertension; SmPC=Summary of Product Characteristics

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc Table 111, Table 111.1, Table 111.2

Assessment of the MAH's response

The MAH has presented the requested information, and data raises no concerns. The high proportion of patients that required dose changes can be explained by the implementation of the approved SmPC posology at the time of MA in the ongoing clinical trial 747-302. These changes affected both subjects non-cirrhotic/CPA and subjects with CP B/C, which explains the high and comparable results across subpopulations. No relevant differences were observed in the proportion of patients requiring any drug holidays, but the actual number of drug holidays required in each treatment group has not been provided, what would be an interesting piece of information to know about the actual tolerability of treatment. This should be provided (OC). The only exception, where a higher proportion of any drug-holiday was noted, was in OCA-treated subjects with hepatic decompensation (56.3% OCA vs 32.4% placebo). These subjects are now contraindicated in the SmPC.

Issue partially solved, but not further pursued within this procedure. The actual number of drug holidays (mean, SD, and if needed, by category, e.g., <1 vs ≥ 2) in each treatment group was not clarified by the MAH.

Question 10

The MAH is invited to provide tabulated results of the overall safety profile of OCA in the total safety population and in the two subsets of patients compensated and decompensated, to better illustrate any existing differences in the safety profile of these patients.

Summary of the MAH's response

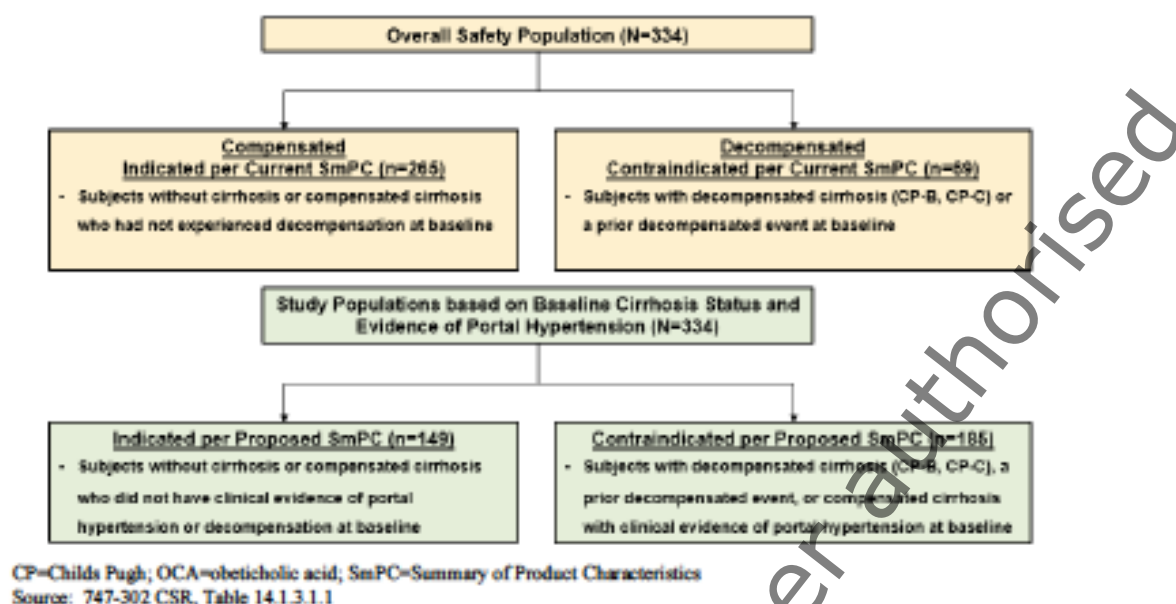
Safety Profile of OCA

The Marketing Authorization Holder (MAH) assessed the frequency of events between obeticholic acid (OCA) and placebo in the overall, compensated (indicated per current summaries of product characteristics [SmPC]), and decompensated (contraindicated per current SmPC) populations in Study 747-302. Given the subjects in these various groups have more advanced primary biliary cholangitis (PBC) disease, and that, as presented in the Type II Variation Serial 0066 submitted 01 July 2021, it will not be feasible to establish the safety and efficacy of Ocaliva in patients with more advanced PBC. The MAH has explored a more appropriate population that maximizes the benefit:risk profile. Therefore, the MAH has now proposed a revised SmPC indication for subjects without cirrhosis or compensated cirrhosis who do not have clinical evidence of portal hypertension or decompensation at baseline.

Treatment with OCA was generally well tolerated in patients with PBC who met the criteria of the proposed SmPC at baseline, and the overall safety profile was consistent with that observed in other PBC studies that excluded patients with more severe disease. The incidence of most treatment-emergent adverse events of special interest (TEAEs) observed in OCA-treated subjects was markedly lower in the proposed SmPC indicated population compared to the overall safety population.

The safety results from Study 747-302 are presented for the overall safety population and by the following baseline disease stages: decompensated (contraindicated per the current SmPC), compensated (indicated per the current SmPC), proposed SmPC indicated (i.e., subjects who had not experienced portal hypertension [PH] or decompensation at baseline), and proposed SmPC contraindicated (i.e., subjects who had experienced PH and/or decompensation at baseline). The presented populations by baseline disease stage are summarized in Figure 30.

Figure 30: Summary of Study Populations in Study 747-302 by Baseline Disease Stage



Study 747-302 Design and Statistical Considerations

Study 747-302 was not designed or intended to determine the benefit:risk in the subpopulations of compensated (indicated per current SmPC), decompensated (contraindicated per current SmPC), proposed SmPC indicated, and proposed SmPC contraindicated. The analysis populations were grouped and programmed retrospectively using baseline data based on the disease stage definitions in Table 57. Programmatic implementation may have been limited depending on the availability of the baseline data.

Subjects in the compensated (indicated per current SmPC) or proposed SmPC indicated populations may have progressed and met contraindicated criteria after baseline and during conduct of the study. These subjects may have remained on investigational product.

In addition, the interpretation of event rates in Study 747-302 may be of limited value due to the differential dropout observed between the treatment groups, with more subjects in the placebo group initiating commercially-available PBC therapy (i.e., commercial Ocaliva, fibrates, or UDCA) while on study. Therefore, the MAH assessment focuses primarily on the event rate differences between the various baseline disease stage OCA treatment groups and provides placebo treatment group event rates for completeness.

Table 57: Baseline Disease Stage Definitions in Study 747-302

Overall
The overall safety population included all randomized subjects who received any amount of investigational product (OCA or placebo).
Decompensated (Contraindicated per current SmPC)
The decompensated subgroup included ITT subjects who had experienced decompensation at baseline.
Compensated (Indicated per current SmPC)
The compensated subgroup included ITT subjects who had not experienced decompensation at baseline.
Proposed SmPC Indicated Population
The proposed indicated SmPC population included ITT subjects who had not experienced evidence of PH or decompensation at baseline. A subject was defined to have PH at baseline if they had any of the following: a previous history of portal hypertension includes procedures for TIPS, sclerotherapy, ligation, HVPG measurement ≥ 10 mmHg, paracentesis, thoracentesis (due to hepatic hydrothorax); previous history or baseline observation of preferred terms for presence of collateral circulations secondary to PH, GI bleeding due to varices or portal hypertension, gastroesophageal varices without bleeding and portal hypertensive gastropathy, ascites, hepatopulmonary syndrome, hepatorenal syndrome, portopulmonary hypertension, hepatic encephalopathy, platelets $< 150 \times 10^9/L$ with splenomegaly and/or with transient elastography > 13 kPa. A subject was defined to have decompensation at baseline if they had any of the following: a Child-Pugh score of B or C; previous history or baseline observation of preferred terms for gastric variceal or oesophageal variceal bleeding, ascites, hepatic hydrothorax, spontaneous bacterial peritonitis, hepatic encephalopathy, hepatorenal/hepatopulmonary/portopulmonary syndrome, prior TIPS or other peritoneo-venous shunt.
Proposed SmPC Contraindicated Population
The proposed SmPC contraindicated population included ITT subjects who had experienced PH and/or decompensation at baseline.

GI=gastrointestinal; HVPG=hepatic venous pressure gradient; ITT=intent-to-treat; OCA=obeticholic acid; PH=evidence of portal hypertension; TIPS=transjugular intrahepatic portosystemic shunt

Overview of Treatment-Emergent Adverse Events in Study 747-302

An overview of treatment-emergent adverse events (TEAEs) by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 58.

Proposed SmPC Indicated Population

In comparison to the overall and compensated (indicated per current SmPC) populations, the proportion of serious TEAEs across treatment groups was lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), a total of 15 (18.5%) subjects in the OCA group and 17 (25.0%) subjects in the placebo group experienced a serious TEAE. Of which, 1 (1.2%) subject in the OCA group reported a TEAE of acute respiratory failure leading to death, which was considered not related to investigational product by the Investigator (Section 2.8.3.1).

The incidence of any TEAEs was balanced across treatment groups (93.8% in the OCA group and 89.7% in the placebo group). Consistent with the overall and compensated populations, more subjects in the OCA group than the placebo group experienced severe TEAEs (45.7% versus 32.4%), treatment-related TEAEs (75.3% versus 55.9%), and TEAEs leading to dose reduction (24.7% versus 10.3%), which were mostly driven by pruritus. Pruritus is a known adverse drug reaction (ADR) per the current SmPC and was an adverse event of special interest (AESI) in Study 747-302. Pruritus is discussed in Section 2.8.3.4.6.

Table 58: Study 747-302 - Overview of Treatment-Emergent Adverse Events by Overall and Baseline Disease Stage (Safety Population [N=334])

Number of subjects with, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Any TEAE	158 (95.2)	162 (96.4)	36 (97.3)	32 (100.0)	122 (94.6)	130 (95.6)	61 (89.7)	76 (93.8)	97 (99.0)	86 (98.9)
Serious TEAE	53 (31.9)	53 (31.5)	13 (35.1)	20 (62.5)	40 (31.0)	33 (24.3)	17 (25.0)	15 (18.5)	36 (36.7)	38 (43.7)
TEAE Leading to Death	2 (1.2)	5 (3.0)	0	3 (9.4)	2 (1.6)	2 (1.5)	0	1 (1.2)	2 (2.0)	4 (4.6)
Severe TEAE	65 (39.2)	86 (51.2)	18 (48.6)	22 (68.8)	47 (36.4)	64 (47.1)	22 (32.4)	37 (45.7)	43 (43.9)	49 (56.3)
Treatment-Related TEAEs	111 (66.9)	133 (79.2)	31 (83.8)	26 (81.3)	80 (62.0)	107 (78.7)	38 (55.9)	61 (75.3)	73 (74.5)	72 (82.8)
TEAE Leading to IP Withdrawal	45 (27.1)	62 (36.9)	9 (24.3)	17 (53.1)	36 (27.9)	45 (33.1)	18 (26.5)	27 (33.3)	27 (27.6)	35 (40.2)
TEAE Leading to Dose Reduction	23 (13.9)	45 (26.8)	5 (13.5)	9 (28.1)	18 (14.0)	36 (26.5)	7 (10.3)	20 (24.7)	16 (16.3)	25 (28.7)
TEAE Leading to IP Interruption	43 (25.9)	48 (28.6)	7 (18.9)	14 (43.8)	36 (27.9)	34 (25.0)	17 (25.0)	21 (25.9)	26 (26.5)	27 (31.0)
TEAE Leading to Study Discontinuation	19 (11.4)	29 (17.3)	1 (2.7)	6 (18.8)	18 (14.0)	23 (16.9)	13 (19.1)	12 (14.8)	6 (6.1)	17 (19.5)

OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.
TEAEs with missing severity are considered severe. TEAEs with a missing relationship are considered related.
Percentages are based on number of subjects in the Safety Population within subgroup and treatment group.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.
Source: 747-302 CSR, Table 14.3.1.2.1, Table 14.3.1.2.1.1, Table 14.3.1.2.1.2

Analysis of Adverse Events

Adverse Events by Incidence

A summary of TEAEs occurring in $\geq 5\%$ of overall OCA-treated subjects by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 59.

Proposed SmPC Indicated Population

In comparison to the overall and compensated populations, individual TEAEs occurred less frequently across treatment groups in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), a total of 76 (93.8%) subjects in the OCA group and 61 (89.7%) subjects in the placebo group reported at least 1 TEAE. Consistent with the overall safety population, the most frequently reported TEAE was pruritus, which had a higher incidence in the OCA group (81.5%) than in the placebo group (47.1%). Pruritus is a known ADR per the current SmPC and was an AESI in Study 747-302. Pruritus is discussed in Section 2.8.3.4.6.

Other frequently reported TEAEs ($\geq 10\%$ of OCA-treated subjects) which were higher in the OCA group compared to placebo included headache (16.0% in the OCA group and 14.7% in the placebo group), arthralgia (14.8% in the OCA group and 8.8% in the placebo group), abdominal pain upper (13.6% in the OCA group and 5.9% in the placebo group), diarrhoea (13.6% in the OCA group and 10.3% in the placebo group), nasopharyngitis (13.6% in the OCA group and 5.9% in the placebo group), nausea (11.1% in the OCA group and 10.3% in the placebo group), and upper respiratory tract infection (11.1% in the OCA group and 4.4% in the placebo group).

For reference, known ADR per the current SmPC include the following:

- Very commonly reported: Abdominal pain and discomfort, Pruritus, Fatigue;
- Commonly reported: Thyroid function abnormality, Dizziness, Palpitations, Oropharyngeal pain, Constipation, Eczema, Rash, Arthralgia, Oedema peripheral, Pyrexia;
- Not known frequency: Hepatic failure, Blood bilirubin increased, Jaundice, Hepatic cirrhosis.

In comparison to the overall and compensated populations, the incidence of most TEAEs observed in OCA-treated subjects was markedly lower in the proposed SmPC indicated population including the following hepatic preferred terms (PTs) which are of particular interest: oedema peripheral (18.5% in the overall, 13.2% in the compensated, and 4.9% in the proposed SmPC indicated populations), blood bilirubin increased (11.9% in the overall, 10.3% in the compensated, and 4.9% in the proposed SmPC indicated populations), ascites (10.7% in the overall, 6.6% in the compensated, and 1.2% in the proposed SmPC indicated populations), portal hypertensive gastropathy (8.3% in the overall, 8.1% in the compensated, and 3.7% in the proposed SmPC indicated populations), and hepatic cirrhosis (6.0% in the overall, 6.6% in the compensated, and 2.5% in the proposed SmPC indicated populations).

Table 59: Study 747-302 - Overview of Treatment-Emergent Adverse Events in ≥5% Overall OCA-treated Subjects by Overall and Baseline Disease Stage (Safety Population [N=334])

System Organ Class Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 TEAE	158 (95.2)	162 (96.4)	36 (97.3)	32 (100.0)	122 (94.6)	130 (95.6)	61 (89.7)	76 (93.8)	97 (99.0)	86 (98.9)
Skin and subcutaneous tissue disorders	101 (60.8)	138 (82.1)	25 (67.6)	22 (68.8)	79 (61.2)	111 (81.6)	38 (55.9)	69 (85.2)	63 (64.3)	69 (79.3)
Pruritus	85 (51.2)	132 (78.6)	19 (51.4)	24 (75.0)	66 (51.2)	108 (79.4)	33 (47.1)	66 (81.5)	53 (54.1)	66 (75.9)
Rash	6 (3.6)	10 (6.0)	1 (2.7)	1 (3.1)	5 (3.9)	9 (6.6)	3 (4.4)	6 (7.4)	3 (3.1)	4 (4.6)
Gastrointestinal disorders	106 (63.9)	117 (69.6)	25 (67.6)	22 (68.8)	81 (62.8)	95 (69.8)	34 (50.0)	51 (63.0)	72 (73.5)	66 (75.9)
Abdominal pain upper	12 (7.2)	25 (14.9)	4 (10.8)	4 (12.5)	8 (6.2)	21 (15.4)	4 (5.9)	11 (13.6)	8 (8.2)	14 (16.1)
Nausea	21 (12.7)	25 (14.9)	5 (13.5)	8 (25.0)	16 (12.4)	17 (12.5)	7 (10.3)	9 (11.1)	14 (14.3)	16 (18.4)
Abdominal pain	18 (10.8)	21 (12.5)	4 (10.8)	5 (15.6)	14 (10.9)	16 (11.8)	5 (7.4)	8 (9.9)	13 (13.3)	13 (14.9)
Diarrhoea	26 (15.7)	21 (12.5)	5 (13.5)	4 (12.5)	21 (16.3)	17 (12.5)	7 (10.3)	11 (13.6)	19 (19.4)	10 (11.5)
Varices oesophageal	28 (16.9)	20 (11.9)	5 (13.5)	4 (12.5)	23 (17.8)	16 (11.8)	6 (8.8)	4 (4.9)	22 (22.4)	16 (18.4)
Constipation	10 (6.0)	19 (11.3)	3 (8.1)	6 (18.8)	7 (5.4)	13 (9.6)	4 (5.9)	6 (7.4)	6 (6.1)	13 (14.9)
Ascites	21 (12.7)	18 (10.7)	8 (21.6)	9 (28.1)	13 (10.1)	9 (6.6)	3 (4.4)	1 (1.2)	18 (18.4)	17 (19.5)
Abdominal distension	8 (4.8)	15 (8.9)	4 (10.8)	6 (18.8)	4 (3.1)	9 (6.6)	1 (1.5)	7 (8.6)	7 (7.1)	8 (9.2)
Portal hypertensive gastropathy	7 (4.2)	14 (8.3)	3 (8.1)	3 (9.4)	4 (3.1)	11 (8.1)	0	3 (3.7)	7 (7.1)	11 (12.6)
Vomiting	12 (7.2)	14 (8.3)	3 (8.1)	3 (9.4)	9 (7.0)	11 (8.1)	4 (5.9)	7 (8.6)	8 (8.2)	7 (8.0)
Gastrooesophageal reflux disease	6 (3.6)	11 (6.5)	0	2 (6.3)	6 (4.7)	9 (6.6)	3 (4.4)	3 (3.7)	3 (3.1)	8 (9.2)
Dyspepsia	8 (4.8)	9 (5.4)	3 (8.1)	3 (9.4)	5 (3.9)	6 (4.4)	2 (2.9)	4 (4.9)	6 (6.1)	5 (5.7)
Infections and infestations	90 (54.2)	91 (54.2)	19 (51.4)	17 (53.1)	71 (55.0)	74 (54.4)	31 (45.6)	43 (53.1)	59 (60.2)	48 (55.2)
Urinary tract infection	30 (18.1)	20 (11.9)	7 (18.9)	3 (9.4)	23 (17.8)	17 (12.5)	9 (13.2)	10 (12.3)	21 (21.4)	10 (11.5)
Nasopharyngitis	14 (8.4)	18 (10.7)	2 (5.4)	2 (6.3)	12 (9.3)	16 (11.8)	4 (5.9)	11 (13.6)	10 (10.2)	7 (8.0)

System Organ Class Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Upper respiratory tract infection	10 (6.0)	14 (8.3)	1 (2.7)	2 (6.3)	9 (7.0)	12 (8.8)	3 (4.4)	9 (11.1)	7 (7.1)	5 (5.7)
Sinusitis	9 (5.4)	11 (6.5)	1 (2.7)	3 (9.4)	8 (6.2)	8 (5.9)	1 (1.5)	5 (6.2)	8 (8.2)	6 (6.9)
Bronchitis	8 (4.8)	10 (6.0)	1 (2.7)	2 (6.3)	7 (5.4)	8 (5.9)	2 (2.9)	3 (3.7)	6 (6.1)	7 (8.0)
Influenza	10 (6.0)	10 (6.0)	1 (2.7)	2 (6.3)	9 (7.0)	8 (5.9)	4 (5.9)	4 (4.9)	6 (6.1)	6 (6.9)
General disorders and administration site conditions	68 (41.0)	78 (46.4)	18 (48.6)	23 (71.9)	50 (38.8)	55 (40.4)	18 (26.5)	29 (35.8)	50 (51.0)	49 (56.3)
Oedema peripheral	18 (10.8)	31 (18.5)	9 (24.3)	13 (40.6)	9 (7.0)	18 (13.2)	1 (1.5)	4 (4.9)	17 (17.3)	27 (31.0)
Fatigue	25 (15.1)	18 (10.7)	10 (27.0)	4 (12.5)	15 (11.6)	14 (10.3)	5 (7.4)	8 (9.9)	20 (20.4)	10 (11.5)
Pyrexia	8 (4.8)	12 (7.1)	1 (2.7)	3 (9.4)	7 (5.4)	9 (6.6)	4 (5.9)	6 (7.4)	4 (4.1)	6 (6.9)
Musculoskeletal and connective tissue disorders	71 (42.8)	66 (39.3)	13 (35.1)	9 (28.1)	58 (45.0)	57 (41.9)	25 (36.8)	32 (39.5)	46 (46.9)	34 (39.1)
Arthralgia	29 (17.5)	23 (13.7)	4 (10.8)	4 (12.5)	25 (19.4)	19 (14.0)	6 (8.8)	12 (14.8)	23 (23.5)	11 (12.6)
Back pain	11 (6.6)	12 (7.1)	1 (2.7)	2 (6.3)	10 (7.8)	10 (7.4)	7 (10.3)	7 (8.6)	4 (4.1)	5 (5.7)
Muscle spasms	5 (3.0)	12 (7.1)	4 (10.8)	1 (3.1)	1 (0.8)	11 (8.1)	0	2 (2.5)	5 (5.1)	10 (11.5)
Pain in extremity	7 (4.2)	9 (5.4)	1 (2.7)	1 (3.1)	6 (4.7)	8 (5.9)	7 (10.3)	6 (7.4)	5 (5.1)	3 (3.4)
Investigations	68 (41.0)	61 (36.3)	17 (45.9)	15 (46.9)	51 (39.5)	46 (33.8)	24 (35.3)	27 (33.3)	44 (44.9)	34 (39.1)
Blood bilirubin increased	25 (15.1)	20 (11.9)	7 (18.9)	6 (18.8)	18 (14.0)	14 (10.3)	8 (11.8)	4 (4.9)	17 (17.3)	16 (18.4)
Respiratory, thoracic and mediastinal disorders	41 (24.7)	55 (32.7)	9 (24.3)	14 (43.8)	32 (24.8)	41 (30.1)	13 (19.1)	23 (28.4)	28 (28.6)	32 (36.8)
Dyspnoea	9 (5.4)	15 (8.9)	2 (5.4)	7 (21.9)	7 (5.4)	8 (5.9)	5 (7.4)	3 (3.7)	4 (4.1)	12 (13.8)
Cough	6 (3.6)	13 (7.7)	0	4 (12.5)	6 (4.7)	9 (6.6)	2 (2.9)	7 (8.6)	4 (4.1)	6 (6.9)
Oropharyngeal pain	3 (1.8)	11 (6.5)	1 (2.7)	2 (6.3)	2 (1.6)	9 (6.6)	2 (2.9)	6 (7.4)	1 (1.0)	5 (5.7)
Nervous system disorders	59 (35.5)	51 (30.4)	15 (40.5)	12 (37.5)	44 (34.1)	39 (28.7)	21 (30.9)	25 (30.9)	38 (38.8)	26 (29.9)
Headache	21 (12.7)	23 (13.7)	5 (13.5)	4 (12.5)	16 (12.4)	19 (14.0)	10 (14.7)	13 (16.0)	11 (11.2)	10 (11.5)

System Organ Class Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Dizziness	14 (8.4)	10 (6.0)	2 (5.4)	2 (6.3)	12 (9.3)	8 (5.9)	8 (11.8)	4 (4.9)	6 (6.1)	6 (6.9)
Hepatobiliary disorders	47 (28.3)	50 (29.8)	14 (37.8)	11 (34.4)	33 (25.6)	39 (28.7)	9 (13.2)	15 (18.5)	38 (38.8)	35 (40.2)
Hepatic cirrhosis	8 (4.8)	10 (6.0)	0	1 (3.1)	8 (6.2)	9 (6.6)	3 (4.4)	2 (2.5)	5 (5.1)	8 (9.2)
Psychiatric disorders	25 (15.1)	31 (18.5)	5 (13.5)	6 (18.8)	20 (15.5)	25 (18.4)	6 (8.8)	12 (14.8)	19 (19.4)	19 (21.8)
Insomnia	16 (9.6)	12 (7.1)	3 (8.1)	2 (6.3)	13 (10.1)	10 (7.4)	2 (2.9)	3 (3.7)	14 (14.3)	9 (10.3)
Blood and lymphatic system disorders	31 (18.7)	30 (17.9)	9 (24.3)	7 (21.9)	22 (17.1)	23 (16.9)	10 (14.7)	10 (12.3)	21 (21.4)	20 (23.0)
Anaemia	13 (7.8)	11 (6.5)	2 (5.4)	4 (12.5)	11 (8.5)	7 (5.1)	5 (7.4)	3 (3.7)	8 (8.2)	8 (9.2)
Vascular disorders	20 (12.0)	25 (14.9)	4 (10.8)	4 (12.5)	16 (12.4)	21 (15.4)	6 (8.8)	10 (12.3)	14 (14.3)	15 (17.2)
Hypertension	7 (4.2)	9 (5.4)	2 (5.4)	0	5 (3.9)	9 (6.6)	1 (1.5)	3 (3.7)	6 (6.1)	6 (6.9)

AE=adverse event; OCA=obeticholic acid; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment Emergent Adverse Event

TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.

AEs were coded using MedDRA version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages are based on number of subjects in the Safety Population within subgroup and treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Source: 747-2024 CSR, Table 14.3.1.3, Table 14.3.1.2.2.1, Table 14.3.1.2.2.2

Adverse Events by Relatedness to Investigational Product

A summary of treatment-related TEAEs in ≥2 OCA-treated subjects by system organ class (SOC) and PT by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations has been presented.

-Proposed SmPC Indicated Population

In comparison to the overall and compensated populations, individual treatment-related TEAEs occurred less frequently across treatment groups in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), 61 (75.3%) subjects in the OCA group and 38 (55.9%) subjects in the placebo group reported treatment-related TEAEs. Consistent with the overall and compensated populations, the difference in incidence of treatment-related TEAEs across treatment groups was largely driven by the occurrence of treatment-related pruritus (71.6% in the OCA group and 42.6% in the placebo group). Pruritus is a known ADR per the current SmPC and was an AESI in Study 747-302 (Section 2.8.3.4.6). Nausea occurred at a higher rate in the OCA group (6.2%) compared to the placebo group (2.9%). With the exception of pruritus and nausea, all other treatment-related TEAEs occurred in $\leq 2.5\%$ OCA-treated subjects.

Adverse Events by Severity

A summary of severe TEAEs in ≥ 2 overall OCA-treated subjects by SOC and PT by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 61.

-Proposed SmPC Indicated Population

In comparison to the overall and compensated populations, individual severe TEAEs occurred less frequently across treatment groups in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the majority of TEAEs were mild or moderate across treatment groups. A total of 37 (45.7%) subjects in the OCA group and 22 (32.4%) subjects in the placebo group had at least one severe TEAE. The most frequently reported severe TEAE was pruritus: 32.1% in the OCA group and 11.8% in the placebo group. With the exception of pruritus, individual PTs of severe TEAEs occurred in ≤ 2 subjects and were generally balanced across treatment groups. There were no severe hepatic events of ascites, oesophageal varices haemorrhage, hepatic cirrhosis, or hepatic failure in OCA-treated subjects in the proposed SmPC indicated population.

Table 61: Study 747-302 - Summary of Severe Treatment-Emergent Adverse Events in ≥ 2 Overall OCA-treated Subjects by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

System Organ Class, a (%) Preferred Term	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Severe TEAE	65 (39.2)	86 (51.2)	18 (48.6)	22 (68.8)	47 (36.4)	64 (47.1)	22 (32.4)	37 (45.7)	43 (43.9)	49 (56.3)
Skin and subcutaneous tissue disorders	16 (9.6)	51 (30.4)	5 (13.5)	8 (25.0)	11 (8.5)	43 (31.6)	9 (13.2)	26 (32.1)	7 (7.1)	25 (28.7)
Pruritus	13 (9.0)	51 (30.4)	5 (13.5)	8 (25.0)	10 (7.8)	43 (31.6)	8 (11.8)	26 (32.1)	7 (7.1)	25 (28.7)
Gastrointestinal disorders	15 (9.0)	23 (13.7)	6 (16.2)	7 (21.9)	9 (7.0)	16 (11.8)	3 (4.4)	7 (8.6)	12 (12.2)	16 (18.4)
Oesophageal varices haemorrhage	3 (1.8)	4 (2.4)	1 (2.7)	1 (3.1)	2 (1.6)	3 (2.2)	1 (1.5)	0	2 (2.0)	4 (4.6)
Abdominal pain upper	1 (0.6)	3 (1.8)	1 (2.7)	2 (6.3)	0	1 (0.7)	0	1 (1.2)	1 (1.0)	2 (2.3)
Ascites	1 (0.6)	3 (1.8)	1 (2.7)	1 (3.1)	0	2 (1.5)	0	0	1 (1.0)	3 (3.4)
Abdominal pain	2 (1.2)	2 (1.2)	0	1 (3.1)	2 (1.6)	1 (0.7)	1 (1.5)	1 (1.2)	1 (1.0)	1 (1.1)
Diarrhoea	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	0	1 (1.0)	2 (2.3)
Melaena	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Vomiting	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Infections and infestations	5 (3.0)	11 (6.5)	1 (2.7)	5 (15.6)	4 (3.1)	6 (4.4)	2 (2.9)	4 (4.9)	3 (3.1)	7 (8.0)
Urinary tract infection	0	3 (1.8)	0	1 (3.1)	0	2 (1.5)	0	2 (2.5)	0	1 (1.1)
Peritonitis bacterial	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Sepsis	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Hepatobiliary disorders	4 (2.4)	10 (6.0)	2 (5.4)	4 (12.5)	2 (1.6)	6 (4.4)	0	1 (1.2)	4 (4.1)	9 (10.3)
Hepatic cirrhosis	1 (0.6)	2 (1.2)	0	0	1 (0.8)	2 (1.5)	0	0	1 (1.0)	2 (2.3)
Hepatic failure	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	0	1 (1.0)	2 (2.3)
Nervous system disorders	12 (7.2)	9 (5.4)	1 (2.7)	3 (9.4)	11 (8.5)	6 (4.4)	6 (8.8)	4 (4.9)	6 (6.1)	5 (5.7)
Cerebrovascular accident	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)

System Organ Class, n (%) Preferred Term	Overall		Current SmPC				Proposed SmPC			
	FBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			FBO N=37	OCA N=32	FBO N=129	OCA N=136	FBO N=68	OCA N=81	FBO N=98	OCA N=87
General disorders and administration site conditions	4 (2.4)	7 (4.2)	3 (8.1)	3 (9.4)	1 (0.8)	4 (2.9)	1 (1.5)	2 (2.5)	3 (3.1)	5 (5.7)
Fatigue	3 (1.8)	2 (1.2)	3 (8.1)	1 (3.1)	0	1 (0.7)	0	0	3 (3.1)	2 (2.3)
Injury, poisoning and procedural complications	7 (4.2)	6 (3.6)	2 (5.4)	3 (9.4)	5 (3.9)	3 (2.2)	4 (5.9)	2 (2.5)	3 (3.1)	4 (4.6)
Fall	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders	4 (2.4)	6 (3.6)	0	3 (9.4)	4 (3.1)	3 (2.2)	0	2 (2.5)	4 (4.1)	4 (4.6)
Acute respiratory failure	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)
Blood and lymphatic system disorders	3 (1.8)	5 (3.0)	3 (8.1)	1 (3.1)	0	4 (2.9)	0	3 (3.7)	3 (3.1)	2 (2.3)
Anaemia	1 (0.6)	3 (1.8)	1 (2.7)	1 (3.1)	0	2 (1.5)	0	1 (1.2)	1 (1.0)	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Musculoskeletal and connective tissue disorders	1 (0.6)	3 (1.8)	0	1 (3.1)	1 (0.8)	2 (1.5)	0	1 (1.2)	1 (1.0)	2 (2.3)
Back pain	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)

AE=adverse event, MedDRA=Medical Dictionary for Regulatory Activities, OCA=obeticolic acid, PBO=placebo, PH=evidence portal hypertension; SmPC=Summary of Product Characteristics TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded. AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Sources: 747-302, CSR Table 14.3.1.4.1; 747-302, Ad Hoc 76.1, Ad Hoc 76.2

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

A summary of TEAEs leading to death by PT by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented Table 62. A listing of all TEAEs leading to death is presented in Table 63.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), 1 subject treated with OCA died of acute respiratory failure; all other TEAEs leading to death (6 subjects) occurred in the proposed SmPC contraindicated population. Details of the fatal event in the proposed SmPC indicated population are briefly described below.

- A female subject with PBC died of acute respiratory failure on 10 Sep 2016 (Study Day 317), approximately 10 months after the initiation of OCA. On 20 Aug 2016 (Study Day 296), the subject was referred to the emergency room for evaluation of moderate left upper quadrant abdominal pain (non-serious adverse event [AE]). On 23 Aug 2016 (Study Day 299), the subject was hospitalized with the diagnosis of Stage 4 B-cell lymphoma (serious TEAE) with renal/breast/lung/central nervous system involvement. The metastatic disease was thought to have originated in the right kidney. Per the Investigator, the subject did not have any risk factors for B-cell lymphoma. Investigational product was withdrawn in response to the events of lymphoma and acute kidney injury (AKI), with the last dose administered on 20 Aug 2016 (Study Day 296). The Investigator assessed the event of lymphoma as severe and AKI as moderate in severity. On 03 Sept 2016 (Study Day 310), the subject completed the first cycle of chemotherapy (R-EPOCH). On 05 Sep 2016 (Study Day 312), the subject was transferred to the intensive care unit as she developed acute hypoxemic respiratory failure (serious TEAE) and subsequently intubated due to worsening hypoxia and respiratory distress on 09 Sep 2016 (Study Day 316). Additional diagnoses were tumour lysis syndrome,

pancytopenia with neutropenia and AKI. The subject's family decided to pursue comfort care and the subject was extubated and died due to the event of acute respiratory failure on the same day. The events of lymphoma, AKI, and the fatal event of acute respiratory failure were all considered not related to investigational product by the Investigator.

Table 62: Study 747-302 - Summary of Treatment-Emergent Adverse Events Leading to Death by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	FBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			FBO N=37	OCA N=32	FBO N=129	OCA N=136	FBO N=68	OCA N=81	FBO N=98	OCA N=87
Subjects with at least 1 TEAE Leading to Death	2 (1.2)	5 (3.0)	0	3 (9.4)	2 (1.6)	2 (1.5)	0	1 (1.2)	2 (2.0)	4 (4.6)
Acute respiratory failure	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Lower respiratory tract infection	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Respiratory failure	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Sepsis	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Subarachnoid haemorrhage	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Hepatocellular carcinoma	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0
Sarcopenia	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0

AE=adverse event; GCP= Good Clinical Practice; ICH= International Conference on Harmonisation; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; FBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
For each row category, a subject with two or more AEs in that category was counted only once for the subject count.
Percentages were based on number of subjects in the Safety Population within each treatment group.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.
Of note, 2 deaths (Subject 234001 in the OCA group and Subject 222001 in the placebo group; both subjects were in the proposed SmPC contraindicated population at baseline) occurred after the subjects withdrew consent; these events were inadvertently reported in the clinical database. These events were excluded from the analyses per ICH/GCP principles (i.e., events occurred after withdrawing consent).
Sources: 747-302 CSR, Table 14.3.1.9.5, Table 14.3.1.9.5.1, Table 14.3.1.9.5.2

Table 63: Study 747-302 - Listing of Treatment-Emergent Adverse Events Leading to Death (Safety Population [N=334])

Subject ID	IP	Current SmPC Status at Baseline	Proposed SmPC Status at Baseline	Preferred Term	Underlying Cause of Death	Relatedness	Onset Day / Day of Death*
207007	OCA	Compensated	Proposed SmPC Indicated	Acute/respiratory failure	Stage 4 B-cell lymphoma with tumour lysis syndrome	Not related	312 / 317
219005	OCA	Decompensated	Proposed SmPC Contraindicated	Respiratory failure	Vertebral fracture, post-op pulmonary infiltrate	Not related	1370 / 1370
297001	OCA	Decompensated	Proposed SmPC Contraindicated	Subarachnoid haemorrhage	Sudden onset severe headache with loss of consciousness	Not related	342 / 348
301005	OCA	Decompensated	Proposed SmPC Contraindicated	Sepsis	No additional information from site	Not related	Unknown / 187
313002	OCA	Compensated	Proposed SmPC Contraindicated	Lower respiratory tract infection	Influenza A and hospital acquired pneumonia	Unlikely	128 / 183
210001	Placebo	Compensated	Proposed SmPC Contraindicated	Sarcopenia	General deterioration No additional information from site	Unlikely	1311 / 1373
219010	Placebo	Compensated	Proposed SmPC Contraindicated	Hepatocellular carcinoma	-	Not related	718 / 843

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; TEAE=treatment-emergent adverse event; SmPC=Summary of Product Characteristics
Note: TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.
Note: AEs are coded using MedDRA Version 24.0.
*Time to onset/death from first dose of investigational product.
Source: 747-302 CSR, Table 14.3.1.9.5, Table 14.3.1.9.5.1, Table 14.3.1.9.5.2, Table 14.3.1.12.6

Other Serious Adverse Events

Serious TEAEs by PT are presented by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 64.

Proposed SmPC Indicated Population

In comparison to the overall and compensated populations, the proportion of serious TEAEs across treatment groups was lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the incidence of serious TEAEs was lower in the

OCA group (15 [18.5%] subjects) than the placebo group (17 [25.0%] subjects). The most frequently reported serious TEAEs were thrombotic thrombocytopenic purpura (TTP) (2 [2.5%] subjects in the OCA group and none in the placebo group) and urinary tract infection (2 [2.5%] subjects in the OCA group and 1 [1.5%] subject in the placebo group), which were all assessed as unlikely or not related to investigational product by the Investigator. All other individual serious TEAEs were reported in ≤ 1 OCA-treated subject.

Table 64: Study 747-302 - Summary of Serious Treatment-Emergent Adverse Events in ≥ 2 Overall OCA-treated Subjects by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Serious TEAE	53 (31.9)	53 (31.5)	13 (35.1)	20 (62.5)	40 (31.0)	33 (24.3)	17 (25.0)	15 (18.5)	16 (16.3)	38 (43.7)
Oesophageal varices haemorrhage	5 (3.0)	4 (2.4)	1 (2.7)	1 (3.1)	4 (3.1)	3 (2.2)	2 (2.9)	0	3 (3.1)	4 (4.6)
Hepatic encephalopathy	5 (3.0)	3 (1.8)	2 (5.4)	2 (6.3)	3 (2.3)	1 (0.7)	0	0	1 (1.0)	3 (3.4)
Urinary tract infection	1 (0.6)	3 (1.8)	0	1 (3.1)	1 (0.8)	2 (1.5)	1 (1.5)	2 (2.5)	0	1 (1.1)
Acute kidney injury	0	2 (1.2)	0	0	0	2 (1.5)	0	0	0	2 (2.3)
Acute respiratory failure	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)
Ascites	4 (2.4)	2 (1.2)	4 (10.8)	1 (3.1)	0	1 (0.7)	0	0	4 (4.1)	2 (2.3)
Cerebrovascular accident	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Coronary artery disease	0	2 (1.2)	0	2 (6.3)	0	0	0	0	0	2 (2.3)
Disease progression	1 (0.6)	2 (1.2)	1 (2.7)	2 (6.3)	0	0	0	0	1 (1.0)	2 (2.3)
Hepatic cirrhosis	0	2 (1.2)	0	0	0	2 (1.5)	0	0	0	2 (2.3)
Hepatic failure	2 (1.2)	2 (1.2)	1 (2.7)	1 (3.1)	1 (0.8)	1 (0.7)	0	0	2 (2.0)	2 (2.3)
Oedema peripheral	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	1 (1.2)	1 (1.0)	1 (1.1)
Pruritus	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Sepsis	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
For each row category, a subject with two or more AEs in that category was counted only once for the subject count.
Percentages were based on number of subjects in the Safety Population within each treatment group.

Adverse Events Leading to Discontinuation of Investigational Product

A summary of TEAEs leading to discontinuation of investigational product by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 65.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), the incidence of TEAEs leading to discontinuation of investigational product was 27 (33.3%) subjects in the OCA group and 18 (26.5%) subjects in the placebo group. Consistent with the overall, decompensated (contraindicated per current SmPC) and compensated (indicated per current SmPC) populations, the most frequently reported TEAE leading to discontinuation of investigational product was pruritus (14.8% in the OCA group and 2.9% in the placebo group). Pruritus is a known ADR per the current SmPC and was an AESI in Study 747-302.

Incidence of other PTs leading to discontinuation of investigational product were low and generally balanced across treatment groups. With the exception of pruritus, other TEAEs leading to investigational product which occurred higher in the OCA group compared to the placebo group included: potential liver injury event (2.5% in the OCA group and none in the placebo group); hyperbilirubinaemia (1.2% in the OCA group and none in the placebo group); and TTP (2.5% in the OCA group and none in the placebo group).

Table 65: Study 747-302 - Summary of Treatment-Emergent Adverse Events Leading to Discontinuation of Investigational Product in ≥ 2 Subjects by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 TEAE Leading Discontinuation of Investigational product	45 (27.1)	62 (36.9)	9 (24.3)	17 (53.1)	36 (27.9)	45 (33.1)	18 (26.5)	27 (33.3)	27 (27.6)	35 (40.2)
Pruritus	3 (1.8)	19 (11.3)	1 (2.7)	2 (6.3)	2 (1.6)	17 (12.5)	2 (2.9)	12 (14.8)	1 (1.0)	7 (8.0)
Blood bilirubin increased	9 (5.4)	6 (3.6)	3 (8.1)	1 (3.1)	6 (4.7)	5 (3.7)	3 (4.4)	3 (3.7)	6 (6.1)	3 (3.4)
Ascites	1 (0.6)	4 (2.4)	1 (2.7)	1 (3.1)	0	3 (2.2)	0	0	1 (1.0)	4 (4.6)
Disease progression	4 (2.4)	3 (1.8)	0	3 (9.4)	4 (3.1)	0	3 (4.4)	0	1 (1.0)	3 (3.4)
Drug-induced liver injury	0	3 (1.8)	0	0	0	3 (2.2)	0	2 (2.5)	0	1 (1.1)
Hepatic cirrhosis	2 (1.2)	2 (1.2)	0	0	2 (1.6)	2 (1.5)	1 (1.5)	0	1 (1.0)	2 (2.3)
Hepatic enzyme increased	2 (1.2)	2 (1.2)	0	0	2 (1.6)	2 (1.5)	2 (2.9)	2 (2.5)	0	0
Hyperbilirubinaemia	2 (1.2)	2 (1.2)	0	1 (3.1)	2 (1.6)	1 (0.7)	0	1 (1.2)	2 (2.0)	1 (1.1)
Jaundice	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	0	1 (1.0)	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Hepatic encephalopathy	7 (4.2)	1 (0.6)	2 (5.4)	1 (3.1)	5 (3.9)	0	0	0	7 (7.1)	1 (1.1)
Bilirubin conjugated increased	2 (1.2)	0	1 (2.7)	0	1 (0.8)	0	0	0	2 (2.0)	0
GGT increased	2 (1.2)	0	0	0	2 (1.6)	0	1 (1.5)	0	1 (1.0)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
 TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
 AEs were coded using MedDRA Version 26.0.
 For each row category, a subject with two or more AEs in that category was counted only once for the subject count.
 Percentages were based on number of subjects in the Safety Population within each treatment group.
 The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
 The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
 Source: 747-302 CSR, Table 14.3.1.9.1, Table 14.3.1.9.1.1, Table 14.3.1.9.1.2

Overview of Adverse Events of Special Interest

An overview of TEAEs by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 66.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), the incidence of hepatic and cardiovascular (CV) TEAEs was lower in both treatment groups, with a larger decrease observed for the OCA-treated subjects when compared to the overall safety and compensated populations.

A total of 71 (87.7%) subjects in the OCA group and 50 (73.5%) subjects in the placebo group reported TEAEs. The majority of TEAEs were mild or moderate in the proposed SmPC indicated population. Severe TEAEs were higher in the OCA group (35.8%) than the placebo group (22.1%), which was mostly driven by pruritus (for pruritus TEAE, see Section 2.8.3.4.6). Severe treatment-emergent pruritus was 32.1% in the OCA group and 11.8% in the placebo group (Table 61).

The most frequently reported ($\geq 10\%$) TEAEs in the proposed SmPC indicated population were pruritus (82.7% in the OCA group and 48.5% in the placebo group) and hepatic (27.2% in the OCA group and 42.6% in the placebo group).

Table 66: Study 747-302 – Summary of Treatment-Emergent AESIs by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 TEAE of Special Interest, n (%)	137 (82.5)	152 (90.5)	34 (91.9)	32 (100.0)	103 (79.8)	120 (88.2)	50 (73.5)	71 (87.7)	87 (88.8)	81 (93.1)
Hepatic, n (%)	97 (58.4)	80 (47.6)	24 (64.9)	22 (68.8)	73 (56.6)	58 (42.6)	29 (42.6)	22 (27.2)	68 (69.4)	54 (66.7)
IRY (PY)	40.855 (237.42)	26.420 (302.80)	71.448 (33.59)	74.798 (29.41)	35.814 (203.83)	21.215 (273.39)	25.754 (112.60)	11.844 (185.75)	54.478 (124.82)	49.551 (117.05)
Cholecystitis/Cholelithiasis, n (%)	9 (5.4)	9 (5.4)	1 (2.7)	2 (6.3)	8 (6.2)	7 (5.1)	1 (1.5)	3 (3.7)	8 (8.2)	6 (6.9)
IRY (PY)	2.605 (345.51)	2.225 (404.56)	1.836 (54.45)	3.966 (50.43)	2.749 (291.05)	1.977 (354.13)	0.692 (144.54)	1.416 (211.92)	3.981 (208.96)	3.115 (192.64)
Cardiovascular, n (%)	7 (4.2)	16 (9.5)	2 (5.4)	2 (5.4)	5 (3.9)	11 (8.1)	2 (2.9)	5 (6.2)	5 (5.1)	11 (12.6)
IRY (PY)	2.013 (347.69)	3.907 (409.56)	3.772 (53.02)	9.438 (52.97)	1.697 (294.67)	3.085 (356.59)	1.385 (144.45)	2.236 (207.90)	2.460 (203.23)	5.500 (199.98)
Dyslipidaemia, n (%)	9 (5.4)	6 (3.6)	3 (8.1)	1 (3.1)	6 (4.7)	5 (3.7)	3 (4.4)	4 (4.9)	6 (6.1)	2 (2.3)
IRY (PY)	2.698 (333.57)	1.479 (405.70)	5.742 (52.25)	1.959 (51.04)	2.133 (281.32)	1.410 (354.67)	2.236 (134.17)	1.977 (207.90)	3.009 (199.40)	1.011 (197.80)
Renal, n (%)	13 (7.8)	17 (10.1)	5 (13.5)	5 (15.6)	8 (6.2)	12 (8.8)	4 (5.9)	8 (9.9)	9 (9.2)	9 (10.3)
IRY (PY)	3.804 (341.76)	4.159 (408.77)	9.329 (53.60)	9.639 (51.87)	2.776 (288.16)	3.362 (356.90)	2.577 (138.05)	3.818 (209.56)	4.440 (202.71)	4.518 (199.22)
Pruritus, n (%)	86 (51.8)	133 (79.2)	19 (51.4)	24 (75.0)	67 (51.9)	109 (80.1)	33 (48.5)	67 (82.7)	53 (54.1)	66 (75.9)
IRY (PY)	39.914 (215.46)	103.926 (127.98)	53.506 (35.51)	116.399 (20.62)	37.232 (179.95)	101.531 (107.86)	34.642 (95.26)	102.046 (65.66)	44.092 (120.20)	105.907 (62.32)

AE=adverse event; AESI=adverse event of special interest; IRY=number of patients with event per 100 patient-years; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence of portal hypertension; PY=patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
Note: TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were included.
AEs were coded using MedDRA Version 34.0.
Patient-years = sum of individual patient-years for each event. Each individual's patient-years were derived as the first event date or an event or min of (last investigational product dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 (days/year) for each unique AESI.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad Hoc 36, Ad Hoc 36.1, Ad Hoc 36.2

Hepatic

A comprehensive evaluation of hepatic events was performed, including analyses of Investigator-reported, hepatic TEAEs (SMQ-based), evaluation of drug-induced serious hepatotoxicity (eDISH), adjudication of hepatic outcomes and hepatic safety events (e.g., drug-induced liver injury [DILI]) based on a broad set of hepatic trigger events (Investigator-reported TEAEs and pre-specified lab thresholds) to determine severity and causality by a blinded, independent adjudication committee.

A summary of the hepatic evaluations by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 67. In comparison to the overall safety population, the incidence of hepatic events observed in OCA group was markedly lower in the proposed SmPC indicated population.

Investigator-reported Hepatic TEAEs

• Overall Safety Population (N=334)

-The number of subjects with at least one hepatic TEAE was 80 (47.6%) in the OCA group and 97 (58.4%) in the placebo group.

• Proposed SmPC indicated Population (N=149)

-Incidence of hepatic PTs in the OCA group (27.2%) were lower than the placebo group (42.6%).

-The difference between OCA-treated subjects and placebo is more pronounced when considering the incidence of exposure-adjusted hepatic TEAEs (11.844 per 100 patient years [PYs] in the OCA group and 25.754 per 100 PYs in the placebo group).

-No difference was observed between treatment groups of exposure-adjusted hepatic SAEs (1.396 per 100 PYs in the OCA group and 1.385 per 100 PYs in the placebo group).

All hepatic outcomes (i.e., European Medicines Agency [EMA] composite endpoints and US Food and Drug Administration [FDA] expanded endpoints) were adjudicated by a blinded, independent Hepatic Outcomes Committee (HOC) to determine whether they met the protocol-specified endpoint criteria. Subsequently, per request from the FDA, all EMA and FDA expanded hepatic outcome events underwent additional blinded clinical review retrospectively by an independent Hepatic Safety Adjudication Committee (HSAC) to determine causality (highly likely drug related, probable drug related, possible drug related, unlikely drug related, insufficient information).

Evaluation of Drug-induced Serious Hepatotoxicity

- Overall Safety Population (N=334)

-More subjects in the OCA group (49.4%) are represented in the normal range for alanine aminotransferase (ALT) and total bilirubin peak excursions compared to placebo (35.5%). Fewer subjects in the OCA group met criteria for the biochemical Hy's law range (peak ALT >3x upper limit of normal [ULN] and peak total bilirubin >2x ULN) and cholestasis range (peak total bilirubin >2x ULN, and ALT <3x ULN).

- Proposed SmPC Indication (N=149)

- More subjects in the OCA group (60.5%) were in the normal range for ALT and total bilirubin peak excursions compared to placebo (45.6%).

- Fewer subjects in the OCA group (12.3%) met criteria for the biochemical Hy's law range compared to placebo (16.2%). Similar trends were observed for the cholestasis range (3.7% in the OCA group and 4.4% in the placebo group).

Adjudicated Hepatic Safety Events

- Overall Safety Population (N=334)

There were 189 hepatic safety events in 85 subjects in the OCA group compared to 230 events in 99 subjects in the placebo group.

– Of those events, 18 subjects had events positively adjudicated as possibly related (n=17) or probably related to investigational product (n=1) events in the OCA group compared to 8 subjects (all possibly related) in the placebo group.

– Of the 18 subjects, 12 in the OCA group had events ≥moderate severity compared to 7 subjects in the placebo group.

- Proposed SmPC Indication (N=149)

– 4 subjects had events positively adjudicated as possibly related to investigational product in the OCA group compared to 1 subject in the placebo group. Of these subjects, 2 subjects had events ≥moderate severity in the OCA group compared to 1 subject in the placebo group.

– No subject had potential liver injury assessed as probable or highly likely by the HSAC, and all cases were reversible with discontinuation of OCA.

– No subject with possible related potential liver injury progressed to liver failure, suffered accelerated disease progression after the event, underwent liver transplantation or died during the study or the follow up period.

– All possible related potential liver injury events in the OCA group occurred within the first 3 months of investigational product, and no uniform pattern of liver injury was present.

Adjudicated Hepatic Outcomes

All hepatic outcomes (i.e., EMA composite endpoints and FDA expanded endpoints) were adjudicated by a blinded, independent HOC to determine whether they met the protocol-specified endpoint criteria.

Subsequently, per request from the FDA, all EMA and FDA expanded hepatic outcome events underwent additional blinded clinical review retrospectively by an independent HSAC to determine causality (highly likely drug related, probable drug related, possible drug related, unlikely drug related, insufficient information).

- Proposed SmPC Indication (N=149)

– EMA Composite Endpoint: A total of 1 subject with 1 event of liver transplant in the OCA group and 1 subject in the placebo group with 1 event of Model for End-Stage Liver Disease (MELD) ≥ 15 were considered possibly related to investigational product by the HSAC.

– FDA Expanded Endpoint: A total of 3 (3.7%) subjects with 4 events in the OCA group and 1 (1.5%) subject with 4 events in the placebo group were considered possibly related to investigational product by the HSAC.

– None of the OCA-treated or placebo subjects experienced a liver-related death. No cases were considered probable or highly likely.

Comprehensive evaluation of hepatic safety events observed in clinical trials of OCA across indications has informed our understanding of OCA's potential for hepatotoxicity. The majority of hepatic TEAEs have been reported in subjects with advanced PBC who either had evidence of decompensation or PH, which forms the basis for our proposed SmPC to further restrict the indication. Restricting the label per the proposed SmPC indication allows for an improved safety profile.

Table 67: Summary of Hepatic Events in Study 747-302: Investigator-reported Hepatic TEAEs, eDISH, Adjudication of Hepatic Outcomes and Hepatic Safety Events by Overall, Compensated (indicated per current SmPC), Decompensated (contraindicated per current SmPC) and Proposed SmPC Indicated and Contraindicated Populations

		Overall		Current SmPC				Proposed SmPC			
				Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
		PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Investigator-reported Hepatic TEAEs											
Subjects with at least 1 Hepatic TEAEs	n (%)	97 (58.4)	89 (52.6)	24 (64.9)	22 (68.8)	73 (56.6)	58 (42.6)	29 (42.6)	22 (27.2)	68 (69.4)	58 (66.7)
	IRY (PY)	40.855 (237.40)	26.42 (302.8)	71.448 (33.59)	74.798 (29.41)	35.814 (203.83)	21.215 (273.39)	25.754 (112.60)	11.844 (185.75)	54.478 (124.82)	49.551 (117.05)
Subjects with at least 1 Serious Hepatic TEAEs	n (%)	16 (9.6)	15 (8.9)	7 (18.9)	6 (18.8)	9 (7.0)	9 (6.6)	2 (2.9)	3 (3.7)	14 (14.3)	12 (13.8)
	IRY (PY)	4.621 (346.32)	3.646 (411.36)	13.864 (50.49)	12.276 (48.88)	3.042 (295.83)	2.483 (362.49)	1.385 (144.40)	1.396 (214.86)	6.934 (201.92)	6.107 (196.51)
Evaluation of Drug-induced Serious Hepatotoxicity (eDISH)											
Subjects meeting eDISH Hy's Law Criteria (All Post-Baseline Measurements)	n (%)	35 (21.1)	24 (14.3)	10 (27.0)	9 (28.1)	25 (19.4)	15 (11.0)	11 (16.2)	10 (12.3)	24 (24.5)	14 (16.1)
Subjects meeting eDISH Tepper's Corollary Criteria (All Post-Baseline Measurements)	n (%)	28 (16.9)	24 (14.3)	0	1 (3.1)	28 (21.7)	23 (16.9)	22 (32.4)	18 (22.2)	6 (6.1)	6 (6.9)
Subjects meeting eDISH Cholestasis Range (All Post-Baseline Measurements)	n (%)	43 (25.9)	35 (20.8)	22 (59.5)	15 (46.9)	21 (16.3)	20 (14.7)	3 (4.4)	3 (3.7)	40 (40.8)	32 (36.8)
Adjudicated Hepatic Safety Events											

		Overall		Current SmPC				Proposed SmPC			
				Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
		PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
All Adjudicated Hepatic Safety Events	n (%) [e]	99 (59.6) [230]	85 (50.6) [189]	27 (73.0) [63]	26 (81.3) [66]	72 (55.8) [167]	59 (43.40) [123]	28 (41.2) [64]	29 (35.8) [58]	71 (72.4) [166]	56 (64.4) [131]
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥mild severity)	n (IR)	8 (2.325)	18 (4.521)	4 (7.470)	8 (18.169)	4 (1.377)	10 (2.824)	1 (0.685)	4 (1.910)	7 (3.533)	14 (7.420)
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥moderate severity)	n (IR)	7 (2.012)	12 (2.923)	4 (7.470)	7 (14.576)	3 (1.019)	5 (1.379)	1 (0.685)	2 (0.931)	6 (2.971)	10 (5.111)
Adjudicated Hepatic Outcomes											
EAIR of Hepatic Outcomes Adjudicated as ≥Possibly Related to IP	n (%), IRY (PY)	2 (1.2), 0.564 (354.56)	10 (6.0), 2.391 (418.19)	1 (2.7), 1.820 (54.95)	4 (12.5), 7.652 (52.27)	1 (0.8), 0.334 (299.61)	6 (4.4)*, 1.640 (365.92)	1 (1.5), 0.689 (145.24)	3 (3.7)*, 1.403 (213.80)	1 (1.0), 0.478 (209.32)	7 (8.0), 3.425 (204.39)

AE=adverse event; IP=investigational product; IRY=number of patients with event per 100 patient year; EAIR=number of patients with event per 100 patient year; eDISH=Evaluation of Drug-induced Serious Hepatotoxicity; OCA=obeticholic acid; PBO = placebo; PY=patient-years; SmPC=Summary of Product Characteristic; TEAE=Treatment-Emergent Adverse Event

* Subject 115005 in the OCA group (compensated population) had ascites at baseline and would have been considered decompensated (contraindicated) at baseline. Ascites was reported in imaging/hospital notes and these were not captured as part of the programmatic grouping, which used eCRF data.

† Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that Subject 272004 had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline. Hepatic outcome included data after initiation of treatment and through last study day. Data after a patient began commercial OCA were included.

		Overall		Current SmPC				Proposed SmPC			
				Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
		PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
All Adjudicated Hepatic Safety Events	n (%) [e]	99 (59.6) [230]	85 (50.6) [189]	27 (73.0) [63]	26 (81.3) [66]	72 (55.8) [167]	59 (43.40) [123]	28 (41.2) [64]	29 (35.8) [58]	71 (72.4) [166]	56 (64.4) [131]
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥mild severity)	n (IR)	8 (2.325)	18 (4.521)	4 (7.470)	8 (18.169)	4 (1.377)	10 (2.824)	1 (0.685)	4 (1.910)	7 (3.533)	14 (7.420)
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥moderate severity)	n (IR)	7 (2.012)	12 (2.923)	4 (7.470)	7 (14.576)	3 (1.019)	5 (1.379)	1 (0.685)	2 (0.931)	6 (2.971)	10 (5.111)
Adjudicated Hepatic Outcomes											
EAIR of Hepatic Outcomes Adjudicated as ≥Possibly Related to IP	n (%), IRY (PY)	2 (1.2), 0.564 (354.56)	10 (6.0), 2.391 (418.19)	1 (2.7), 1.820 (54.95)	4 (12.5), 7.652 (52.27)	1 (0.8), 0.334 (299.61)	6 (4.4)*, 1.640 (365.92)	1 (1.5), 0.689 (145.24)	3 (3.7)*, 1.403 (213.80)	1 (1.0), 0.478 (209.32)	7 (8.0), 3.425 (204.39)

AE=adverse event; IP=investigational product; IRY=number of patients with event per 100 patient year; EAIR=number of patients with event per 100 patient year; eDISH=Evaluation of Drug-induced Serious Hepatotoxicity; OCA=obeticholic acid; PBO = placebo; PY=patient-years; SmPC=Summary of Product Characteristic; TEAE=Treatment-Emergent Adverse Event

* One Subject in the OCA group (compensated population) had ascites at baseline and would have been considered decompensated (contraindicated) at baseline. Ascites was reported in imaging/hospital notes and these were not captured as part of the programmatic grouping, which used eCRF data.

† Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that Subject 272004 had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

TEAE is any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA are excluded.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline. Hepatic outcome included data after initiation of treatment and through last study day. Data after a patient began commercial OCA were included.

Investigator-Reported Hepatic TEAEs

Hepatic decompensation/disorder events were defined by Hepatic Disorders Standardised MedDRA Queries (SMQ), excluding the following sub-SMQs: alcohol related, congenital, familial, neonatal, and genetic disorders of the liver, liver infections, and pregnancy-related hepatic disorders.

Proposed SmPC Indicated Population

In comparison to the overall and compensated populations, the majority of hepatic TEAEs observed in OCA-treated subjects were meaningfully reduced in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the rates of hepatic PTs in the OCA group were lower than the placebo group (22 [27.2%] subjects in the OCA group and 29 [42.6%] subjects in the placebo group). The PT of portal hypertensive gastropathy occurred at a higher rate in the OCA group compared to the placebo group (3.7% in the OCA group and none in the placebo group). The majority of other reported PTs of hepatic TEAEs either occurred at a similar incidence across treatment groups or at a lower incidence in the OCA group than the placebo group.

The majority of hepatic TEAEs were mild to moderate in severity. The incidence of severe hepatic TEAEs was low across treatment groups and occurred in 1 (1.2%) subject each in the OCA group: hepatic enzyme increased blood bilirubin increased (unlikely related per Investigator) and potential liver injury events (see Section 2.8.3.4.1.3 for mini narrative on adjudicated potential liver injury events). None of these events were reported as life-threatening or fatal.

The incidence of serious hepatic TEAEs remained low overall (3 [3.7%] subjects in the OCA group and 2 [2.9%]) subjects in the placebo group).

Exposure-Adjusted Incidence of Hepatic Adverse Events of Special Interest

An analysis of exposure-adjusted incidences of hepatic TEAEs and serious hepatic TEAEs by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 70 and Table 71, respectively.

The trend for exposure-adjusted hepatic TEAEs was generally similar to those observed for the unadjusted rates. Importantly, when evaluating the clinically relevant serious hepatic events, no meaningful difference was observed in the exposure adjusted rates between the compensated and the proposed SmPC indicated populations.

Proposed SmPC Indicated Population

In comparison to the overall population, the incidence of exposure-adjusted hepatic TEAEs observed in OCA-treated subjects was meaningfully reduced in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the incidence of exposure-adjusted hepatic TEAEs was 11.844 per 100 PYs in the OCA group and 25.754 per 100 PYs in the placebo group. The incidence of exposure-adjusted serious hepatic TEAEs was 1.396 per 100 PYs in the OCA group and 1.385 per 100 PYs in the placebo group.

Table 70: Study 747-302 – Exposure-Adjusted Incidence Rate of Hepatic Treatment-Emergent Adverse Events in ≥2 Overall OCA-treated Subjects by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (FY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Hepatic TEAE	40.855 (337.42)	26.42 (302.8)	71.448 (33.59)	74.798 (29.41)	35.814 (203.83)	21.215 (273.39)	25.754 (112.60)	11.844 (185.75)	54.478 (124.82)	49.551 (117.05)
Blood bilirubin increased	7.253 (344.68)	4.903 (407.94)	13.151 (53.23)	11.818 (50.77)	6.176 (291.46)	3.920 (357.17)	5.549 (144.17)	1.886 (212.05)	8.478 (200.31)	8.168 (195.89)
Varices oesophageal	8.954 (312.73)	5.188 (385.5)	9.911 (50.45)	8.558 (46.74)	8.769 (262.28)	4.723 (338.76)	4.532 (132.40)	1.903 (210.22)	12.201 (189.52)	9.128 (175.28)
Ascites	6.303 (333.15)	4.472 (402.54)	16.239 (49.26)	20.118 (44.74)	4.579 (283.89)	2.515 (357.81)	2.105 (142.54)	0.465 (215.07)	9.443 (190.61)	9.068 (187.48)
Portal hypertensive gastropathy	2.026 (345.44)	3.501 (399.86)	5.797 (51.75)	5.800 (51.72)	1.362 (293.69)	3.160 (348.14)	0 (146.06)	1.419 (214.36)	3.511 (199.39)	5.836 (188.50)
Hepatic cirrhosis	2.296 (348.48)	2.463 (406.08)	0 (54.98)	1.837 (54.45)	2.726 (293.50)	2.559 (351.63)	2.066 (143.13)	0.938 (213.25)	2.435 (203.35)	4.149 (192.84)
Hepatic encephalopathy	3.162 (347.88)	1.95 (410.33)	12.306 (48.76)	9.990 (50.05)	1.672 (299.12)	0.833 (360.28)	0 (146.06)	0.466 (214.82)	5.450 (201.83)	3.580 (195.51)
Jaundice	2.896 (345.34)	1.919 (416.8)	7.569 (53.83)	3.716 (53.83)	2.051 (292.50)	1.653 (362.98)	2.104 (142.60)	1.892 (211.39)	3.453 (202.75)	1.947 (205.41)
Blood alkaline phosphatase increased	1.418 (352.52)	1.201 (416.32)	3.708 (53.94)	3.794 (52.71)	1.005 (298.58)	0.125 (363.61)	1.386 (144.30)	0 (215.07)	1.441 (208.23)	2.484 (201.26)
Oesophageal varices haemorrhage	1.422 (351.68)	1.206 (414.57)	1.822 (54.90)	3.927 (50.92)	1.348 (296.79)	0.825 (363.65)	1.385 (144.40)	0 (215.07)	1.447 (207.28)	2.506 (199.50)
Alanine aminotransferase increased	1.417 (352.87)	0.97 (412.37)	1.823 (54.87)	1.898 (52.68)	1.342 (298.01)	0.834 (359.69)	1.390 (143.88)	0.476 (210.15)	1.435 (208.99)	1.484 (202.22)
Aspartate aminotransferase increased	1.136 (351.97)	0.969 (412.59)	1.823 (54.87)	0 (54.48)	1.010 (297.10)	1.117 (358.12)	1.400 (142.90)	0.476 (210.15)	0.957 (209.07)	1.482 (202.44)
Drug-induced liver injury	0 (355.4)	0.954 (419.47)	0 (54.98)	1.833 (53.18)	0 (300.43)	0.819 (366.37)	0 (146.06)	0.931 (214.81)	0 (209.35)	0.977 (204.66)

Preferred Term, IRY (FY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Hyperbilirubinaemia	3.14 (350.34)	0.954 (419.08)	9.617 (51.99)	1.850 (54.06)	2.011 (298.35)	0.822 (365.02)	0.685 (145.97)	0.936 (213.64)	4.893 (204.36)	0.974 (205.44)
Hypoalbuminaemia	0.281 (355.33)	0.959 (419.06)	1.822 (54.90)	5.654 (53.06)	0 (300.43)	0.275 (363.90)	0 (146.06)	0.471 (212.18)	0.478 (209.27)	1.465 (204.77)
International normalised ratio increased	0.566 (353.62)	0.954 (419.35)	1.823 (54.85)	3.683 (54.31)	0.335 (298.77)	0.548 (365.04)	0 (146.06)	0.938 (213.32)	0.964 (207.56)	0.971 (206.03)
Hepatic cyst	0.282 (354.18)	0.72 (416.75)	1.860 (53.75)	0 (54.48)	0 (300.43)	0.828 (362.27)	0 (146.06)	0.948 (210.88)	0.480 (208.13)	0.486 (205.87)
Hepatic failure	1.189 (354.23)	0.718 (417.96)	3.653 (54.75)	1.835 (54.50)	0.668 (299.47)	0.550 (363.46)	0 (146.06)	0 (215.07)	1.922 (208.17)	1.479 (202.90)
Hepatic mass	0.853 (351.78)	0.721 (416.12)	1.823 (54.87)	1.939 (51.57)	0.674 (296.91)	0.549 (364.55)	0 (146.06)	0 (215.07)	1.458 (205.72)	1.492 (201.05)
Portal hypertension	0.568 (352.18)	0.716 (418.89)	0 (54.98)	0 (54.48)	0.673 (297.20)	0.823 (364.41)	0.698 (143.28)	0.466 (214.67)	0.479 (208.89)	0.979 (204.22)
Bilirubin conjugated increased	1.134 (352.89)	0.475 (421.17)	1.822 (54.89)	3.678 (54.38)	1.007 (297.99)	0 (366.78)	0.687 (145.51)	0 (215.07)	1.447 (207.38)	0.970 (206.10)
Gastric varices	0 (355.4)	0.481 (415.83)	0 (54.98)	0 (54.48)	0 (300.43)	0.553 (361.36)	0 (146.06)	0 (215.07)	0 (209.35)	0.996 (200.77)
Hepatic enzyme increased	1.129 (354.39)	0.475 (420.8)	0 (54.98)	0 (54.48)	1.336 (299.41)	0.546 (366.32)	2.758 (145.04)	0.932 (214.61)	0 (209.35)	0 (206.19)
Hepatic fibrosis	0.282 (355.09)	0.477 (419.41)	1.829 (54.66)	1.897 (52.71)	0 (300.43)	0.273 (366.70)	0 (146.06)	0 (215.07)	0.478 (209.03)	0.979 (204.34)
Hepatomegaly	0.282 (354.5)	0.476 (420.53)	0 (54.98)	0 (54.48)	0.334 (299.52)	0.546 (366.06)	0.689 (145.15)	0 (215.07)	0 (209.35)	0.973 (205.47)
Ocular icterus	1.435 (348.55)	0.476 (420.51)	3.775 (52.98)	1.861 (53.73)	1.015 (295.57)	0.273 (366.78)	0 (146.06)	0 (215.07)	2.469 (202.49)	0.974 (205.44)
Spider naevus	1.141 (350.67)	0.477 (419.58)	0 (54.98)	0 (54.48)	1.353 (295.69)	0 (366.78)	2.121 (141.43)	0 (215.07)	0.478 (209.23)	0.978 (204.51)

AE=adverse event; IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension; PY=Patient-years; PT=preferred term; SmPC=Summary of Product Characteristics; SOC=system organ class; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

Note: Patient-years = sum of individual PYs for each event. Each individual's PYs will be derived as the first onset date of an event or min of (last investigational product dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Table 71: Study 747-302 – Exposure-Adjusted Incidence Rate of Hepatic Serious Treatment-Emergent AEs by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Hepatic Serious TEAE	4.620 (346.32)	3.646 (411.36)	13.864 (50.49)	12.276 (48.88)	3.042 (295.83)	2.483 (362.49)	1.385 (144.40)	1.396 (214.86)	6.934 (201.92)	6.107 (196.51)
Oesophageal varices haemorrhage	1.422 (351.68)	0.958 (417.57)	1.822 (54.90)	1.855 (53.92)	1.348 (296.79)	0.825 (363.65)	0.000 (0.00)	0 (215.07)	1.447 (207.28)	1.975 (202.50)
Hepatic encephalopathy	1.413 (353.89)	0.718 (417.71)	3.684 (54.29)	3.927 (50.93)	1.001 (299.60)	0.273 (366.98)	0 (146.06)	0 (215.07)	2.406 (207.83)	1.480 (202.64)
Ascites	1.139 (351.27)	0.477 (419.55)	7.868 (50.84)	1.886 (53.02)	0 (300.43)	0.273 (366.53)	0 (146.06)	0 (215.07)	1.949 (205.21)	0.978 (204.49)
Hepatic cirrhosis	0 (355.40)	0.475 (421.12)	0 (54.98)	0 (54.48)	0 (300.43)	0.545 (366.64)	0 (146.06)	0 (215.07)	0 (209.35)	0.971 (206.05)
Hepatic failure	0.563 (355.26)	0.476 (420.49)	1.821 (54.91)	1.835 (54.50)	0.333 (300.38)	0.273 (365.99)	0 (146.06)	0 (215.07)	0.956 (209.21)	0.974 (205.43)
Blood bilirubin increased	0 (355.40)	0.237 (421.23)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.76)	0 (146.06)	0.465 (215.04)	0 (209.35)	0 (206.19)
Drug-induced liver injury	0 (355.40)	0.237 (421.16)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.68)	0 (146.06)	0.465 (214.97)	0 (209.35)	0 (206.19)
Hepatic enzyme increased	0 (355.40)	0.237 (421.17)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.70)	0 (146.06)	0.465 (214.98)	0 (209.35)	0 (206.19)
Jaundice hepatocellular	0 (355.40)	0.237 (421.20)	0 (54.98)	1.838 (54.42)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.13)
Varices oesophageal	0.281 (355.27)	0.238 (420.47)	1.823 (54.84)	0 (54.48)	0 (300.43)	0.273 (365.99)	0 (146.06)	0 (215.07)	0.478 (209.21)	0.487 (205.40)
Hepatic function abnormal	0.281 (355.27)	0 (421.26)	1.823 (54.84)	0 (54.48)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.22)	0 (206.19)
Hepatic hydrothorax	0.281 (355.31)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (300.35)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.26)	0 (206.19)

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Hepatocellular carcinoma	0.365 (355.28)	0 (421.26)	1.822 (54.90)	0 (54.48)	0.333 (300.38)	0 (366.78)	0 (146.06)	0 (215.07)	0.956 (209.22)	0 (206.19)

AE=adverse event; IRY=number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo;

PH=evidence portal hypertension; PY=patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 63, Ad hoc 63.1, Ad hoc 63.2

Evaluation of Drug-induced Serious Hepatotoxicity

Evaluation of drug-induced serious hepatotoxicity (eDISH) screening plot analyses were based on central and local laboratory results. Each data point represents the peak ALT and peak total bilirubin values from a single subject, and these values may have occurred at different timepoints over the observation period. As a sensitivity analysis, eDISH figures were also presented for the entire course of the study up to the last safety study day.

The tabulated summary for the overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 72. eDISH comparing proposed SmPC indicated versus proposed SmPC contraindicated populations for total bilirubin vs. ALT are presented in Figure 31.

Proposed SmPC Indicated Population

The majority of subjects were in the normal range for ALT and total bilirubin peak excursions, with more subjects in the OCA group represented in the normal range compared to placebo.

In an evaluation of all postbaseline measurements for the proposed SmPC indicated population, there was a total of 10 (12.3%) subjects in the OCA group and 11 (16.2%) subjects in the placebo group in the biochemical Hy's law range (peak ALT of >3x ULN and peak total bilirubin >2x ULN).

Table 72: Evaluation of Drug-Induced Serious Hepatotoxicity Summary – Conventional Units by Baseline Disease Stage (Safety Population [N=344])

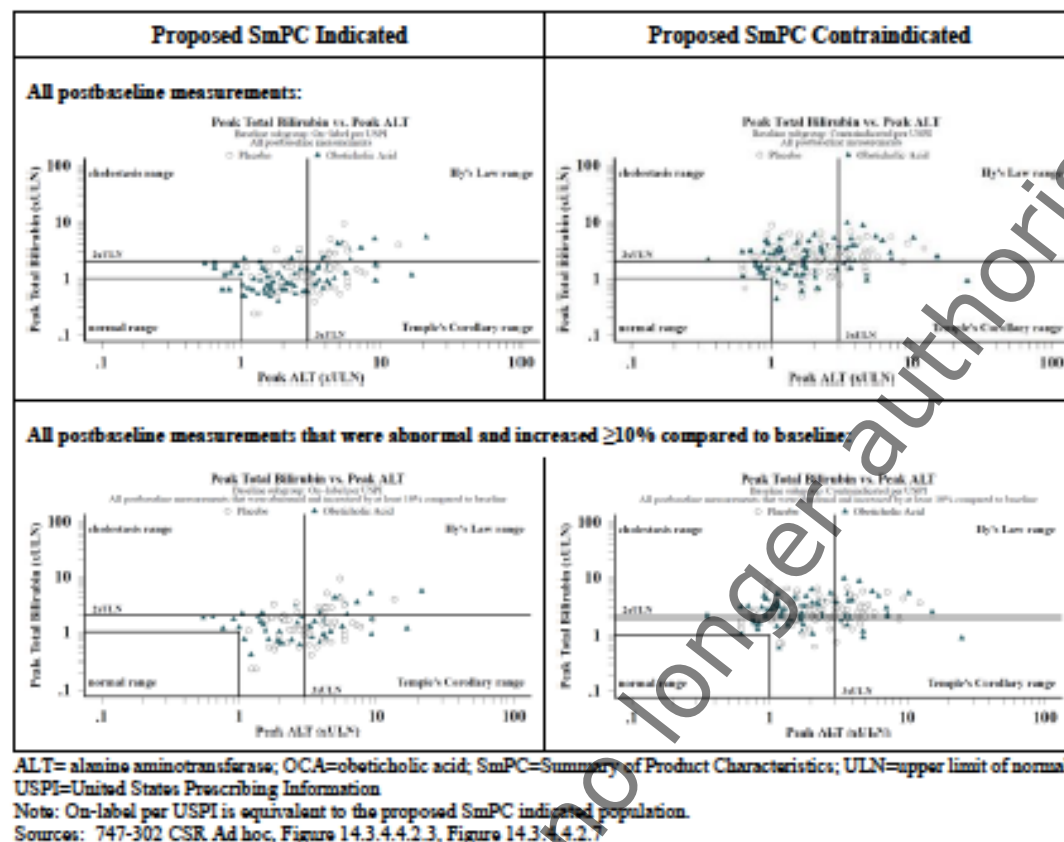
Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
All postbaseline measurements										
Normal Range	59 (35.5)	83 (49.4)	5 (13.5)	7 (21.9)	54 (41.9)	76 (55.9)	31 (45.6)	49 (60.5)	28 (28.6)	34 (39.1)
Temple's Corollary Range	28 (16.9)	24 (14.3)	0	1 (3.1)	28 (21.7)	23 (16.9)	22 (32.4)	18 (22.2)	6 (6.1)	6 (6.9)
Cholestasis Range	43 (25.9)	35 (20.8)	22 (59.5)	15 (46.9)	21 (16.3)	20 (14.7)	3 (4.4)	3 (3.7)	40 (40.8)	32 (36.8)
Hy's Law	35 (21.1)	24 (14.3)	10 (27.0)	9 (28.1)	25 (19.4)	15 (11.0)	11 (16.2)	10 (12.3)	24 (24.5)	14 (16.1)
All postbaseline measurements that were abnormal and increased by at least 10% compared to baseline										
Normal Range	41 (24.7)	38 (22.6)	2 (5.4)	5 (15.6)	39 (30.2)	33 (24.3)	22 (32.4)	21 (25.9)	19 (19.4)	17 (19.5)
Temple's Corollary Range	27 (16.3)	21 (12.5)	0	1 (3.1)	27 (20.9)	20 (14.7)	21 (30.9)	15 (18.5)	6 (6.1)	6 (6.9)
Cholestasis Range	42 (25.3)	35 (20.8)	21 (56.8)	14 (43.8)	21 (16.3)	21 (15.4)	3 (4.4)	3 (3.7)	39 (39.8)	32 (36.8)
Hy's Law	34 (20.5)	23 (13.7)	9 (24.3)	9 (28.1)	25 (19.4)	14 (10.3)	11 (16.2)	10 (12.3)	23 (23.5)	13 (14.9)

OCA=obstructive acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline. Sources: 747-302 Ad hoc, Figure 14.3.4.4.1.3, Figure 14.3.4.4.2.3, Figure 14.3.4.4.3.3, Figure 14.3.4.2.9.1.4, Figure 14.3.4.4.1.7, Figure 14.3.4.4.2.7, Figure 14.3.4.4.3.7

Figure 31: Evaluation of Drug-Induced Serious Hepatotoxicity - Total Bilirubin vs ALT by Baseline Disease Stage (Proposed SmPC Indicated vs Proposed SmPC Contraindicated Populations) (Safety Population [N=344])



Adjudicated Hepatic Safety Events

As a retrospective assessment, hepatic safety events were identified via a set of biochemical and adverse event (SMQ based) triggers per HSAC. These cases underwent clinical review by the HSAC of all available data (medical history, concomitant medications, vital signs, lab values, liver imaging, pathology reports, and noninvasive tests) for each identified subject to determine liver injury status (including causality and severity). The adjudication committee remained blinded to investigational product allocation and assessed the potential for liver injury, assigned likelihood of causality and degree of severity, and provided potential etiology for all cases.

Potential hepatic safety events (e.g., DILI) were identified programmatically using SMQ searches of hepatic AEs, central and local laboratory data, and investigational product interruption records from the clinical database for hepatic injury. Hepatic AEs are defined as events included in the Hepatic Disorders SMQ, excluding the following sub-SMQs: alcohol related; congenital, familial, neonatal, and genetic disorders of the liver; liver infections; and pregnancy-related hepatic disorders. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, lab values, liver imaging and pathology reports, and non-invasive tests (NITs). Adjudication committees remained blinded to investigational product allocation.

Per the HSAC Charter, all cases adjudicated as potential evidence for liver injury are then assessed for causality (investigational product relatedness) and severity based on the Drug-Induced Liver Injury Network (DILIN) index (Table 11).

Table 11: Hepatic Safety Adjudication Causality Assessment

Causality Assessment Score	Descriptor	Details
Insufficient Information	Insufficient details in case package to make any assessment	Cases that do not have enough information provided to be assigned one of the below 4 categories, will be designated as having insufficient information. Members will be asked to specify what additional information is required to complete the causality assessment.
Unlikely drug related	Confidence of causality assessment is <25%	A role for study drug is unlikely based on the available information. Another etiology is likely to be the cause of injury.
Possible drug related	Confidence of causality assessment is between 25% to 49%	The available evidence does not definitively exclude the possibility of a causal role for study drug, but another etiology is more likely to be the cause of injury.
Probable drug related	Confidence of causality assessment is between 50% to 74%	Causality is supported by the preponderance of evidence; the drug is more likely to be the causal agent rather than not. Testing rules out some/most other likely causes.
Highly likely drug related	Confidence of causality assessment is between 75% to 100%	The evidence is beyond a reasonable doubt (positive rechallenge)

Blinded case level assessments of hepatic events in the overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations are presented in Table 78.

All hepatic events had sufficient information for a causality assessment. There was 1 subject in the OCA group and 1 subject in the placebo group with hepatic events that were not assessable for a severity assessment.

Proposed SmPC Indicated Population

In comparison with the overall population, the incidence of hepatic safety events was lower in OCA-treated subjects in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), hepatic safety event rate in the OCA group (29 [35.8%] subjects) was lower compared to the placebo group (28 [41.2%] subjects).

The majority of the hepatic safety events were mild (18 [22.2%] subjects in the OCA group and 14 [20.6%] subjects in the placebo group) and moderate (8 [9.9%] subjects in the OCA group and 11 [16.2%] subjects in the placebo group). The incidence of moderate-severe, and severe hepatic safety events was similar across treatment groups.

After blinded HSAC review, 4 subjects with 9 events in the OCA group and 1 subject with 2 events in the placebo group reported hepatic safety events that were adjudicated positively adjudicated as possibly related to investigational product (see mini narratives below). There were no potential liver injury events in the proposed SmPC indicated population assessed as probable or highly likely related to investigational product by the HSAC. The majority of subjects with possible causality were on concomitant medications with potential hepatotoxicity at the time of the potential liver injury event. All possible hepatic safety events occurred within the first 3 months of investigational product, and no uniform pattern of liver injury was present.

A listing of the positively adjudicated possible related events in the proposed SmPC indicated population are described below and presented in Table 74.

OCA:

- A female subject was found to have elevated transaminases (ALT and aspartate aminotransferase [AST] >5x baseline) on 02 Aug 2017 (Study Day 92). Other liver biochemistry was stable and consistent with baseline. Concomitant and potential hepatotoxic medication included rifampicin, which was initiated on Study Day 15. Rifampicin and investigational product were stopped, and the subject was admitted for a liver biopsy. Synthetic liver function remained normal, and no subsequent endpoint was reached. Elevated transaminases returned to baseline approximately 1 month after withdrawal of rifampicin and OCA. The Investigator judged the cause of the potential liver injury event to be most likely rifampicin.
- A female subject was found to have an elevation in all liver biochemistries (ALT and AST >5x ULN and total bilirubin >3x ULN) on 22 Jun 2018 (Study Day 80). The subject had been diagnosed with cholelithiasis on 22 May 2018 (Study Day 49). It is unclear from the documentation whether there were any gallstone-related or obstructive symptoms. Investigational product was ceased on 22 Jun 2018 (Study Day 80) and the subject underwent a laparoscopic cholecystectomy on 02 Aug 2018 (Study Day 121). On 12 Aug 2018 (Study Day 131) all liver biochemistry had improved significantly; no further blood tests are available for review (end of study [EOS]). The subject was also taking ibuprofen and simvastatin at the time of the event.
- A female subject experienced a significant elevation in alkaline phosphatase (ALP) (ALP >1000 U/L and >5% increase from baseline) on Study Day 91 with a lesser degree of gamma-glutamyl transferase (GGT), total bilirubin, ALT, and AST elevation. OCA was dose reduced to 10 mg every other day on Study Day 135. ALP remained persistently elevated and OCA was withdrawn on Study Day 241 due to pruritis and rash. There was mild improvement in peak ALP after OCA withdrawal, but ALP did not return to baseline and remained >1000 U/L with a >15% increase from baseline. There was no associated synthetic liver function abnormality and the subject did not reach any endpoint by the end of study.

- A female subject experienced a single occasion of elevated ALT, AST (ALT/AST >3x baseline and >5x ULN), and GGT, without total bilirubin or ALP changes on Study Day 92. No changes were made to OCA dosing. Subsequent labs showed resolution of lab abnormalities without OCA dechallenge.

Placebo:

- A female subject with an elevation of predominantly GGT (467 U/L from baseline value of 261 U/L) and total bilirubin (2.5 mg/dL from baseline value of 1.4 mg/dL) with more modest elevation of ALT, AST, and ALP on Study Day 104. Investigational product was discontinued and the event was judged by the Investigator as probably related to investigational product. Concomitant medications included rifampicin at the time of the event. Laboratory results after Study Day 104 were unavailable.

Table 73: Study 747-302: Summary of Hepatic Safety Events by Highest Causality and Highest Severity by Blinded HSAC Assessments by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=69	OCA N=81	PBO N=98	OCA N=87
Hepatic Safety Events, n (%) [e]	99 (59.6) [230]	85 (50.6) [189]	27 (73.0) [63]	26 (81.3) [66]	72 (55.8) [167]	59 (43.4) [123]	28 (41.1) [64]	29 (35.8) [58]	71 (72.4) [166]	56 (64.4) [131]
Highest Causality by Blinded HSAC, n (%) [e]										
Highly Likely Drug Related	0	0	0	0	0	0	0	0	0	0
Probable Drug Related	0	1 (0.6) [4]	0	1 (3.1) [4]	0	0	0	0	0	1 (1.1) [4]
Possible Drug Related	8 (4.8) [22]	17 (10.1) [38]	4 (10.8) [11]	7 (21.9) [16]	4 (3.1) [11]	10 (7.4) [22]	1 (1.5) [2]	4 (4.9) [9]	7 (7.1) [20]	13 (14.9) [29]
Unlikely Drug Related	91 (54.8) [205]	67 (39.9) [141]	23 (62.2) [51]	18 (56.3) [40]	68 (52.7) [154]	49 (36.0) [101]	27 (39.7) [62]	25 (30.9) [49]	64 (65.3) [143]	42 (48.3) [92]
Insufficient Information	0	0	0	0	0	0	0	0	0	0
Highest Severity by Blinded HSAC, n (%)										
Mild	41 (24.7)	37 (22.0)	5 (13.5)	3 (9.4)	36 (27.9)	34 (25.0)	14 (20.6)	18 (22.2)	27 (27.6)	19 (21.8)
Moderate	46 (27.7)	33 (19.6)	17 (45.9)	16 (50.0)	29 (22.5)	17 (12.5)	11 (16.2)	8 (9.9)	35 (35.7)	25 (28.7)
Moderate-Severe	4 (2.4)	8 (4.8)	1 (2.7)	4 (12.5)	3 (2.3)	4 (2.9)	1 (1.5)	2 (2.5)	3 (3.1)	6 (6.9)
Severe	7 (4.2)	5 (3.0)	4 (10.8+)	2 (6.3)	3 (2.3)	3 (2.2)	1 (1.5)	0	6 (6.1)	5 (5.7)
Fatal	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Not Assessable	1 (0.6)	1 (0.6)	0	0	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)	0	0

AE=adverse event; e=number of events; HSAC=Hepatic Safety Adjudication Committee; OCA=obeticholic acid; PBO=placebo; PH=evidence of portal hypertension; SmPC=Summary of Product Characteristic

Notes: Adjudicated data were used. Laboratory triggers were identified for on-treatment subjects + 100 days after initiation of drug holiday/interruption or discontinuation of investigational product.

AE triggers were identified post-baseline and prior to discontinuation of investigational product or within 30 days after discontinuation of investigational product. Data after a patient began commercial OCA were excluded from analyses.

For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group and subgroup.

Table 74: Study 747-302: Listing of Subjects in the OCA group with Hepatic Safety Events Assessed as at Least Possible Related to Investigational Product by the Blinded HSAC in the Proposed SmPC Indicated Population (N=149)

Subject ID	IP	Blinded HSAC Highest Severity	Days OCA start to injury onset	Transaminases elevated	ALP & GGT elevated	Bilirubin elevation above BL	Alternate Diagnosis / Concomitant Medication	MAH Clinical Comments
136002	OCA	Moderate-severe	85	Y	N	N	Rifampicin	Investigator assessment: most likely due to Rifampicin
162004	OCA	Moderate	80	Y	N	Y	Ibuprofen, Simvastatin, Biliary stone passage	Cholecystolithiasis Dx D49 Unexpectedly high GGT at screening No blood tests after cholecystectomy
219036	OCA	Mild	91	N	Y	N	-	Very high ALP at screening, other liver biochemistry at ULN (fluctuating), significant spike in ALT but no major elevation in other liver biochemistry and no synthetic function impairment (Bili, Alb, INR). ALP remained high despite IP cessation
238006	OCA	Mild	97	Y	N	N	Intercurrent illness	Mild, OCA continued throughout (5 years), no further events, good response
297004	PBO	Moderate	104	N	Y	Y	Rifampicin	-

Alb=albumin; Bili=bilirubin; BL=baseline; HSAC=Hepatic Safety Adjudication Committee; INR= international normalized ratio; N=No; OCA=obeticholic acid; PBO=placebo; SmPC=Summary of Product Characteristics; Y=Yes
Source: Data on file

Table 74: Study 747-302: Listing of Subjects in the OCA group with Hepatic Safety Events Assessed as at Least Possible Related to Investigational Product by the Blinded HSAC in the Proposed SmPC Indicated Population (N=149)

IP	Blinded HSAC Highest Severity	Days OCA start to injury onset	Transaminases elevated	ALP & GGT elevated	Bilirubin elevation above BL	Alternate Diagnosis / Concomitant Medications	MAH Clinical Comments
OCA	Moderate-severe	85	Y	N	N	Rifampicin	Investigator assessment: most likely due to Rifampicin
OCA	Moderate	80	Y	N	Y	Roprosin, Simvastatin, Biliary stone passage	Cholecystolithiasis Dx D+9 Unexpectedly high GGT at screening No blood tests after cholecystectomy
OCA	Mild	91	N	Y	N	-	Very high ALP at screening, other liver biochemistry at ULN (fluctuating), significant spike in ALT but no major elevation in other liver biochemistry and no synthetic function impairment (Bili, Alb, INR). ALP remained high despite IP cessation
OCA	Mild	97	Y	N	N	Intercurrent illness	Mild, OCA continued throughout (5 years), no further events, good response
PBO	Moderate	104	N	Y	Y	Rifampicin	-

Alb=albumin; Bili=bilirubin; BL=baseline; HSAC=Hepatic Safety Adjudication Committee; INR= international normalized ratio; N=No; OCA=obeticholic acid; PBO=placebo; SmPC=Summary of Product Characteristics; Y=Yes
Source: Data on file

Exposure-Adjusted Incidence of Adjudicated Drug-Induced Liver Injury

An analysis of exposure-adjusted incidences of adjudicated hepatic safety events assessed as at least possibly related by the HSAC by baseline disease stage is presented in Table 75.

Proposed SmPC Indicated Population

In comparison to the overall population, the exposure-adjusted incidence of hepatic safety events that were assessed as possible, probable, or highly likely by the HSAC in the OCA-treated subjects was lower in the proposed SmPC indicated population. Of note, none of the cases in the proposed SmPC indicated population were considered probable or highly likely by the HSAC.

In the proposed SmPC indicated population (N=149), the exposure-adjusted incidence of hepatic safety events that were assessed as at least possible by the HSAC was higher in the OCA group (1.910 per 100 PYs) compared to the placebo group (0.685 per 100 PYs). The exposure-adjusted incidence of hepatic safety events that were assessed as at least possible and moderate in severity was higher in the OCA group (0.931 per 100 PYs) compared to the placebo group (0.685 per 100 PYs).

Table 75: Study 747-302: Exposure Adjusted Incidence Rate of Hepatic Safety Event Cases Assessed as at Least Possible Related to Investigational Product by Severity by Overall and Baseline Disease Stage (Safety Population [N=334])

n (IR)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Adjudicated Hepatic Safety Events (Possible/probably/highly likely causality and $\geq$ mild severity)	8 (2.325)	18 (4.521)	4 (7.470)	8 (18.169)	4 (1.377)	10 (2.824)	1 (0.685)	4 (1.910)	7 (3.533)	14 (7.420)
Adjudicated Hepatic Safety Events (Possible/probably/highly likely causality and $\geq$ moderate severity)	7 (2.012)	12 (2.923)	4 (7.470)	7 (14.576)	3 (1.019)	5 (1.379)	1 (0.685)	2 (0.931)	6 (2.971)	10 (5.111)

AE=adverse event; IR=number of patients with event per 100 patient year; OCA=obeticholic acid; PH=portal hypertension; SmPC=Summaries of product characteristics
Notes: Adjudicated data are used. Laboratory triggers are identified for on-treatment subjects + 100 days after initiation of drug holiday/interruption or discontinuation of investigational product. AE triggers are identified post-baseline and prior to discontinuation of IP or within 30 days after discontinuation of investigational product. Data after a patient begins commercial OCA are excluded from analyses.
Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last investigational product date-30 days, commercial OCA date, death date, and of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique event.
For each row category, a subject with two or more events in that category is counted only once for the subject count.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302 Ad hoc, Table 14.3.4.2.20, Table 14.3.4.2.20.1, Table 14.3.4.2.20.2

Adjudicated Hepatic Outcomes

All hepatic outcomes (EMA Composite Endpoint and FDA Expanded Endpoint as defined in Table 76) were adjudicated by a blinded, independent HOC to determine whether they met the protocol-specified endpoint criteria.

Subsequently, per request from the FDA, all EMA and FDA expanded hepatic outcome events underwent additional blinded clinical review retrospectively by an independent HSAC to determine causality (highly likely drug related, probable drug related, possible drug related, unlikely drug related, insufficient information).

Table 76: Study 747-302 –EMA Composite Endpoint and FDA Expanded Endpoints

EMA Composite Endpoint: All Subjects
• Death (all-cause) • Liver transplant • MELD score ≥ 15 • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: – Variceal bleed – Hepatic encephalopathy (as defined by a West Haven score of ≥ 2) – Spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis) • Uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)
FDA Expanded Endpoints:
Group 1 (applies to all subjects)
• Death (all-cause) • Liver transplant • Hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥ 2), spontaneous bacterial peritonitis (confirmed by diagnostic paracentesis OR presence of $>250/\text{mm}^3$ polymorph leukocyte [PMNs] in the ascitic fluid), or bacterial empyema (confirmed by diagnostic thoracentesis OR presence of $>250/\text{mm}^3$ PMNs in the pleural fluid) • Uncontrolled or refractory ascites (requiring large volume paracentesis) • PH syndromes (hepatorenal syndrome as defined by International Ascites Club [Angeli 2019], portopulmonary syndrome, or hepatopulmonary syndrome) • MELD-Na score ≥ 15 if MELD-Na < 12 at baseline • MELD score ≥ 15 if MELD-Na ≥ 12 at baseline
Group 2 (applies to subjects without decompensation at Baseline)
Progression to decompensated liver disease (for subjects without decompensation at baseline), prioritized as follows: • New onset of hepatic hydrothorax, variceal bleeding, or ascites requiring treatment with sodium restriction, diet modification, or diuretics • Hepatic encephalopathy requiring lactulose and/or rifaximin • New onset of Child-Pugh ≥ 7 or total bilirubin $> 3 \text{ mg/dL}$
Group 3 (applies to subjects without decompensation or clinical evidence of portal hypertension at Baseline)
Progression to clinical evidence of PH without decompensation (for subjects without decompensation or clinical evidence of portal hypertension at baseline) • Endoscopic evidence of PH without bleeding (i.e., gastroesophageal varices [requiring banding or progression to large varices if no or small varices were observed at baseline] or portal hypertensive gastropathy • Platelets $< 150 \times 10^9/\text{L}$ with splenomegaly and/or with transient elastography $> 15 \text{ kPa}$

Proposed SmPC Indicated Population

- EMA Composite Endpoint: A total of 1 subject with 1 event in the OCA group and 1 subject in the placebo group with 1 event were considered possibly related to investigational product by the HSAC.

A subject in the OCA group had a liver transplant (see Question #13 for more details); Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that this subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

- A subject in the placebo group had a MELD score ≥ 15

• FDA Expanded Endpoint: A total of 3 (3.7%) subjects with 4 events in the OCA group and 1 (1.5%) subject with 4 events in the placebo group were considered possibly related to investigational product by the HSAC.

- One subject in the OCA group had a liver transplant; see Question #13 for more details); Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that the subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC
- One subject in the OCA group had new onset of total bilirubin >3 mg/dL
- One subject in the OCA group had a new onset of CP ≥ 7 and new onset of total bilirubin >3 mg/dL
- One subject in the placebo group had a MELD score ≥ 15

No subjects in either the OCA group or the placebo group had hepatic outcomes adjudicated as probable or highly likely, and the majority of hepatic outcomes were adjudicated as unlikely.

2.8.3.4.1.5. Adjudicated Liver Transplants and Deaths

All liver transplants and deaths were independently adjudicated in a blinded manner by the HSAC.

Adjudicated liver transplants and deaths by blinded HSAC causality assessment are summarized in Question #13.

Cholecystitis/Cholelithiasis

Cholecystitis/cholelithiasis TEAESIs were defined by Gallbladder related disorders narrow SMQ and Gallstone related disorders narrow SMQ.

Cholecystitis/cholelithiasis TEAESIs and serious cholecystitis/cholelithiasis TEAESIs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 77 and Table 78, respectively.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), 3 (3.7%) subjects in the OCA group and 1 (1.5%) subject in the placebo group reported a cholecystitis/cholelithiasis TEAESI. Cholelithiasis was the only PT reported across treatment groups. All cholecystitis/cholelithiasis TEAESIs were mild to moderate in severity.

Of these, 1 OCA-treated subject in the proposed SmPC indicated population reported a serious TEAESI:

- A female subject with PBC in the proposed SmPC indicated population reported a serious TEAESI of cholelithiasis on 16 Dec 2019 (Study Day 1133), approximately 3 years and 1 month after initiation of OCA. The subject had a history of gallbladder stones and was hospitalized for an elective laparoscopic assisted cholecystectomy due to cholelithiasis. The event of cholelithiasis was considered resolved on 17 Dec 2019 (Study Day 1134). The Investigator and the MAH assessed the event of cholelithiasis as moderate in severity and unlikely related to the investigational product.

In addition, 1 OCA-treated subject in the proposed SmPC indicated population reported a serious AESI of cholelithiasis that was not treatment-emergent (i.e., after 30 days of permanently discontinuing investigational product), which was considered possibly related by the Investigator and unlikely related by the Marketing Authorization Holder (MAH). The event was assessed as moderate in severity and resolved after an elective laparoscopic cholecystectomy was performed.

Table 77: Study 747-302 - Cholecystitis/Cholelithiasis Treatment-Emergent AESIs in ≥1 Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cholecystitis/Cholelithiasis TEAE	9 (5.4)	9 (5.4)	1 (2.7)	2 (6.3)	8 (6.2)	7 (5.1)	1 (1.5)	3 (3.7)	8 (8.2)	6 (6.9)
Cholelithiasis	4 (2.4)	7 (4.2)	0	1 (3.1)	4 (3.1)	6 (4.4)	1 (1.5)	3 (3.7)	3 (3.1)	4 (4.6)
Hyperplastic cholecystopathy	0	2 (1.2)	0	0	0	2 (1.5)	0	0	0	2 (2.3)
Bile duct stone	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Cholecystitis acute	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Biliary colic	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0
Cholecystitis	3 (1.8)	0	1 (2.7)	0	2 (1.6)	0	0	0	3 (3.1)	0
Cholecystitis chronic	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2

Table 78: Study 747-302 - Cholecystitis/Cholelithiasis Serious Treatment-Emergent AESIs in ≥1 Overall Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Serious Cholecystitis/Cholelithiasis TEAE	2 (1.2)	3 (1.8)	1 (2.7)	1 (3.1)	1 (0.8)	2 (1.5)	0	1 (1.2)	2 (2.0)	2 (2.3)
Bile duct stone	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Cholecystitis acute	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Cholelithiasis	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Cholecystitis	2 (1.2)	0	1 (2.7)	0	1 (0.8)	0	0	0	2 (2.0)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 62, Ad hoc 62.1, Ad hoc 62.2

Exposure-Adjusted Incidence of Cholecystitis/Cholelithiasis Adverse Events of Special Interest

An analysis of exposure-adjusted incidences of cholecystitis/cholelithiasis TEAEs and serious cholecystitis/cholelithiasis TEAEs by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 79 and Table 80.

Proposed SmPC Indicated Population

The incidence of exposure-adjusted cholecystitis/cholelithiasis TEAEs was 1.416 per 100 PYs in the OCA group and 0.692 per 100 PYs in the placebo group. The incidence of exposure-adjusted serious cholecystitis/cholelithiasis TEAEs was 0.468 per 100 PYs in the OCA group and 0 per 100 PYs in the placebo.

Table 79: Study 747-302 – Exposure-Adjusted Incidence Rate of Cholecystitis/Cholelithiasis Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cholecystitis/Cholelithiasis TEAE	2.605 (345.51)	2.225 (404.56)	1.836 (54.45)	3.966 (50.43)	2.749 (291.05)	1.977 (354.13)	0.692 (144.54)	1.416 (211.92)	3.981 (200.96)	3.115 (182.64)
Cholelithiasis	1.136 (352.07)	1.719 (407.28)	0 (54.98)	1.981 (50.49)	1.346 (297.10)	1.682 (356.79)	0.692 (144.54)	1.416 (211.92)	1.416 (202.33)	2.048 (195.36)
Hyperplastic cholecystopathy	0 (355.40)	0.480 (417.02)	0 (54.98)	0 (54.48)	0 (300.43)	0.552 (362.54)	0 (146.06)	0 (215.07)	0 (209.35)	0.990 (201.95)
Bile duct stone	0 (355.40)	0.238 (420.93)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.45)	0 (146.06)	0 (215.07)	0 (209.35)	0.486 (205.86)
Cholecystitis acute	0 (355.40)	0.237 (421.20)	0 (54.98)	1.838 (54.42)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.14)
Biliary colic	0.283 (353.18)	0 (421.26)	0 (54.98)	0 (54.48)	0.335 (298.20)	0 (366.78)	0 (146.06)	0 (215.07)	0.483 (207.12)	0 (206.19)
Cholecystitis	0.853 (351.85)	0 (421.26)	1.836 (54.45)	0 (54.48)	0.673 (297.39)	0 (366.78)	0 (146.06)	0 (215.07)	1.458 (205.79)	0 (206.19)
Cholecystitis chronic	0.282 (354.62)	0 (421.26)	0 (54.98)	0 (54.48)	0.334 (299.64)	0 (366.78)	0 (146.06)	0 (215.07)	0.479 (208.56)	0 (206.19)

AE=adverse event; IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension; PY=Patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Table 80: Study 747-302 – Exposure-Adjusted Incidence Rate of Cholecystitis/Cholelithiasis Serious Treatment-Emergent AESIs by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cholecystitis/Cholelithiasis Serious TEAE	0.568 (352.35)	0.715 (419.74)	1.836 (54.45)	1.838 (54.42)	0.336 (297.90)	0.547 (365.32)	0 (146.06)	0.468 (213.70)	0.969 (206.30)	0.971 (206.05)
Bile duct stone	0 (355.40)	0.237 (421.17)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.69)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.10)
Cholecystitis acute	0 (355.40)	0.237 (421.17)	0 (54.98)	1.838 (54.42)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.14)
Cholelithiasis	0 (355.40)	0.238 (419.89)	0 (54.98)	0 (54.48)	0 (300.43)	0.274 (365.41)	0 (146.06)	0.468 (213.70)	0 (209.35)	0 (206.19)
Cholecystitis	0.568 (352.35)	0 (421.26)	1.836 (54.45)	0 (54.48)	0.336 (297.90)	0 (366.78)	0 (146.06)	0 (215.07)	0.969 (206.30)	0 (206.19)

AE=adverse event; IRY=number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension; PY=Patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad hoc 63, Ad hoc 63.1, Ad hoc 63.2

Cardiovascular

A comprehensive evaluation of CV events was performed, including analyses of CV events by PT, CV TEAESIs (defined in the section below), adjudication of a broad set of CV trigger events by an independent adjudication committee, changes in lipoproteins, and Framingham Risk Score (FRS).

Given the results outlined below, the MAH does not propose to include CV-identified risk in the proposed SmPC.

Investigator-Reported Cardiovascular AESIs

CV TEAEs were defined by the embolic and thrombotic events broad SMQ, ischaemic heart disease broad SMQ, or central nervous system vascular disorders narrow SMQ. Of note, 2 events of TTP in 2 OCA treated subjects were captured in the SMQ search criteria for CV TEAEs. However, since the underlying pathophysiology for TTP is not related to atherosclerotic vascular disease, the TTP cases are described in more detail in the renal TEAE section.

CV TEAEs and serious CV TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 81 and Table 82, respectively.

Proposed SmPC Indicated Population

In comparison to the overall population, the rate for majority of CV TEAEs observed in OCA-treated subjects was significantly lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), 5 (6.2%) subjects in the OCA group and 2 (2.9%) subjects in the placebo group reported a CV TEAE.

Apart from TTP, which is described in more detail in the renal TEAE section, no pattern was observed for individual CV PTs and no CV PT was reported by > 1 subject in either treatment group.

The incidence of serious CV TEAEs was similar across treatment groups (2.5% in the OCA group and 1.5% in the placebo group), with 2 and 1 subjects who reported serious TEAEs of TTP and cerebrovascular accident, respectively.

Table 81: Study 747-302 - Cardiovascular Treatment-Emergent AESIs in ≥1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cardiovascular TEAE	7 (4.2)	16 (9.5)	2 (5.4)	5 (15.6)	5 (3.9)	11 (8.1)	2 (2.9)	5 (6.2)	5 (5.1)	11 (12.6)
Angina pectoris	1 (0.6)	2 (1.2)	0	1 (3.1)	1 (0.8)	1 (0.7)	1 (1.5)	1 (1.2)	0	1 (1.1)
Cerebrovascular accident	1 (0.6)	2 (1.2)	1 (2.7)	0	0	2 (1.5)	0	1 (1.2)	1 (1.0)	1 (1.1)
Coronary artery disease	0	2 (1.2)	0	2 (6.3)	0	0	0	0	0	2 (2.3)
Myocardial infarction	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Subarachnoid haemorrhage	0	2 (1.2)	0	2 (6.3)	0	0	0	0	0	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Portal vein thrombosis	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Pulmonary embolism	1 (0.6)	1 (0.6)	0	0	1 (0.8)	1 (0.7)	0	0	1 (1.0)	1 (1.1)
Reversible cerebral vasoconstriction syndrome	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Thrombophlebitis	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Thrombosis	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Venous recanalization	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Venous thrombosis	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: The PT of thrombotic thrombocytopenic purpura (TTP) is included in the SMQs of both CV and renal TEAEs. While these events were captured as part of the broad SMQ based search for CV and renal TEAEs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in the section describing renal TEAEs (Section 2.8.3.4.5).

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AESs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

Table 82: Study 747-302 - Cardiovascular Serious Treatment-Emergent AESIs in ≥1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Serious Cardiovascular TEAE	3 (1.8)	7 (4.2)	1 (2.7)	3 (9.4)	2 (1.6)	4 (2.9)	1 (1.5)	2 (2.5)	2 (2.0)	5 (5.7)
Cerebrovascular accident	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Coronary artery disease	0	2 (1.2)	0	2 (6.3)	0	0	0	0	0	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Angina pectoris	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Myocardial infarction	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Pulmonary embolism	1 (0.6)	1 (0.6)	0	0	1 (0.8)	1 (0.7)	0	0	1 (1.0)	1 (1.1)
Subarachnoid haemorrhage	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Mesenteric vein thrombosis	1 (0.6)	0	1 (2.7)	0	0	0	0	0	1 (1.0)	0
Paraplegia	1 (0.6)	0	0	0	1 (0.8)	0	1 (1.5)	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: The PT of thrombotic thrombocytopenic purpura (TTP) is included in the SMQs of both CV and renal TEAEs. While these events were captured as part of the broad SMQ based search for CV and renal TEAEs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in the section describing renal TEAEs (Section 2.8.3.4.5).

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 62, Ad hoc 62.1, Ad hoc 62.2

Exposure-Adjusted Incidence of Cardiovascular Adverse Events of Special Interest

Exposure-adjusted incidences of CV TEAEs and serious CV TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 83 and Table 84, respectively.

The trend for exposure-adjusted CV TEAEs was generally similar to those observed for the unadjusted rates. Importantly, when evaluating the clinically relevant serious CV events, no meaningful difference was observed in the exposure adjusted rates between the OCA and placebo treated subjects in both the compensated and the proposed SmPC indicated populations.

Proposed SmPC Indicated Population

In comparison to the overall population, the incidence of exposure-adjusted CV TEAEs observed in OCA-treated subjects was reduced significantly in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the incidence of exposure-adjusted CV TEAEs was 2.386 per 100 PYs in the OCA group and 1.385 per 100 PYs in the placebo group. The incidence of exposure-adjusted serious CV TEAEs was 0.931 per 100 PYs in the OCA group and 0.689 per 100 PYs in the placebo group.

Table 83: Study 747-302 – Exposure-Adjusted Incidence Rate of Cardiovascular Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cardiovascular TEAE	2.013 (347.69)	3.907 (409.56)	3.772 (53.02)	9.438 (52.97)	1.697 (294.67)	3.085 (356.59)	1.385 (144.45)	2.386 (209.58)	2.460 (203.23)	5.500 (199.95)
Angina pectoris	0.282 (354.64)	0.476 (420.03)	0 (54.98)	1.841 (54.31)	0.334 (299.67)	0.273 (363.72)	0.688 (145.30)	0.467 (214.01)	0 (209.35)	0.485 (206.02)
Cerebrovascular accident	0.283 (353.49)	0.475 (421.10)	1.885 (53.06)	0 (54.48)	0 (300.43)	0.546 (366.63)	0 (146.06)	0.465 (214.98)	0.483 (207.43)	0.485 (206.12)
Coronary artery disease	0 (355.40)	0.476 (420.47)	0 (54.98)	3.725 (53.69)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.974 (205.41)
Myocardial infarction	0 (355.40)	0.476 (419.93)	0 (54.98)	1.838 (54.40)	0 (300.43)	0.274 (363.54)	0 (146.06)	0 (215.07)	0 (209.35)	0.976 (204.87)
Subarachnoid haemorrhage	0 (355.40)	0.475 (420.94)	0 (54.98)	3.693 (54.15)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.971 (205.87)
Thrombotic thrombocytopenic purpura	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.62)	0 (146.06)	0.931 (214.90)	0 (209.35)	0 (206.19)
Portal vein thrombosis	0 (355.40)	0.238 (419.83)	0 (54.98)	0 (54.48)	0 (300.43)	0.274 (363.35)	0 (146.06)	0 (215.07)	0 (209.35)	0.488 (204.76)
Pulmonary embolism	0.284 (351.87)	0.237 (421.19)	0 (54.98)	0 (54.48)	0.337 (296.90)	0.273 (366.78)	0 (146.06)	0 (215.07)	0.486 (205.82)	0.485 (206.12)
Reversible cerebral vasoconstriction syndrome	0 (355.40)	0.238 (420.87)	0 (54.98)	1.849 (54.08)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.486 (205.80)
Thrombophlebitis	0 (355.40)	0.238 (420.98)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.51)	0 (146.06)	0 (215.07)	0 (209.35)	0.486 (205.92)
Thrombosis	0 (355.40)	0.239 (418.77)	0 (54.98)	0 (54.48)	0 (300.43)	0.275 (364.30)	0 (146.06)	0.470 (212.58)	0 (209.35)	0 (206.19)
Venous recanalisation	0 (355.40)	0.238 (419.65)	0 (54.98)	0 (54.48)	0 (300.43)	0.274 (363.17)	0 (146.06)	0 (215.07)	0 (209.35)	0.489 (204.58)

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Venous thrombosis	0 (355.40)	0.238 (419.48)	0 (54.98)	0 (54.48)	0 (300.43)	0.274 (365.00)	0 (146.06)	0.469 (213.28)	0 (209.35)	0 (206.19)
Carotid artery stenosis	0.281 (355.31)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (300.33)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.25)	0 (206.19)
Mesenteric vein thrombosis	0.281 (355.36)	0 (421.26)	1.820 (54.93)	0 (54.48)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.31)	0 (206.19)
Paraplegia	0.282 (354.56)	0 (421.26)	0 (54.98)	0 (54.48)	0.334 (299.59)	0 (366.78)	0.689 (145.22)	0 (215.07)	0 (209.35)	0 (206.19)
Splenic infarction	0.283 (354.87)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (299.89)	0 (366.78)	0 (146.06)	0 (215.07)	0.479 (208.81)	0 (206.19)

AE=Adverse event; IRY=number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=portal hypertension; PY=patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: The PT of thrombotic thrombocytopenic purpura (TTP) is included in the SMQs of both CV and renal TEAEs. While these events were captured as part of the broad SMQ based search for CV and renal TEAEs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in the section describing renal TEAEs (Section 2.8.3.4.3).

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Table 84: Study 747-302 – Exposure-Adjusted Incidence Rate of Cardiovascular Serious Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Cardiovascular Serious TEAE	0.855 (350.99)	1.666 (420.15)	1.820 (54.93)	5.589 (53.68)	0.676 (296.06)	1.091 (366.47)	0.689 (145.22)	0.931 (214.90)	0.972 (205.78)	2.436 (205.85)
Cerebrovascular accident	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.63)	0 (146.06)	0.465 (214.98)	0 (209.35)	0.485 (206.12)
Coronary artery disease	0 (355.40)	0.476 (420.47)	0 (54.98)	3.725 (53.69)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.974 (205.41)
Thrombotic thrombocytopenic purpura	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.62)	0 (146.06)	0.931 (214.90)	0 (209.35)	0 (206.19)
Angina pectoris	0 (355.40)	0.237 (421.09)	0 (54.98)	1.841 (54.31)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.02)
Myocardial infarction	0 (355.40)	0.237 (421.18)	0 (54.98)	1.838 (54.40)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.11)
Pulmonary embolism	0.284 (351.87)	0.237 (421.19)	0 (54.98)	0 (54.48)	0.337 (296.90)	0.273 (366.71)	0 (146.06)	0 (215.07)	0.486 (205.82)	0.485 (206.12)
Subarachnoid haemorrhage	0 (355.40)	0.237 (421.24)	0 (54.98)	1.836 (54.46)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.18)
Mesenteric vein thrombosis	0.281 (355.36)	0 (421.26)	1.820 (54.93)	0 (54.48)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.31)	0 (206.19)
Paraplegia	0.282 (354.56)	0 (421.26)	0 (54.98)	0 (54.48)	0.334 (299.59)	0 (366.78)	0.689 (145.22)	0 (215.07)	0 (209.35)	0 (206.19)

IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension; PY=Patient-years; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: The PT of thrombotic thrombocytopenic purpura (TTP) is included in the SMQs of both CV and renal TEAEs. While these events were captured as part of the broad SMQ based search for CV and renal TEAEs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in the section describing renal TEAEs (Section 2.8.3.4.5).

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

Adverse events were coded using MedDRA Version 24.0.

Adjudicated Cardiovascular Events

All suspected Major Adverse Cardiovascular Events (MACE), including CV death, non-fatal myocardial infarction, non-fatal stroke, and additional CV events were adjudicated by an independent CV adjudication committee in a blinded fashion.

Potential events were identified programmatically using searches for fatal events, hospitalizations, and SMQ based searches for CV TEAEs. SMQ trigger events included ischaemic heart disease, cardiac failure, Torsade de pointes/ QT interval of the electrocardiogram (QT) prolongation, arrhythmia related investigations, signs and symptoms, cardiac arrhythmia terms [including bradyarrhythmias and tachyarrhythmias], and central nervous system haemorrhages and cerebrovascular conditions. Events were reviewed in conjunction with evaluation of medical history, concomitant medications, vital signs, prespecified lab values, and electrocardiograms (ECGs). Adjudication committee members remained blinded to investigational product treatment assignment (CAC Charter, Version 7).

A panel of up to 7 independent CV experts (in groups of 3) adjudicated a broad set of suspected CV events and hospitalizations while blinded to study treatment assignment. Endpoints assessed by the CV adjudication committee included non-fatal myocardial infarction (MI), non-fatal stroke, CV death, hospitalization for unstable angina, all causes of death, transient ischemic attack, coronary/peripheral revascularization procedures, arrhythmias, or hospitalization/urgent visit for heart failure. Event adjudication required agreement between at least two reviewers; independent review was conducted by the third member if the initial two members were not in agreement.

Adjudicated MACE is summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 85.

Proposed SmPC Indicated Population

In comparison to the overall population, the incidence of MACE observed in OCA-treated subjects was significantly lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), 1 (1.2%) subject in the OCA group experienced an adjudicated stroke as a complication of a thrombotic microangiopathy (this subject was diagnosed with TTP, narrative is provided below). Three (4.4%) subjects in the placebo group reported an adjudicated MACE; arrhythmia and heart failure were reported in 1 (1.5%) and 2 (2.9%) subjects, respectively.

- A female subject with PBC reported serious TEAEs of cerebrovascular accident and TTP on 10 Oct 2019 (Study Day 441), approximately 1 year and 3 months after the initiation of OCA. While the subject was in the proposed SmPC indicated population when she began OCA, she had an elastography score of 16.5 kPa measured on 29 Jan 2019 (Study Day 187) which would exclude use of OCA per the proposed SmPC. This subject presented several months later to the emergency department for evaluation and was admitted to the intensive care unit with the diagnosis of sub-acute stroke (serious TEAE of cerebrovascular accident) and subsequently a confirmed a diagnosis of TTP with disintegrin and metalloproteinase with thrombospondin motifs activity at 2%. Investigational product was withdrawn in response to the events of cerebrovascular accident and TTP. The event of cerebrovascular accident was considered resolved on 26 Oct 2019 (Study Day 457) and TTP was considered resolved on 04 Dec 2019 (Study Day 496). Both events were considered severe in severity and unlikely related to investigational product.

In summary, when considering the proposed SmPC indicated population, there is no clear signal for an increased CV risk based on analyses of the adjudicated CV events in a rigorous manner.

Table 85: Study 747-302 – Summary of Adjudicated Cardiovascular Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subject with at least 1 Adjudicated CV TEAE	3 (1.8)	5 (3.0)	0	3 (9.4)	3 (2.3)	2 (1.5)	3 (4.4)	1 (1.2)	0	4 (4.6)
Revascularization Procedure	0	2 (1.2)	0	2 (6.3)	0	0	0	0	0	2 (2.3)
Stroke	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	0
Cardiovascular Death	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Myocardial Infarction	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	0
Arrhythmia	1 (0.6)	0	0	0	1 (0.8)	0	1 (1.5)	0	0	0
Heart Failure	2 (1.2)	0	0	0	2 (1.6)	0	2 (2.9)	0	0	0

OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: Adjudicated cardiovascular events included data after initiation of treatment and through discontinuation of study treatment or within 30 days after the discontinuation of study treatment. Data after a patient began commercial OCA were excluded.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302 Ad hoc Table 14.3.1.15.1, Table 14.3.1.15.1.1, Table 14.3.1.15.1.2

Exposure-Adjusted Incidence of Adjudicated CV Events

Exposure-adjusted incidences of MACE by PT is summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 86.

Proposed SmPC Indicated Population

In comparison to the overall population, the incidence of exposure-adjusted adjudicated CV events in OCA-treated subjects was reduced significantly in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), the incidence of exposure-adjusted adjudicated

CV events was lower in the OCA group (0.465 per 100 PYs in the OCA group and 2.121 per 100 PYs in the placebo group).

Table 86: Exposure-Adjusted Incidence Rate of Adjudicated Treatment-Emergent Cardiovascular Events in Study 747-302 by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Adjudicated Cardiovascular TEAE	0.855 (350.81)	1.189 (420.45)	0 (54.98)	5.574 (53.82)	1.014 (295.83)	0.546 (366.63)	2.121 (141.46)	0.465 (214.98)	0 (209.35)	1.947 (205.46)
Revascularization Procedure	0 (355.40)	0.476 (420.61)	0 (54.98)	3.716 (53.82)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.933 (205.54)
Stroke	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.346 (366.63)	0 (146.06)	0.465 (214.98)	0 (209.35)	0.485 (206.12)
Cardiovascular Death	0 (355.40)	0.237 (421.26)	0 (54.98)	1.836 (54.48)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.19)
Myocardial Infarction	0 (355.40)	0.237 (421.18)	0 (54.98)	1.838 (54.40)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0 (209.35)	0.485 (206.11)
Arrhythmia	0.285 (351.25)	0 (421.26)	0 (54.98)	0 (54.48)	0.338 (296.27)	0 (366.78)	0.705 (141.90)	0 (215.07)	0 (209.35)	0 (206.19)
Heart Failure	0.563 (354.96)	0 (421.26)	0 (54.98)	0 (54.48)	0.667 (299.99)	0 (366.78)	1.373 (145.62)	0 (215.07)	0 (209.35)	0 (206.19)

AE=adverse event; IP=investigational product; IRY=number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PH=evidence of portal hypertension; PT=preferred term; PY=Patient-years; SOC=system organ class; TEAE=treatment-emergent adverse event
Notes: TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
Patient-years=number of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302 Ad hoc, Table 14.3.1.15.2, Table 14.3.1.15.2.1, Table 14.3.1.15.2.2

Lipoprotein Evaluations

Mean total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) values over time are summarized by overall and proposed SmPC indicated populations in Figure 32.

Overall (N=334)

At baseline, the mean value for each of the lipid parameters was similar across treatment groups, with values meeting the criteria of Abnormal for total cholesterol (defined as ≥ 200 mg/dL) and LDL (defined as ≥ 100 mg/dL). Mean values across OCA and placebo groups were ~ 269 mg/dL, ~ 152 mg/dL, ~ 72 mg/dL and for total cholesterol, LDL, and HDL, respectively.

Overall, mean total cholesterol values decreased over time, with a more rapid decrease observed in the first 6 months in the OCA group compared to the placebo group. Mean LDL values were also similar across OCA and placebo treatment groups, which decreased over time in both treatment groups. In the OCA group, an early decrease in HDL was observed by Month 1, with values approaching baseline by Month 18.

Proposed SmPC Indicated Population (N=149)

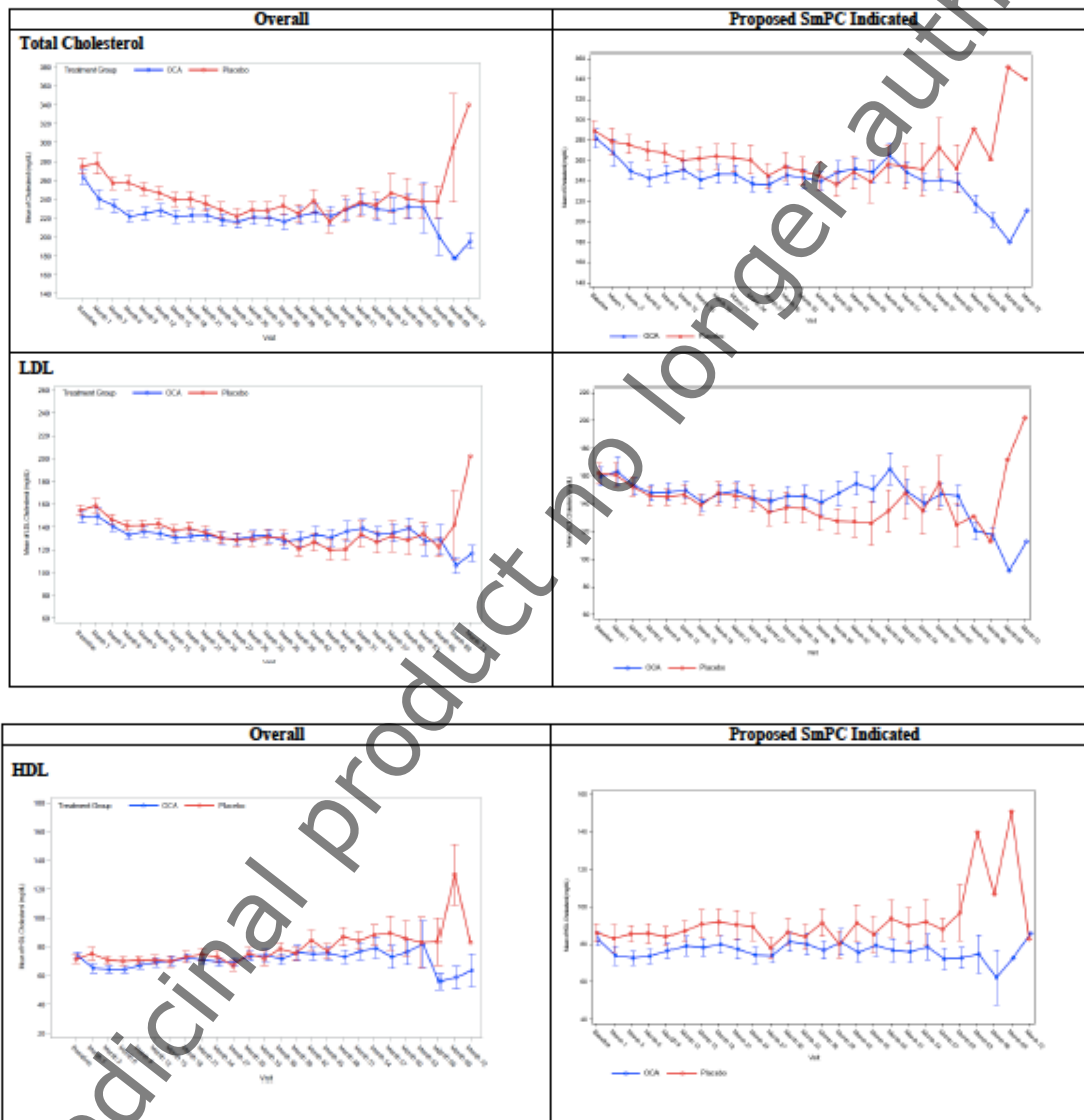
In the proposed SmPC indicated population, mean total cholesterol values decreased over time, with a more rapid decrease observed in the first 6 months in the OCA group compared to the placebo group. Mean cholesterol decreased from 282.0 mg/dL (baseline) to 242.6 mg/dL (Month 6) and 245.8 mg/dL (Month 30) in the OCA group. Mean cholesterol decreased from 289.4 mg/dL (baseline) to 269.8 mg/dL (Month 6) and 254.1 mg/dL (Month 30) in the placebo group.

Mean LDL values were similar across OCA and placebo treatment groups, with decreased values observed over time. Mean LDL cholesterol decreased from 159.77 mg/dL (baseline) to 147.93 mg/dL (Month 6) and 145.85 mg/dL (Month 30) in the OCA group. Mean LDL cholesterol decreased from 162.27 mg/dL (baseline) to 145.92 mg/dL (Month 6) and 137.26 mg/dL (Month 30) in the placebo group. Most subjects reported concomitant use of lipid-modifying agents, with higher use reported in the placebo group (60.3% subjects) compared to the OCA group (54.3% subjects).

Lipid data for very few subjects is available at later timepoints, leading to high variability in mean values and an apparent rise in LDL at Month 42; data at later timepoints should thus be interpreted with caution. Overall, decreased LDL values were observed over time.

In the OCA group, an early decrease in HDL was observed by Month 1, with values approaching baseline by Month 12 and remaining stable out to Month 30. Mean HDL levels decreased from 82.91 mg/dL (baseline) to 74.12 mg/dL (Month 1), with a low of 72.90 mg/dL (Month 3), before increasing to 79.39 mg/dL (Month 12) and 81.54 mg/dL (Month 30). Mean HDL cholesterol values were relatively stable over time in the placebo group (86.38 mg/dL [baseline], 83.42 mg/dL [Month 1], 85.72 mg/dL [Month 3], 87.24 mg/dL [Month 12], 86.75 mg/dL [Month 30]).

Figure 32: Mean (SE) Serum Lipid Values Over Time by Baseline Disease Stage (Overall vs Proposed SmPC Indicated Population) (Safety Population [N=344])



HDL=high-density lipoprotein; LDL=low-density lipoprotein; OCA=obeticholic acid; SmPC=Summary of Product Characteristics; VLDL=very-low density protein
Source: 747-302 Ad hoc, Figure 14.3.4.2.5.1; 747-302, Ad hoc 40.1

Shift analyses from baseline to postbaseline LDL cholesterol levels by visit are provided in Table 87 (compensated vs decompensated populations) and Table 88 (proposed SmPC indicated vs proposed SmPC contraindicated populations). In the proposed SmPC indicated population, the majority of subjects in both treatment groups met the criteria of Abnormal for LDL at baseline, defined as ≥ 100

mg/dL. Few subjects shifted from Normal LDL levels at baseline to Abnormal LDL levels, with no notable differences observed between treatment groups.

Shift analyses from baseline to postbaseline HDL cholesterol levels by visit are provided in Table 89 (compensated vs decompensated populations) and Table 90 (proposed SmPC indicated vs proposed SmPC contraindicated populations). In the proposed SmPC indicated population, the majority of subjects in both treatment groups met the criteria of Normal for HDL at baseline, defined as ≥ 40 mg/dL in men or ≥ 50 mg/dL in women. More subjects in the OCA group shifted from Normal HDL levels at baseline to Abnormal HDL levels by Month 1 (19.5% in the OCA group and 0 in the placebo group). This shift was maintained at Month 3 (16.4% in the OCA group and 3.1% in the placebo group), Month 12 (14.0% in the OCA group and 6.1% in the placebo group), and Month 24 (13.6% in the OCA group and 6.9% in the placebo group). By Month 42, the shift from Normal to Abnormal had normalized between treatment groups.

Table 87: LDL Shift Analysis by Overall and Baseline Disease Stage (Compensated vs Decompensated) (Safety Population [N=344])

LDL (mg/dL)	Overall				Current SmPC							
	PBO N=166		OCA N=168		Decompensated (Contraindicated)				Compensated (Indicated)			
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Month 1												
n	5	66	15	51	2	11	3	7	3	55	12	44
Normal	4 (5.6)	5 (7.0)	14 (21.2)	3 (4.5)	2 (15.4)	2 (15.4)	3 (30.0)	1 (10.0)	2 (3.4)	3 (5.2)	11 (19.6)	2 (3.6)
Abnormal	1 (1.4)	61 (85.9)	1 (1.5)	48 (72.7)	0	9 (69.2)	0	6 (60.0)	1 (1.7)	52 (89.7)	1 (1.8)	42 (73.0)
Month 3												
n	23	135	33	115	7	28	10	20	16	107	23	95
Normal	22 (13.9)	12 (7.6)	27 (18.2)	10 (6.8)	7 (20.0)	5 (8.6)	10 (33.3)	3 (10.0)	15 (12.2)	9 (7.3)	17 (14.4)	7 (5.9)
Abnormal	1 (0.6)	123 (77.8)	6 (4.1)	105 (70.9)	0	25 (71.4)	0	17 (56.7)	1 (0.8)	98 (79.7)	6 (5.1)	88 (74.6)
Month 12												
n	18	102	22	87	5	16	5	12	13	86	17	75
Normal	15 (12.5)	14 (11.7)	17 (15.6)	11 (10.1)	4 (19.0)	2 (9.5)	5 (29.4)	2 (11.8)	11 (11.1)	12 (12.1)	12 (13.0)	9 (9.8)
Abnormal	3 (2.5)	88 (73.3)	5 (4.6)	76 (69.7)	1 (4.5)	14 (66.7)	0	10 (58.8)	2 (2.0)	74 (74.7)	5 (5.4)	66 (71.7)
Month 24												
n	11	60	18	62	2	7	4	5	9	53	14	57
Normal	9 (12.7)	10 (14.1)	13 (16.3)	16 (20.0)	2 (22.2)	2 (22.2)	4 (44.4)	1 (11.1)	7 (11.3)	8 (12.9)	9 (12.7)	15 (21.1)
Abnormal	2 (2.8)	50 (70.4)	5 (6.3)	46 (57.5)	0	5 (55.6)	0	4 (44.4)	2 (3.2)	45 (72.6)	5 (7.0)	42 (59.2)
Month 42												
n	3	27	8	36	1	0	1	4	2	27	7	32

LDL (mg/dL)	Overall				Current SmPC							
	PBO N=166		OCA N=168		Decompensated (Contraindicated)				Compensated (Indicated)			
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Normal	3 (10.0)	9 (30.0)	4 (9.1)	8 (18.2)	1 (100.0)	0	1 (20.0)	1 (20.0)	2 (6.9)	9 (31.0)	3 (7.7)	7 (17.9)
Abnormal	0	18 (60.0)	4 (9.1)	28 (63.6)	0	0	0	3 (60.0)	0	18 (62.1)	4 (10.3)	25 (64.1)

LDL=low density lipoprotein; OCA=obeticholic acid; PBO=placebo; SmPC=Summary of Product Characteristics

Notes: Percentages are based on number of subjects with a non-missing result (n values) for the given parameter at baseline and specific post baseline visit.

Only central laboratory data were used. LDL: normal (< 100 mg/dL) and abnormal (≥ 100 mg/dL).

Data after 30 days of study treatment discontinuation or after initiation of commercial OCA are excluded.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Source: 747-302 Ad hoc, Table 14.3.4.2.7, Table 14.3.4.2.7.2

Table 88: LDL Shift Analysis by Overall and Baseline Disease Stage (Proposed SmPC Indicated vs Proposed SmPC Contraindicated) (Safety Population [N=344])

LDL (mg/dL)	Overall				Proposed SmPC							
	PBO N=166		OCA N=168		Indicated				Contraindicated			
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Month 1												
n	5	66	15	51	3	34	5	33	2	32	10	18
Normal	4 (5.6)	5 (7.0)	14 (21.2)	3 (4.5)	2 (5.4)	3 (8.1)	4 (10.5)	2 (5.3)	2 (5.9)	2 (5.9)	10 (35.7)	1 (3.6)
Abnormal	1 (1.4)	61 (85.9)	1 (1.5)	48 (72.7)	1 (2.7)	31 (83.8)	1 (2.6)	31 (81.6)	0	30 (88.2)	0	17 (60.7)
Month 3												
n	23	135	33	115	7	57	9	62	16	78	24	53
Normal	22 (13.9)	12 (7.6)	27 (18.2)	10 (6.8)	6 (9.4)	5 (7.8)	4 (5.6)	4 (5.6)	16 (17.0)	7 (7.4)	23 (29.9)	8 (15.3)
Abnormal	1 (0.6)	123 (77.8)	6 (4.1)	105 (70.9)	1 (1.6)	52 (81.3)	5 (7.0)	58 (81.7)	0	71 (75.5)	1 (1.3)	45 (61.0)
Month 12												
n	18	102	22	87	5	44	6	48	13	58	16	39
Normal	15 (12.5)	14 (11.7)	17 (15.6)	11 (10.1)	4 (8.2)	7 (14.3)	3 (5.6)	4 (7.4)	11 (15.5)	7 (9.9)	14 (25.3)	7 (12.7)
Abnormal	3 (2.5)	88 (73.3)	5 (4.6)	76 (69.7)	1 (2.0)	37 (75.5)	3 (5.6)	44 (81.5)	2 (2.8)	51 (71.8)	2 (3.6)	32 (58.2)
Month 24												
n	11	60	18	62	4	26	4	38	7	34	14	24
Normal	9 (12.7)	10 (14.1)	13 (16.3)	16 (20.0)	3 (10.0)	6 (20.0)	0	6 (14.3)	6 (14.6)	9 (9.8)	13 (34.2)	10 (26.3)
Abnormal	2 (2.8)	50 (70.4)	5 (6.3)	46 (57.5)	1 (3.3)	20 (66.7)	4 (9.5)	32 (76.2)	1 (2.4)	30 (73.2)	1 (2.6)	14 (36.8)
Month 42												
n	3	27	8	36	1	16	3	21	2	11	5	15
Normal	3 (10.0)	9 (30.0)	4 (9.1)	8 (18.2)	1 (5.9)	6 (35.3)	0	1 (4.2)	2 (15.4)	3 (23.1)	4 (20.0)	7 (35.0)

LDL (mg/dL)	Overall				Proposed SmPC							
	PBO N=166		OCA N=168		Indicated				Contraindicated			
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Abnormal	0	18 (60.0)	4 (9.1)	28 (63.6)	0	10 (58.6)	3 (12.5)	20 (83.3)	0	8 (61.5)	1 (5.0)	8 (40.0)

LDL=low density lipoprotein; OCA=obeticholic acid; PBO=placebo; PH=portal hypertension; SmPC=Summary of Product Characteristics

Notes: Percentages are based on number of subjects with a non-missing result (n values) for the given parameter at baseline and specific post baseline visit.

Only central laboratory data were used. LDL: normal (<100 mg/dL) and abnormal (≥100 mg/dL).

Data after 30 days of study treatment discontinuation or after initiation of commercial OCA are excluded.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

Source: 747-302 Ad hoc, Table 14.3.4.2.7, Table 14.3.4.2.7.1

Table 89: HDL Shift Analysis by Overall and Baseline Disease Stage (Compensated vs Decompensated) (Safety Population [N=344])

HDL (mg/dL)	Overall				Current SmPC							
	PBO N=166		OCA N=168		Decompensated (Contraindicated)				Compensated (Indicated)			
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Month 1												
n	58	16	60	11	9	4	9	2	49	12	51	9
Normal	55 (74.3)	2 (12.7)	45 (63.4)	2 (2.8)	6 (46.2)	0	6 (54.5)	0	49 (80.3)	2 (3.3)	39 (65.0)	2 (3.3)
Abnormal	3 (4.1)	14 (18.9)	15 (21.1)	9 (12.7)	3 (23.1)	4 (30.8)	3 (27.3)	2 (18.2)	0	10 (16.4)	12 (20.0)	7 (11.7)
Month 3												
n	116	43	120	31	18	17	18	12	98	26	102	19
Normal	104 (63.4)	7 (4.4)	94 (62.3)	5 (3.3)	14 (40.0)	1 (2.9)	13 (43.3)	0	90 (72.6)	6 (4.8)	81 (66.9)	5 (4.1)
Abnormal	12 (7.5)	36 (22.6)	26 (17.2)	26 (17.2)	4 (11.4)	16 (45.7)	5 (16.7)	12 (40.0)	8 (6.5)	20 (16.1)	21 (17.4)	14 (11.6)
Month 12												
n	88	33	96	15	11	11	12	4	77	22	84	11
Normal	79 (65.3)	8 (6.6)	79 (71.2)	5 (4.5)	9 (40.9)	1 (4.5)	10 (62.5)	1 (6.3)	70 (70.7)	7 (7.1)	69 (72.6)	4 (4.2)
Abnormal	9 (7.4)	25 (20.7)	17 (15.3)	10 (9.0)	2 (9.1)	10 (45.5)	2 (12.5)	3 (18.8)	7 (7.1)	15 (15.2)	15 (15.8)	7 (7.4)

HDL (mg/dL)	Overall				Current SmPC							
					Decompensated (Contraindicated)				Compensated (Indicated)			
	PBO N=166		OCA N=168		PBO N=36		OCA N=30		PBO N=127		OCA N=136	
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Month 24												
n	56	14	71	11	5	4	7	2	51	10	64	9
Normal	48 (85.7)	4 (5.7)	60 (84.5)	4 (4.9)	3 (33.3)	1 (11.1)	6 (85.7)	1 (11.1)	45 (73.8)	3 (4.9)	54 (74.0)	3 (4.1)
Abnormal	8 (11.4)	10 (14.3)	11 (13.4)	7 (8.5)	2 (22.2)	3 (33.3)	1 (11.1)	1 (11.1)	6 (9.8)	7 (11.5)	10 (13.7)	6 (8.2)
Month 42												
n	22	8	38	6	1	0	3	2	21	8	35	4
Normal	22 (73.3)	3 (10.0)	37 (84.1)	4 (9.1)	1 (100.0)	0	3 (60.0)	1 (20.0)	21 (72.4)	3 (10.3)	34 (87.2)	3 (7.7)
Abnormal	0	5 (16.7)	1 (2.3)	2 (4.5)	0	0	0	1 (20.0)	0	5 (17.2)	1 (2.6)	1 (2.6)

HDL=high density lipoprotein; OCA=obeticholic acid; PBO=placebo; SmPC=Summary of Product Characteristics

Notes: Percentages are based on number of subjects with a non-missing result (n values) for the given parameter at baseline and specific post baseline visit.

Only central laboratory data were used. HDL: normal (≥ 40 mg/dL in men, or ≥ 50 mg/dL in women) and abnormal (< 40 mg/dL in men, or < 50 mg/dL in women).

Data after 30 days of study treatment discontinuation or after initiation of commercial OCA are excluded.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Source: 747-302 Ad hoc, Table 14.3.4.2.7, Table 14.3.4.2.7.2

Table 90: HDL Shift Analysis by Overall and Baseline Disease Stage (Proposed SmPC Indicated vs Contraindicated) (Safety Population [N=344])

HDL (mg/dL)	Overall				Proposed SmPC							
					Indicated				Contraindicated			
	PBO N=166		OCA N=168		PBO N=67		OCA N=76		PBO N=96		OCA N=80	
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Month 1												
n	58	16	60	11	30	8	37	4	28	8	23	7
Normal	55 (74.3)	2 (2.7)	45 (63.4)	2 (2.8)	30 (78.9)	1 (2.6)	29 (70.7)	1 (2.4)	25 (69.4)	1 (2.8)	16 (53.3)	1 (3.3)
Abnormal	3 (4.1)	14 (18.9)	15 (21.1)	9 (12.7)	0	7 (18.4)	8 (19.5)	3 (7.3)	3 (8.3)	7 (19.4)	7 (23.3)	6 (20.0)
Month 3												
n	116	43	120	31	55	10	65	8	61	33	55	23
Normal	104 (65.4)	7 (4.4)	94 (62.3)	5 (3.3)	53 (81.5)	2 (3.1)	53 (72.6)	3 (4.1)	51 (54.3)	5 (5.3)	41 (52.6)	2 (2.6)
Abnormal	12 (7.5)	36 (22.6)	26 (17.2)	26 (17.2)	2 (3.1)	8 (12.3)	12 (16.4)	5 (6.8)	10 (10.6)	28 (29.8)	14 (17.9)	21 (26.9)
Month 12												
n	88	33	96	15	41	8	52	5	47	25	44	10
Normal	79 (65.3)	8 (6.6)	79 (71.2)	5 (4.5)	38 (77.6)	3 (6.1)	44 (77.2)	3 (5.3)	41 (56.9)	5 (6.9)	35 (64.8)	2 (3.7)
Abnormal	9 (7.4)	25 (20.7)	17 (15.3)	10 (9.0)	3 (6.1)	5 (10.2)	8 (14.0)	2 (3.5)	6 (8.3)	20 (27.8)	9 (16.7)	8 (14.8)
Month 24												
n	56	14	71	11	26	3	40	4	30	11	31	7
Normal	48 (85.7)	4 (5.7)	60 (73.2)	4 (4.9)	24 (82.8)	2 (6.9)	34 (77.3)	2 (4.5)	24 (58.5)	2 (4.9)	26 (68.4)	2 (5.3)
Abnormal	8 (11.4)	10 (14.3)	11 (13.4)	7 (8.5)	2 (6.9)	1 (3.4)	6 (13.6)	2 (4.5)	6 (14.6)	9 (22.0)	5 (13.2)	5 (13.2)
Month 42												
n	22	8	38	6	13	4	22	2	9	4	16	4

HDL (mg/dL)	Overall				Proposed SmPC							
	PBO N=166		OCA N=163		Indicated				Contraindicated			
					PBO N=67		OCA N=76		PBO N=96		OCA N=80	
	Baseline		Baseline		Baseline		Baseline		Baseline		Baseline	
	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)	Normal n (%)	Abnormal n (%)
Normal	22 (73.3)	3 (10.0)	37 (84.1)	4 (9.1)	13 (76.5)	1 (5.9)	21 (87.5)	2 (8.3)	9 (69.2)	2 (15.4)	16 (80.0)	2 (10.0)
Abnormal	0	5 (16.7)	1 (2.3)	2 (4.5)	0	3 (17.6)	1 (4.2)	0	0	2 (15.4)	0	2 (10.0)

HDL=high density lipoprotein; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics

Notes: Percentages are based on number of subjects with a non-missing result (n values) for the given parameter at baseline and specific post baseline visit.

Only central laboratory data were used. HDL: normal (≥ 40 mg/dL in men, or ≥ 50 mg/dL in women) and abnormal (< 40 mg/dL in men, or < 50 mg/dL in women).

Data after 30 days of study treatment discontinuation or after initiation of commercial OCA are excluded.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

Source: 747-302 Ad hoc, Table 14.3.4.2.7, Table 14.3.4.2.7.1

Framingham Risk Scores

In order to assess CV risk in a comprehensive manner, Framingham risk score (FRS) at baseline and on treatment was assessed. The FRS is a well-characterized risk assessment tool used as a first step in coronary risk assessment. It includes risk factors of gender, age, total cholesterol, HDL cholesterol, systolic blood pressure, and smoking status to assess an individual's 10-year risk for myocardial infarction and cardiac death. An FRS score of $< 10\%$ indicates a 10-year predicted low risk for a coronary event, FRS of 10% to 20% indicates intermediate risk, and FRS of $\geq 20\%$ indicates high risk for a coronary event.

FRS was summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations at baseline, M12, and M42 in Table 91.

Proposed SmPC Indicated Population

In comparison to the overall population, mean FRS in OCA-treated subjects was lower in the proposed SmPC indicated population.

In the proposed SmPC indicated population (N=149), mean FRS was 7% in the OCA group and 9% in the placebo group at baseline. Values remained $< 10\%$ at Month 12 and Month 42 in the OCA and placebo groups, indicating a 10-year predicted low risk for a coronary event.

Table 91: Summary of Framingham Risk Score in Study 747-302 by Visit by Overall and Baseline Disease Stage (Safety Population [N=334])

Framingham Risk Score (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Baseline										
n	160	155	36	29	124	126	66	76	94	79
Mean (SD)	10.2 (10.6)	8.7 (9.1)	13.0 (13.8)	8.5 (6.6)	9.4 (9.4)	8.7 (9.6)	8.6 (9.5)	7.1 (6.2)	14.3 (11.3)	10.2 (11.0)
SE	0.8	0.7	2.3	1.2	0.8	0.9	1.2	0.7	1.2	1.2
Median (Q1, Q3)	6.7 (3.9, 12.4)	6.1 (3.6, 11.0)	7.5 (4.5, 14.1)	6.1 (3.3, 11.7)	6.4 (3.7, 12.1)	6.1 (3.6, 10.1)	5.3 (3.4, 9.4)	5.6 (3.5, 7.9)	7.6 (4.4, 12.8)	7.1 (3.6, 12.2)
Min, Max	0.6, 61.6	0.7, 75.5	2.5, 61.6	1.6, 23.0	0.6, 61.1	0.7, 75.5	0.6, 61.1	0.7, 55.9	0.8, 61.6	1.6, 75.5
Month 12										
n	114	116	22	17	92	99	47	59	67	57
Mean (SD)	10.3 (9.7)	8.9 (10.0)	10.1 (10.9)	9.6 (8.7)	10.4 (9.5)	8.7 (10.3)	9.0 (9.3)	7.1 (6.6)	11.3 (10.0)	10.7 (12.4)
SE	0.9	0.9	2.3	2.1	1.0	1.0	1.3	0.9	1.2	1.6
Median (Q1, Q3)	7.6 (4.1, 12.813)	5.7 (3.2, 10.3)	7.6 (3.8, 11.1)	6.8 (4.1, 10.0)	7.6 (4.4, 13.0)	5.6 (3.1, 10.7)	5.3 (3.2, 10.6)	5.4 (2.8, 7.3)	8.6 (4.6, 13.3)	7.3 (3.7, 13.9)
Min, Max	0.6, 51.6	0.6, 82.8	2.1, 51.6	0.8, 31.0	0.6, 48.5	0.6, 82.8	0.6, 42.1	0.6, 32.7	1.4, 51.6	0.8, 82.8
Month 42										
n	26	40	1	5	25	35	16	22	10	18
Mean (SD)	9.1 (6.8)	9.0 (6.5)	3.2 (NA)	7.1 (4.6)	9.3 (6.5)	9.3 (6.7)	7.4 (5.7)	9.2 (7.0)	11.8 (7.8)	8.8 (5.9)
SE	1.3	1.0	NA	2.1	1.4	1.1	1.4	1.5	2.5	1.4
Median (Q1, Q3)	7.9 (4.1, 12.6)	7.9 (4.0, 10.6)	3.2 (3.2, 3.2)	4.8 (4.0, 8.1)	8.1 (4.2, 12.6)	7.9 (4.0, 11.2)	5.3 (3.9, 10.6)	8.1 (3.5, 11.8)	11.0 (4.7, 14.4)	7.8 (4.8, 9.1)
Min, Max	1.0, 26.9	1.7, 24.8	3.2, 3.2	3.7, 14.7	1.0, 26.9	1.7, 24.8	1.0, 22.3	1.7, 24.8	3.2, 26.9	2.8, 23.6

Dyslipidaemia

Dyslipidaemia TEAEs were defined by the Dyslipidaemia SMQ.

Dyslipidaemia TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 92.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), the incidence rate of dyslipidaemia TEAEs was similar across treatment groups (4.9% in the OCA group and 4.4% in the placebo group). The most frequently reported dyslipidaemia TEAE was low density lipoprotein increased (2 [2.5%] subjects in the OCA group and none in the placebo group).

All dyslipidaemia TEAEs in the proposed SmPC indicated population were mild to moderate in severity. No subjects reported serious dyslipidaemia TEAEs or a TEAE leading to discontinuation.

Table 92: Study 747-302 - Dyslipidaemia Treatment-Emergent AESIs in ≥1 Overall Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=163	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Dyslipidaemia TEAE	9 (5.4)	6 (3.6)	3 (8.1)	1 (3.1)	6 (4.7)	5 (3.7)	3 (4.4)	4 (4.9)	6 (6.1)	2 (2.3)
Low density lipoprotein increased	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Blood cholesterol increased	1 (0.6)	1 (0.6)	1 (2.7)	1 (3.1)	0	0	0	0	1 (1.0)	1 (1.1)
Dyslipidaemia	3 (1.8)	1 (0.6)	1 (2.7)	0	2 (1.6)	1 (0.7)	1 (1.5)	0	2 (2.0)	1 (1.1)
Hypercholesterolaemia	4 (2.4)	1 (0.6)	1 (2.7)	0	3 (2.3)	1 (0.7)	1 (1.5)	1 (1.2)	3 (3.1)	0
Hypertriglyceridaemia	1 (0.6)	1 (0.6)	1 (2.7)	0	0	1 (0.7)	0	1 (1.2)	1 (1.0)	0
Hyperlipidaemia	1 (0.6)	0	0	0	1 (0.8)	0	1 (1.5)	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2

Exposure-Adjusted Incidence of Dyslipidaemia TEAESIs

Exposure-adjusted incidences of dyslipidaemia TEAESIs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 93.

The trend for exposure adjusted dyslipidaemia TEAESIs was generally similar to those observed for the unadjusted rates.

Proposed SmPC Indicated Population

The incidence of exposure-adjusted dyslipidaemia TEAESIs was 1.924 per 100 PYs in the OCA group and 2.236 per 100 PYs in the placebo group.

Table 93: Study 747-302 – Exposure-Adjusted Incidence Rate of Dyslipidaemia Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=163	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Dyslipidaemia TEAE	2.698 (333.57)	1.409 (405.76)	2.133 (281.32)	1.410 (354.67)	5.742 (52.25)	1.959 (51.04)	2.236 (134.17)	1.924 (207.90)	3.009 (199.40)	1.011 (197.80)
Low density lipoprotein increased	0 (355.40)	0.478 (418.60)	0 (300.43)	0.549 (364.12)	0 (54.98)	0 (54.48)	0 (146.06)	0.942 (212.41)	0 (209.35)	0 (206.19)
Blood cholesterol increased	0.261 (355.00)	0.239 (417.82)	0 (300.43)	0 (366.78)	1.823 (54.87)	1.959 (51.04)	0 (146.06)	0 (215.07)	0.478 (209.24)	0.493 (202.73)
Dyslipidaemia	0.839 (349.39)	0.240 (416.31)	0.677 (295.22)	0.276 (361.83)	1.846 (54.17)	0 (54.48)	0.705 (141.90)	0 (215.07)	0.964 (207.49)	0.497 (201.24)
Hypercholesterolaemia	1.160 (344.79)	0.239 (418.22)	1.029 (291.63)	0.275 (363.74)	1.881 (53.16)	0 (54.48)	0.697 (143.43)	0.472 (212.03)	1.490 (201.37)	0 (206.19)
Hypertriglyceridaemia	0.283 (353.59)	0.238 (419.79)	0 (300.43)	0.274 (365.32)	1.881 (53.16)	0 (54.48)	0 (146.06)	0.468 (213.60)	0.482 (207.53)	0 (206.19)
Hyperlipidaemia	0.285 (330.30)	0 (421.26)	0.339 (295.32)	0 (366.78)	0 (54.98)	0 (54.48)	0.709 (140.95)	0 (215.07)	0 (209.35)	0 (206.19)

AE=adverse event; GSPH=clinically evidence portal hypertension; IRY= number of patients with event per 100 patient-year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PY=Patient-years; TEAE=treatment-emergent adverse event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Renal

Renal TEAESIs were defined as events included in the following broad SMQs: acute renal failure, chronic kidney disease, proteinuria, renovascular disorders, or tubulointerstitial diseases. This represents a heterogenous groups of terms representing both primary (e.g., leukocyturia, haematuria) and secondary

renal (e.g., renal lymphoma, diabetic nephropathy) and urinary tract pathology (e.g., urinary tract infection) as well as signs that could be associated with a renal or hepatic etiology (e.g., hyponatraemia, hypoalbuminaemia).

The PT of TTP is included in the SMQs of both CV and renal TEAESIs. TTP belongs to the spectrum of thrombotic microangiopathies potentially affecting the vasculature of any organ (most commonly renal and cerebral). It presents with spontaneous thrombi formation as well as bleeding due to a deficiency of the functional enzyme ADAMTS13, which cleaves ultra large von Willebrand factor (VWF) multimers released from endothelial cells into smaller multimers, making them less adhesive to platelets. With the deficiency, the ultra large VWF multimers are released and bind spontaneously to platelets to form aggregates within microvessels. While these events are captured as part of the broad SMQ based search for CV and renal TEAESIs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in this section describing renal events.

Renal TEAESIs are summarized by overall and baseline disease stage in Table 94.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), 8 (9.9%) subjects in the OCA group and 4 (5.9%) subjects in the placebo group reported renal TEAESIs. Apart from the PTs of TTP which was reported by 2 subjects in the OCA group (2.5%), the remaining renal events were reported by 1 OCA-treated subject (1.2%) each: AKI, hypoalbuminaemia, proteinuria, diabetic nephropathy, leukocyturia, and renal failure. See below for brief narratives for TTP and AKI.

With the exception of TTP, all other renal TEAESIs in OCA-treated subjects were mild to moderate in severity.

The renal TEAESIs of TTP in the proposed SmPC indicated population are briefly discussed below. None of the cases were considered related to investigational product.

- A female subject presented to hospital with confusion and a syncope having been severely thrombocytopenic for at least 27 days prior to the presentation. The TESAE of TTP was diagnosed on 06 Jun 2016 (Study Day 111), approximately 4 months after the initiation of OCA. The patient began rifampicin approximately 3 months after the initiation of OCA, and it was ongoing at the time of the event. Investigational product was initially interrupted and later withdrawn in response to the event. The peak creatinine documented following the diagnosis of TTP was mildly elevated at 1.5 mg/dL (reference range: 0.6-1.3). The subject was treated with steroids, plasmapheresis, and Rituximab. The event was considered resolved with sequelae (plasmapheresis [as needed]) on 09 Jul 2016 (Study Day 144). The Investigator assessed the event of TTP as severe and not related to investigational product.
- A female subject with PBC reported serious TEAESIs of cerebrovascular accident and TTP on 10 Oct 2019 (Study Day 441), approximately 1 year and 3 months after the initiation of OCA. While the subject was programmatically assigned to the proposed SmPC indicated population upon initiation of OCA, elastography score of 16.5 kPa was measured on 29 Jan 2019 (Study Day 187). On 10 Oct 2019 (Study Day 441) the subject presented to the emergency department for evaluation and was admitted to the intensive care unit with the diagnosis of sub-acute stroke (serious TEAE of cerebrovascular accident) and subsequently a confirmed a diagnosis of TTP with disintegrin and metalloproteinase with thrombospondin motifs activity noted low at 2%. Investigational product was withdrawn in response to the events of cerebrovascular accident and TTP. The event of cerebrovascular accident was considered resolved on 26 Oct 2019 (Study Day 457) and TTP was considered resolved on 04 Dec 2019 (Study Day 496). Both events were considered severe in severity and unlikely related to investigational product.

Examining the two cases of TTP that occurred in subjects receiving OCA, 1 had ongoing treatment with rifampicin at the time of the event. Rifampicin has a reported association with TTP (Hamad 2020, Fahal 1992, Gupta 2005). The second subject with TTP was likely idiopathic, which is consistent with current understanding (Joly 2017).

1 non-serious TEAE of AKI was reported in 1 OCA-treated subject in the proposed SmPC indicated population and is briefly discussed below. The Investigator considered the event not related to investigational product.

- A female subject with PBC was referred to the emergency room on 20 Aug 2016 (Study Day 296) for evaluation of moderate left upper quadrant abdominal pain (non-serious AE). On 23 Aug 2016 (Study Day 299), the subject was hospitalized with the diagnosis of Stage 4 B-cell lymphoma (SAE) with renal/breast/lung/central nervous system involvement. The metastatic disease was thought to have originated from the right kidney. On the same day, the subject was reported to have "acute kidney injury" on the basis of an elevated serum urea level but otherwise normal renal function tests (note: urea is commonly elevated in metastatic lymphoma patients). Investigational product was withdrawn in response to the events of lymphoma and AKI, with the last dose administered on 20 Aug 2016 (Study Day 296). The Investigator assessed the event of lymphoma as severe and AKI as moderate in severity. On 03 Sept 2016 (Study Day 310), the subject completed the first cycle of chemotherapy (R-EPOCH). On 05 Sep 2016 (Study Day 312), the subject was transferred to the intensive care unit as she developed acute hypoxemic respiratory failure (serious adverse event [SAE]) and subsequently intubated due to worsening hypoxia and respiratory distress on 09 Sep 2016 (Study Day 316). Additional diagnoses were tumour lysis syndrome, and pancytopenia with neutropenia. The subject's family decided to pursue comfort care and the subject was extubated and died due to the event of acute respiratory failure on the same day. The events of lymphoma, AKI, and the fatal event of acute respiratory failure were all considered not related to investigational product by the Investigator. One event of renal failure (non-serious) and one event of diabetic nephropathy (non-serious) was reported in 1 OCA-treated subjects in the proposed SmPC indicated population. These events were considered mild and not related to investigational product by the Investigator.
- A female subject with PBC and a history of pruritus, initiated OCA study treatment on 13 Jan 2017. The subject's serum creatinine at baseline on 12 Jan 2018 was 0.87 mg/dL (reference range: 0.51 – 0.96 mg/dL). On 23 Feb 2018 (D42), the subject experienced an episode of severe pruritus and was maintained rifampicin, phenobarbital, and cholestyramine with the addition of bezafibrate. On 11 Jul 2018 (D180), a serum creatinine value of 0.92 mg/dL was reported for the subject a MELD score of 6.4. Approximately 8 months after the initiation of OCA, the subject discontinued study treatment on 21 Aug 2018 (D221), the same day she was admitted for a planned liver transplantation due to intractable pruritus. On 03 Sept 2018 (D234), the subject underwent a successful liver transplantation without complication and was initiated on treatments with tacrolimus, mycophenolate mofetil, sulfamethoxazole/trimethoprim, valganciclovir hydrochloride, prednisone, and magnesium hydroxide. Subsequently, an event of renal failure was recorded on 17 Sept 2018 (D248) having discontinued bezafibrate treatment shortly before on 14 Sept 2018 (D245). At the onset of the renal failure event, the subject reported the concurrent AEs of anaemia, chills, constipation, diarrhoea, and oral candidiasis. The subject remained on hydrochlorothiazide, tacrolimus, and sulfamethoxazole through the event of renal failure. On 18 Oct 2018 (D279), a peak serum creatinine value of 1.20 mg/dL (reference range: 0.51 – 0.96 mg/dL) was reported. The subject withdrew from the study 18 Oct 2018 (D279).

- A male subject with PBC and a history of pruritus, type 1 diabetes mellitus (insulin dependent), and hypertension (on hydrochlorothiazide since 2006) initiated OCA study treatment on 05 Dec 2016. Serum creatinine at baseline on 02 Dec 2016 was 1.02 mg/dL (reference range: 0.67 – 1.17 mg/dL). On 12 Dec 2016 the subject was reported to have a moderate increase in blood pressure determined by the investigator to be unlikely related to study treatment and the subject was initiated on amlodipine the same day after discontinuing hydrochlorothiazide on 11 Dec 2016. Due to excessive pain of the cervical and thoracic spine, the subject initiated celecoxib and diclofenac sodium on 30 Nov 2017 before discontinuing these therapies on 10 Dec 2017. On 07 April 2018 the subject initiated ibuprofen and pseudoephedrine for acute frontal sinusitis before discontinuing these therapies on 07 May 2018. The subject was administered diclofenac sodium and meloxicam transiently in for spine pain in Aug 2018. On 11 Sept 2019, the subject had a serum creatinine level of 1.22 mg/dL (reference range: 0.67 – 1.17 mg/dL). Subsequently, the subject experienced an event of mild diabetic nephropathy on 09 Dec 2019, which the investigator determined was not related to study treatment. The subject had insulin-dependent type 1 diabetes mellitus at the time of study enrollment per reported medical history (unknown onset date). The presence of proteinuria was not provided. On 09 Dec 2019, the subject had a serum creatinine level of 1.28 mg/dL (reference range: 0.67 – 1.17 mg/dL). The subject was administered meloxicam for spine pain in Sept 2019. Peak serum creatinine was observed on 17 Dec 2020 of 1.54 mg/dL. The subject discontinued study treatment on 01 Dec 2021 due to study termination by the MAH.

Table 94: Study 747-302 - Renal Treatment-Emergent AESIs in $\geq$ 1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Renal TEAE	13 (7.8)	17 (10.1)	5 (13.5)	5 (15.6)	8 (6.2)	12 (8.8)	4 (5.9)	8 (9.9)	9 (9.2)	9 (10.3)
Acute kidney injury	2 (1.2)	5 (3.0)	0	2 (6.3)	2 (1.6)	3 (2.2)	0	1 (1.2)	2 (2.0)	4 (4.6)
Hypalbuminaemia	1 (0.6)	4 (2.4)	1 (2.7)	3 (9.4)	0	1 (1.7)	0	1 (1.2)	1 (1.0)	3 (3.4)
Hyponatremia	1 (0.6)	2 (1.2)	0	2 (6.3)	1 (0.8)	0	1 (1.5)	0	0	2 (2.3)
Proteinuria	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Diabetic nephropathy	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Haematuria	2 (1.2)	1 (0.6)	1 (2.7)	0	1 (0.8)	1 (0.7)	0	0	2 (2.0)	1 (1.1)
Hyperkalaemia	1 (0.6)	1 (0.6)	1 (2.7)	0	0	1 (0.7)	0	0	1 (1.0)	1 (1.1)
Leukocyturia	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Renal failure	1 (0.6)	1 (0.6)	1 (2.7)	0	0	1 (0.7)	0	1 (1.2)	1 (1.0)	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

Note: The PT of thrombotic thrombocytopenic purpura (TTP) is included in the SMQs of both CV and renal TEAEs. While these events were captured as part of the broad SMQ based search for CV and renal TEAEs, because of the very unique underlying mechanism, TTP events are more appropriately considered separately and are summarized in the section describing renal TEAEs.

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

For each row category, a subject with two or more AEs in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline. Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2

Exposure-Adjusted Incidence of Renal TEAEs

An analysis of exposure-adjusted incidences of renal TEAEs and serious renal TEAEs by baseline disease stage is presented in Table 95 and Table 96.

Proposed SmPC Indicated Population

In the proposed SmPC indicated population (N=149), the incidence of exposure-adjusted renal TEAEs was 3.818 per 100 PYs in the OCA group and 2.877 per 100 PYs in the placebo group.

The incidence of exposure-adjusted serious renal TEAEs was 0.931 per 100 PYs in the OCA group and 0 per 100 PYs in the placebo group. The serious renal TEAE reported in the OCA group was TTP.

Table 95: Study 747-302 – Exposure-Adjusted Incidence Rate of Renal Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Renal TEAE	3.804 (341.76)	4.159 (408.77)	9.329 (53.60)	9.639 (51.87)	2.776 (288.16)	3.362 (356.90)	2.877 (139.05)	3.818 (209.56)	4.440 (202.71)	4.518 (199.22)
Acute kidney injury	0.567 (352.78)	1.188 (420.96)	0 (54.98)	3.682 (54.32)	0.672 (297.80)	0.818 (366.64)	0 (146.06)	0.485 (215.02)	0.967 (206.72)	1.942 (205.94)
Hypoalbuminaemia	0.281 (355.33)	0.959 (416.96)	1.822 (54.90)	5.654 (53.06)	0 (300.43)	0.275 (363.90)	0 (146.06)	0.471 (219.18)	0.478 (209.27)	1.465 (204.77)
Hyponatremia	0.283 (353.41)	0.477 (419.39)	0 (54.98)	3.802 (52.61)	0.335 (298.43)	0 (366.78)	0.694 (144.06)	0.613 (207.07)	0 (209.35)	0.979 (204.32)
Proteinuria	0 (355.40)	0.475 (420.77)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.29)	0 (146.06)	0.466 (214.66)	0 (209.35)	0.485 (206.12)
Thrombotic thrombocytopenic purpura	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.62)	0 (146.06)	0.931 (214.90)	0 (209.35)	0 (206.19)
Diabetic nephropathy	0 (355.40)	0.239 (419.28)	0 (54.98)	0 (54.48)	0 (300.43)	0.274 (364.80)	0 (146.06)	0.469 (213.08)	0 (209.35)	0 (206.19)
Haematuria	0.567 (352.53)	0.240 (417.06)	1.848 (54.12)	0 (54.48)	0.335 (298.41)	0.275 (362.58)	0 (146.06)	0 (215.07)	0.969 (206.48)	0.495 (202.00)
Hypokalaemia	0.282 (355.09)	0.237 (421.18)	1.829 (54.66)	0 (54.48)	0 (300.43)	0.273 (366.70)	0 (146.06)	0 (215.07)	0.478 (209.03)	0.485 (206.11)
Leukocyturia	0 (355.40)	0.237 (421.25)	0 (54.98)	0 (54.48)	0 (300.43)	0.273 (366.77)	0 (146.06)	0.465 (215.06)	0 (209.35)	0 (206.19)
Renal failure	0.281 (355.34)	0.237 (421.25)	1.821 (54.92)	0 (54.48)	0 (300.43)	0.273 (366.77)	0 (146.06)	0.465 (215.06)	0.478 (209.29)	0 (206.19)
Blood bicarbonate decreased	0.282 (355.22)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (300.25)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.17)	0 (206.19)
Blood creatinine increased	0.567 (352.73)	0 (421.26)	0 (54.98)	0 (54.48)	0.672 (297.76)	0 (366.78)	1.395 (143.39)	0 (215.07)	0 (209.35)	0 (206.19)

Preferred Term, IRY (PV)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Blood urea increased	0.283 (352.93)	0 (421.26)	0 (54.98)	0 (54.48)	0.336 (297.95)	0 (366.78)	0.696 (143.58)	0 (215.07)	0 (209.35)	0 (206.19)
Bone cyst	0.283 (353.06)	0 (421.26)	0 (54.98)	0 (54.48)	0.335 (298.08)	0 (366.78)	0.696 (143.71)	0 (215.07)	0 (209.35)	0 (206.19)
Chronic kidney disease	0.283 (353.92)	0 (421.26)	0 (54.98)	0 (54.48)	0.335 (298.95)	0 (366.78)	0 (146.06)	0 (215.07)	0.481 (207.87)	0 (206.19)
Hyperparathyroidism	0.282 (354.78)	0 (421.26)	0 (54.98)	0 (54.48)	0.334 (299.81)	0 (366.78)	0 (146.06)	0 (215.07)	0.479 (208.73)	0 (206.19)
Metabolic acidosis	0.281 (355.93)	0 (421.26)	1.821 (54.90)	0 (54.48)	0 (300.43)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.27)	0 (206.19)

AE=adverse event; IP=investigational product; IRY= number of patients with event per 100 patient year, MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PH=essential portal hypertension; PT=preferred term; PY=Patient-years; SmPC= Summaries of product characteristics; SOC=system organ class; TEAE=treatment-emergent adverse event

TEAE was any event (starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsened in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

AEs were coded using MedDRA Version 24.0.

Note: Patient-years sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last investigational product dose date/90 days, commercial OCA date, death date, and of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT. The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Sources: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Table 96: Study 747-302 – Exposure-Adjusted Incidence Rate of Serious Renal Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Serious Renal TEAE	0.563 (354.99)	0.950 (421.00)	1.829 (54.66)	0 (54.48)	0.333 (300.33)	1.091 (366.52)	0 (146.06)	0.931 (214.90)	0.957 (208.93)	0.960 (206.10)
Acute kidney injury	0 (355.40)	0.475 (421.16)	0 (54.98)	0 (54.48)	0 (300.43)	0.545 (366.69)	0 (146.06)	0 (215.07)	0 (209.34)	0.970 (206.10)
Thrombotic thrombocytopenic purpura	0 (355.40)	0.475 (421.10)	0 (54.98)	0 (54.48)	0 (300.43)	0.546 (366.62)	0 (146.06)	0.931 (214.90)	0 (209.33)	0 (206.19)
Hyperkalemia	0.282 (355.09)	0.237 (421.18)	1.829 (54.66)	0 (54.48)	0 (300.43)	0.273 (366.70)	0 (146.06)	0 (215.07)	0.478 (209.03)	0.485 (206.11)
Blood bicarbonate decreased	0.281 (355.30)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (300.33)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.23)	0 (206.19)
Hyperparathyroidism	0.281 (355.30)	0 (421.26)	0 (54.98)	0 (54.48)	0.333 (300.33)	0 (366.78)	0 (146.06)	0 (215.07)	0.478 (209.23)	0 (206.19)

AE=adverse event; IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PH=evidence portal hypertension; PT=preferred term; PY=Patient-years; SOC=system organ class; SmPC=Summary of product characteristics; TEAE=treatment-emergent adverse event TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded. AEs were coded using MedDRA Version 24.0.

Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline. Source: 747-302, Ad hoc 63, Ad hoc 63.1, Ad hoc 63.2

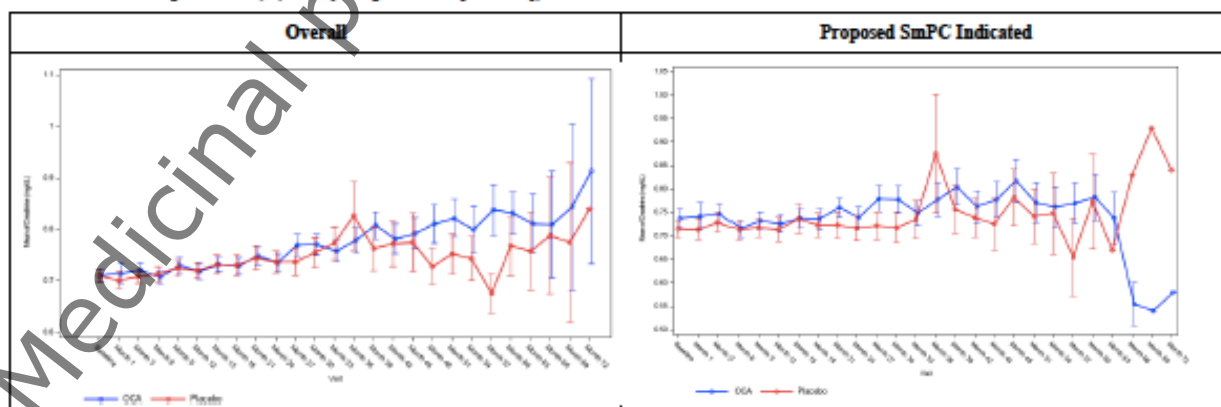
Renal Function Evaluations

Analyses of serum chemistry parameters included markers of renal function (serum creatinine, estimated glomerular filtration rate [eGFR]). Mean creatinine values over time are displayed in Figure 33 (overall versus proposed SmPC indicated populations) and Figure 34 (compensated versus decompensated populations). Mean eGFR values over time are displayed in Figure 35 (overall), Figure 36 (proposed SmPC indicated versus proposed SmPC contraindicated populations), and Figure 37 (compensated versus decompensated populations).

Proposed Indicated SmPC Population

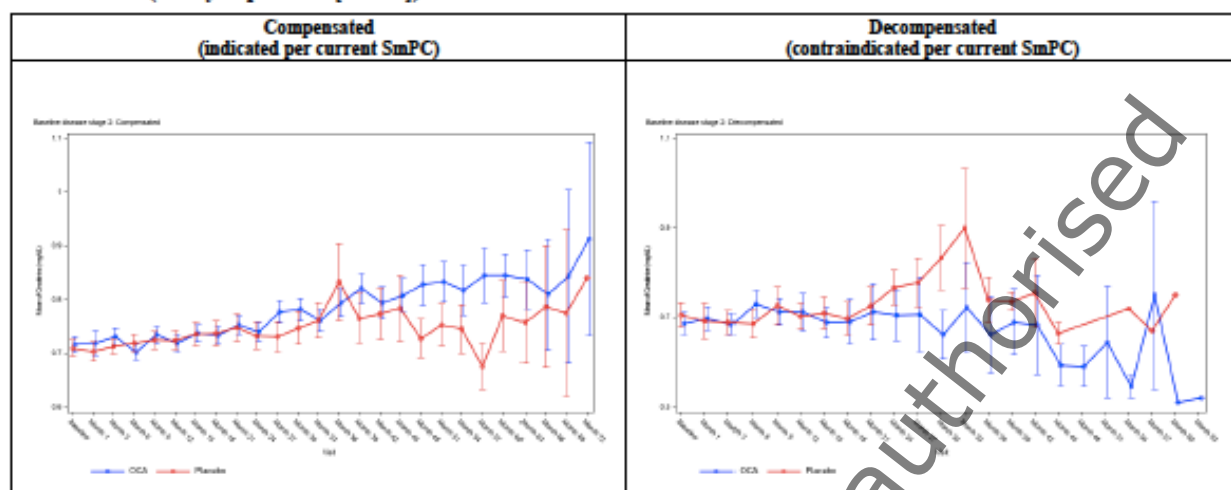
In the proposed SmPC indicated population (N=149), no clinically significant changes over time or across treatment groups were observed for serum creatinine or eGFR.

Figure 33: Mean (SE) Serum Creatinine Values Over Time by Baseline Disease Stage (Overall vs Proposed SmPC Indicated Populations) (Safety Population [N=334])



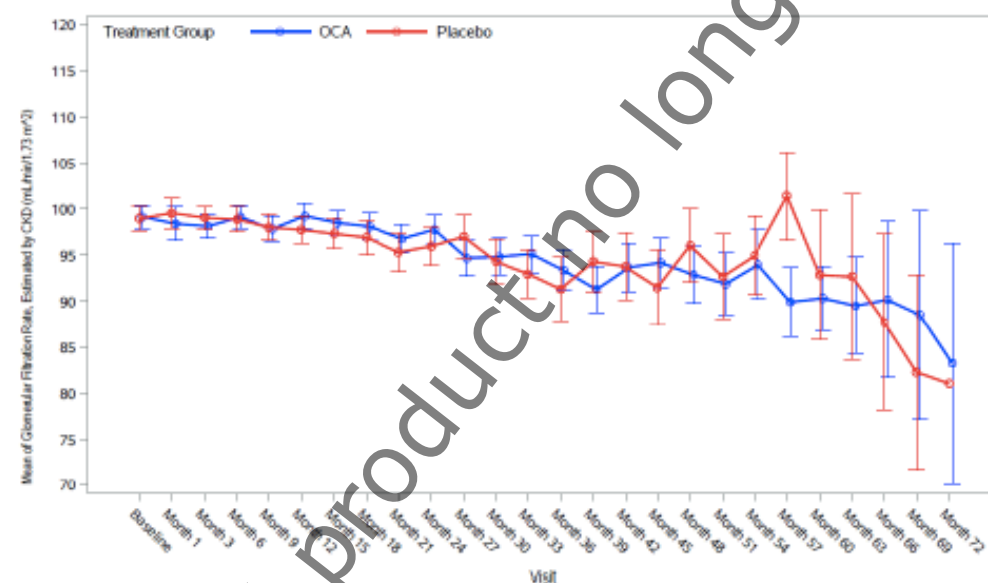
OCA=obeticholic acid; SmPC=Summary of Product Characteristics
Sources: 747-302, Ad hoc Figures 40, 40.1

Figure 34: Mean (SE) Serum Creatinine Values Over Time by Baseline Disease Stage (Compensated vs Decompensated) (Safety Population [N=334])



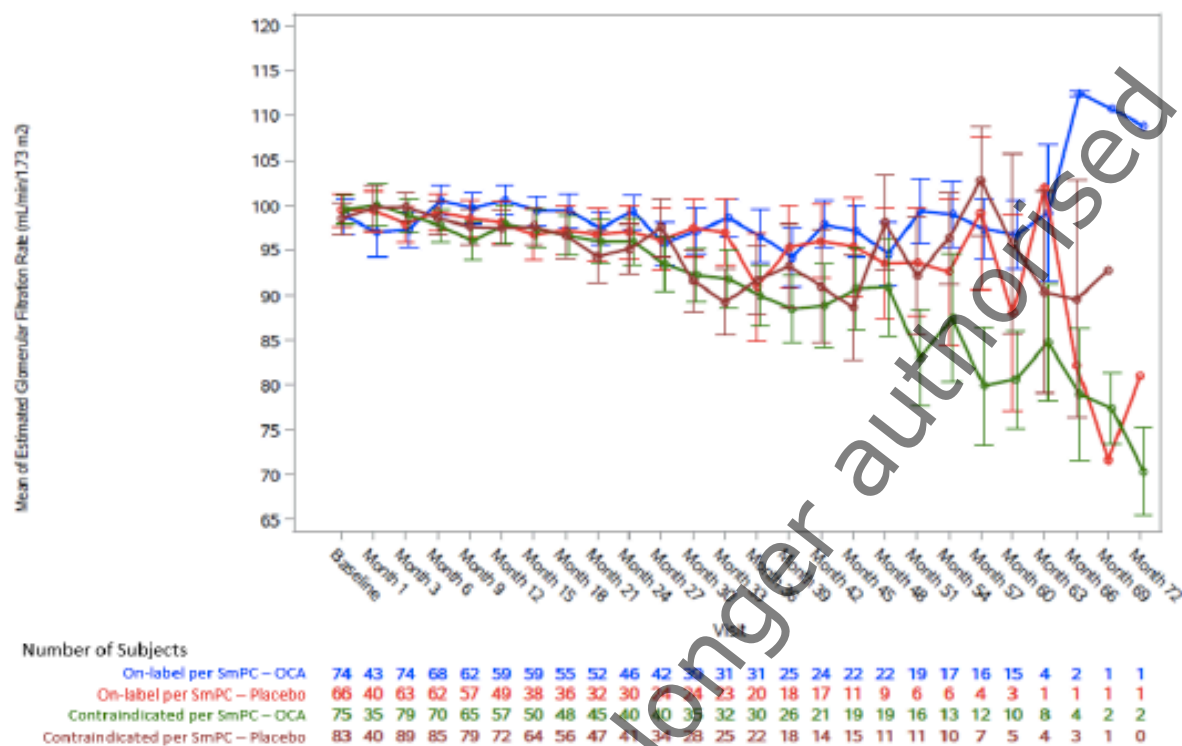
OCA=obeticholic acid; SmPC=Summary of Product Characteristics
Sources: 747-302, Ad hoc Figure 40.2

Figure 35: Mean (SE) Change in Estimated Glomerular Filtration Rate Values Over Time by Overall (Safety Population [N=334])



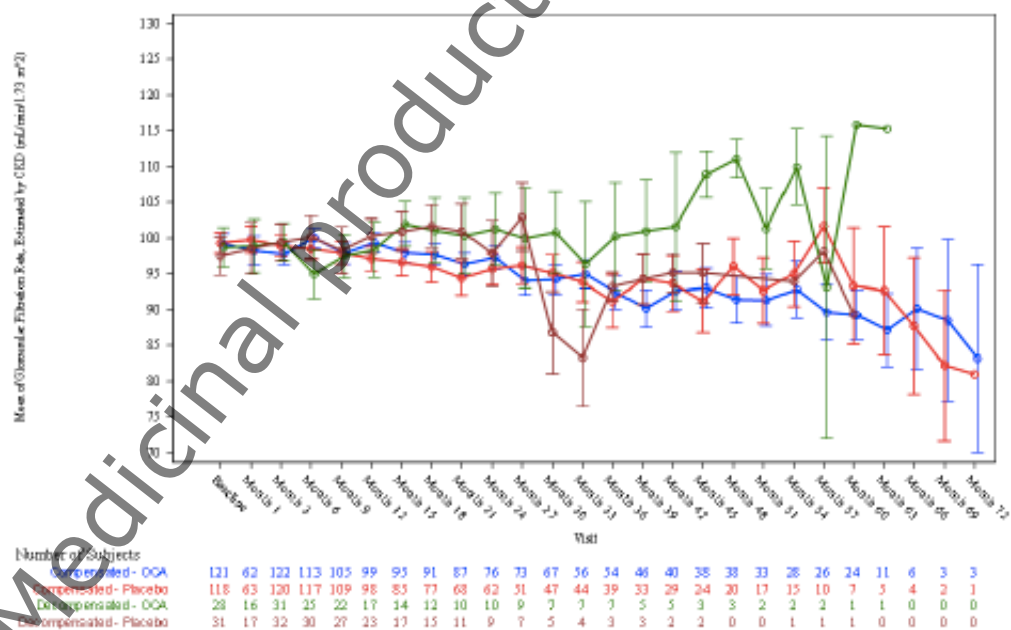
Number of Subjects
OCA 149 78 153 138 127 116 109 103 97 86 82 74 63 61 51 45 41 41 35 30 28 25 12 6 3 3
Placebo 149 80 152 147 136 121 102 92 79 71 58 52 48 42 36 31 26 20 17 16 11 8 5 4 2 1
OCA=obeticholic acid
Sources: 747-302, Ad hoc Figure 38.1

Figure 36: Mean (SE) Change in Estimated Glomerular Filtration Rate Values Over Time by Baseline Disease Stage (Proposed SmPC Indicated vs Proposed SmPC Contraindicated Populations) (Safety Population [N=334])



OCA=obeticholic acid; SmPC=Summary of Product Characteristics
Sources: 747-302, Ad hoc Figure 78.2

Figure 37: Mean (SE) Change in Estimated Glomerular Filtration Rate Values Over Time by Baseline Disease Stage (Compensated vs Decompensated) (Safety Population [N=334])



OCA=obeticholic acid
Sources: 747-302, Ad hoc Figure 78.5

Pruritus

Pruritus TEAEs were defined as any preferred term within the Pruritus Not Elsewhere Classified (NEC) high level term or any preferred term including "prur". Pruritus is a well characterized and known ADR of OCA.

Pruritus TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 97.

Proposed SmPC Indicated Population

The incidence for pruritus was higher in the OCA group (82.7%) compared to the placebo group (48.5%).

The majority of pruritus events were mild to moderate and managed with temporary interruption of OCA treatment or use of medications such as antihistamines for control of symptoms. The incidence of serious pruritus TEAEs was low; 1 subject in the OCA group and none in the placebo group reported a serious TEAE of pruritus.

Pruritus TEAEs that led to discontinuation of investigational product were reported in 14.8% OCA-treated subjects compared with 2.9% of placebo subjects.

Table 97: Study 747-302 - Pruritus Treatment-Emergent AEs in ≥1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=39	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Pruritus TEAE	86 (51.8)	133 (79.2)	19 (51.4)	24 (75.0)	67 (51.9)	109 (80.1)	33 (48.5)	67 (82.7)	53 (54.1)	66 (75.9)
Pruritus	85 (51.2)	132 (78.6)	19 (51.4)	24 (75.0)	66 (51.2)	108 (79.4)	32 (47.1)	66 (81.5)	53 (54.1)	66 (75.9)
Eye pruritus	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Pruritus allergic	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Rash pruritic	1 (0.6)	1 (0.6)	0	0	1 (0.8)	1 (0.7)	1 (1.5)	0	0	1 (1.1)
Vulvovaginal pruritus	1 (0.6)	1 (0.6)	0	0	1 (0.8)	1 (0.7)	0	0	1 (1.0)	1 (1.1)
Cholestatic pruritus	1 (0.6)	0	0	0	1 (0.8)	0	1 (1.5)	0	0	0

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.
Percentages were based on number of subjects in the Safety Population within each treatment group.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2

Exposure-Adjusted Incidence of Pruritus TEAEs

Exposure-adjusted incidence of pruritus TEAEs and serious pruritus TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 98 and Table 99, respectively.

Proposed SmPC Indicated Population

The incidence of exposure-adjusted pruritus TEAEs was 102.046 per 100 PYs in the OCA group and 34.642 per 100 PYs in the placebo group.

The incidence of exposure-adjusted serious pruritus TEAEs was 0.465 per 100 PYs in the OCA group and 0 per 100 PYs in the placebo group.

Table 98: Study 747-302 – Exposure-Adjusted Incidence Rate of Pruritus Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Pruritus TEAE	39.914 (215.46)	103.926 (127.98)	37.232 (179.95)	101.531 (107.36)	53.506 (35.51)	116.399 (20.62)	34.642 (95.26)	102.046 (65.66)	44.092 (120.20)	105.907 (62.32)
Pruritus	39.407 (215.70)	100.839 (130.90)	36.629 (180.19)	97.930 (110.28)	53.506 (35.51)	116.399 (20.62)	33.510 (95.49)	96.268 (68.56)	44.092 (120.20)	105.866 (62.34)
Eye pruritus	0 (355.40)	0.480 (416.86)	0 (300.43)	0.552 (362.38)	0 (54.98)	0 (54.48)	0 (146.06)	0.465 (215.03)	0 (209.35)	0.495 (201.83)
Pruritus allergic	0 (355.40)	0.482 (415.07)	0 (300.43)	0.555 (360.59)	0 (54.98)	0 (54.48)	0 (146.06)	0.958 (208.88)	0 (209.35)	0 (206.19)
Rash pruritic	0.285 (350.63)	0.240 (417.05)	0.338 (295.66)	0.276 (362.57)	0 (54.98)	0 (54.48)	0.708 (141.28)	0 (215.07)	0 (209.35)	0.495 (201.98)
Vulvovaginal pruritus	0.282 (354.11)	0.238 (420.26)	0.334 (299.13)	0.273 (365.79)	0 (54.98)	0 (54.48)	0 (146.06)	0 (215.07)	0.481 (308.05)	0.487 (205.20)
Cholestatic pruritus	0.282 (355.17)	0 (421.26)	0.333 (300.19)	0 (366.78)	0 (54.98)	0 (54.48)	0.686 (145.82)	0 (215.07)	0 (209.35)	0 (206.19)

AE=adverse event; CSPH=clinically evidence portal hypertension; IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PY=Patient-years; SmPC=Summary of Product Characteristics; TEAE=treatment-emergent adverse event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad hoc 36, Ad hoc 36.1, Ad hoc 36.2

Table 99: Study 747-302 – Exposure-Adjusted Incidence Rate of Serious Pruritus Treatment-Emergent Adverse Events by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, IRY (PY)	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Number of Subjects with at least 1 Serious Pruritus TEAE	0 (355.40)	0.475 (421.12)	0 (300.43)	0.345 (366.64)	0 (54.98)	0 (54.48)	0 (146.06)	0.465 (215.01)	0 (209.35)	0.485 (206.11)
Pruritus	0 (355.40)	0.475 (421.12)	0 (300.43)	0.545 (366.64)	0 (54.98)	0 (54.48)	0 (146.06)	0.465 (215.01)	0 (209.35)	0.485 (206.11)

AE=adverse event; CSPH=clinically evidence portal hypertension; IRY= number of patients with event per 100 patient year; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticolic acid; PY=Patient-years; SmPC=Summary of Product Characteristics; TEAE=treatment-emergent adverse event
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
AEs were coded using MedDRA Version 24.0.
Note: Patient-years = sum of individual patient-years for each event. Each individual's patient-years will be derived as the first onset date of an event or min of (last IP dose date+30 days, commercial OCA date, death date, end of study date) if no event minus the first dose date plus 1 divided by 365.25 days/year for each unique SOC/PT.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad hoc 63, Ad hoc 63.1, Ad hoc 63.2

Management of Pruritus

Management strategies for pruritus are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 100.

Proposed SmPC Indicated Population

An assessment of management strategies for pruritus was conducted in the proposed SmPC indicated population; results are as follows:

- 23.5% of subjects in the OCA group reported a drug interruption (i.e., a drug holiday) or a decrease in dose to manage pruritus. Most subjects who reported a drug interruption for pruritus experienced a single interruption.
- A medication was used to manage pruritus in approximately 54.3% of subjects in the OCA group. The most commonly used medications to manage pruritus were antihistamines (33.3% of subjects) and bile acid sequestrants (BAS) (18.5% of

subjects). A total of 33.3% of OCA-treated subjects reported use of “other” types of medications, which most frequently included rifampicin, naltrexone, and selective serotonin inhibitors; no trend was observed for any particular medication class.

Table 100: Study 747-302 - Management Strategies for Treatment-Emergent AESI of Pruritus by Overall and Baseline Disease Stage (Safety Population [N=334])

Management Strategy, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subject with at least 1 Pruritus TEAE of Special Interest	86 (51.8)	133 (79.2)	19 (51.4)	24 (75.0)	67 (51.9)	109 (80.1)	33 (48.5)	67 (82.7)	53 (54.1)	66 (75.9)
Interruption of Investigational Product ^a	8 (4.8)	28 (16.7)	1 (2.7)	5 (15.6)	7 (5.4)	23 (16.9)	5 (7.4)	19 (23.5)	3 (3.1)	9 (10.3)
Decreased Dose of Investigational Product ^b	9 (5.4)	36 (21.4)	1 (2.7)	5 (15.6)	8 (6.2)	31 (22.8)	4 (5.9)	19 (23.5)	5 (5.1)	17 (19.5)
Any Medication Initiated for Pruritus	47 (28.3)	86 (51.2)	12 (32.4)	15 (46.9)	35 (27.1)	71 (52.2)	19 (27.9)	44 (54.3)	28 (28.6)	42 (48.3)
Bile Acid Sequestrants	14 (8.4)	36 (21.4)	4 (10.8)	8 (25.0)	10 (7.8)	28 (20.6)	5 (7.4)	15 (18.5)	9 (9.2)	21 (24.1)
Antihistamines	22 (13.3)	47 (28.0)	4 (10.8)	5 (15.6)	18 (14.0)	42 (30.9)	12 (17.6)	27 (33.3)	10 (10.2)	20 (23.0)
Corticosteroids	4 (2.4)	8 (4.8)	0	0	4 (3.1)	8 (5.9)	2 (2.9)	5 (6.2)	2 (2.0)	3 (3.4)
Other	24 (14.5)	49 (29.2)	7 (18.9)	9 (28.1)	17 (13.2)	40 (29.4)	8 (11.8)	27 (33.3)	16 (16.3)	22 (25.3)

AE=adverse event; AESI=adverse events of special interest; CP=Child-Pugh Score; CRF=case report form; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

^a Subjects report more than one actions with multiple occurrences for the pruritus are counted only once.

^b Interruption and decreased dose of investigational product are based on AE CRF and exposure CRF.

Source: 747-302 CSR, Table 14.3.1, Table 14.3.1.1.1, Table 14.3.1.1.2, Table 14.3.1.13.1; 747-302 Ad hoc, Table 14.3.1.13.1.1, Table 14.3.1.13.1.2

Laboratory Values Over Time

Haematology and Coagulation

No clinically significant changes over time or across treatment groups were observed with respect to Haematology and Coagulation parameters.

Serum Chemistry

Analyses of serum chemistry parameters and liver biochemistry included markers of hepatocellular injury (ALT, AST), cholestasis (GGT, ALP, bilirubin [total and direct]), liver synthetic function (INR, albumin), and portal hypertension (platelet count).

Mean serum chemistry parameter values over time are summarized by overall versus proposed SmPC indicated populations in Figure 38 and by compensated versus decompensated populations in Figure 39.

Proposed SmPC Indicated Population

Consistent trends in serum chemistry parameters were observed in the overall and proposed SmPC indicated populations.

Assessment of the MAH's response

As initially noted, Study 747-302 shows a more concerning overall safety profile as compared to that reported in the initial submission, given the higher incidence rates of all types of TEAEs overall and as compared to placebo treated patients. OCA treated patients showed a higher incidence of TEAEs, severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death, both in the general safety population and the subset of patients with compensated liver disease. In addition, the higher rates observed in OCA treated patients for some relevant AESI like cardiovascular events (including adjudicated MACE), renal events (including AKI), DILI and portal hypertensive gastropathy events, liver transplant and death adjudicated events, both in the overall safety population and for the subset of

patients with compensated disease are a matter of major concern.

The MAH recognizes there is some potential safety risk given the imbalance observed in the overall safety population of Study 747-302 and cannot exclude a contributory role of OCA. Therefore, the MAH has proposed to further restrict the SmPC indicated population to patients with PBC without cirrhosis or with compensated cirrhosis who do not have clinical evidence of portal hypertension or a prior decompensation event. This analysis was not pre-specified and the newly proposed target population for OCA is data driven by an otherwise limited number of subjects of Study 747-302. Thus, it is uncertain if a more benign safety profile can be firmly concluded in this subset of PBC patients.

A reduction in the overall incidence of serious TEAEs (18.5% OCA vs 25% placebo in the newly proposed indication vs 31.5% OCA vs 31.9% placebo in the overall safety population) and TEAE leading to death (1.2% OCA vs 0 placebo in the restricted indication vs 3.0% OCA and 1.2% in the overall safety population) in the restricted PBC population is noted, with lower rates of serious TEAEs in OCA. The incidence of TEAEs leading to death remain higher in OCA: 3.0% OCA vs 1.2% placebo in the overall population vs 1.2% OCA vs 0 placebo, but numbers are too limited to draw firm conclusion. The lower incidence of serious TEAEs in the restricted PBC population is not totally unexpected considering that most serious TEAEs are related to the severity and progression of the disease. By contrary, the incidence of severe TEAE (45.7% OCA vs 32.4% placebo), treatment related TEAEs (75.3% OCA vs 55.9% placebo), TEAE leading to IP withdrawal (33.3% OCA vs 26.5% placebo), to dose reductions (24.7% OCA vs 10.3% placebo), dose interruptions (25.9% OCA vs 25.0% placebo) or to treatment discontinuation (14.8% OCA vs 19.1% placebo) do not show relevant changes compared to those reported for the overall safety population and most of them remain higher for OCA treated subjects, which is not totally reassuring. Incidence of thrombotic and cardiovascular disorders (6.2% OCA vs 2.9% placebo), renal AESI (9.9% OCA vs 5.9% placebo), including AKI and renal failure events, cholelithiasis (3.7% OCA vs 1.5% placebo), portal hypertensive gastropathy (3.7% OCA vs 0 placebo), DILI (2.5% OCA vs 0 placebo), liver transplant (1 case each in the early stage PBC population) or all-cause deaths (8 events in OCA vs 2 in placebo) are observed more frequently in OCA treated subjects compared to placebo treated patients even in the newly proposed subset of early stage PBC patients. The number of events are sometimes too limited to firmly conclude, but the imbalance observed in the overall safety population remains in this restricted early stage PBC subset, which is concerning. Moreover, treatment is associated with significantly high incidences of pruritus (81.5% in OCA vs 47.1% placebo, which lead to treatment interruption in 23.5% OCA subjects and pharmacological treatment in 54.3% in OCA vs 7.4% and 27.9%, respectively, in placebo), and gastrointestinal disorders (63% OCA vs 50% placebo), including higher rates of severe cases, which have an important impact in patient's health condition and that reflects an overall worse health condition in OCA treated subjects. A slightly higher frequency of fatigue was also observed in the OCA group (9.9% OCA vs 7.4% placebo). In addition, the similar rates of hepatic TEAEs observed in OCA and placebo treated subjects in the newly proposed early stage PBC population raise doubts on the actual benefit of treatment.

RMM currently in place are considered insufficient. A thorough revision of the SmPC Section 4.4. and 4.8 to properly reflect relevant risks is needed.

In summary, even if an apparent less toxic safety profile is seen in this subset of PBC patients, still an increased toxicity and poor tolerability of OCA treatment is noted in the subset of patients with an early stage, mostly asymptomatic and slow progressive condition. Moreover, it is important to note that this population was not pre-specified but it is data driven and it is comprised by a low number of patients that hampers the interpretation of the reported results. In addition, the anticipated long-term exposure in clinical practice and difficulties to identify and exclude patients at increased risk of relevant events, add further concerns, particularly in the absence of a demonstrated clinical benefit in changing the disease progression.

Question 11

The high rate of severe TEAEs both in the general safety population (51.2% OCA vs 39.2% placebo) and in the subset of compensated patients (47.1% vs 36.4%) is noted. This is mainly driven by pruritus TEAEs, but also by a higher rate of severe gastrointestinal disorders (oesophageal varices haemorrhage, abdominal pain, vomiting, melaena, and ascites), infections, hepatobiliary disorders (hepatic cirrhosis, hepatic failure), acute respiratory failure, back pain, and cerebrovascular accident are reported in OCA treated patients, which is concerning. The MAH is invited to present the safety profile of severe TEAEs for the two subsets of patients with compensated and decompensated disease and discuss to what extent any differences at all would be expected.

Summary of the MAH's response

The MAH assessed the frequency of events between OCA and placebo in the overall, compensated (indicated per current SmPC), and decompensated (contraindicated per current SmPC) populations. Given the subjects in these various groups have more advanced PBC disease and many of which are now contraindicated, the MAH has explored a more appropriate population that maximizes the benefit:risk profile. Therefore, the MAH has now proposed a revised SmPC population to contraindicate patients with compensated cirrhosis with evidence of portal hypertension (PH) and/or hepatic decompensation at baseline.

A summary of severe TEAEs in ≥ 2 overall OCA-treated subjects by SOC and PT by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations is presented in Table 101.

The incidence of severe TEAEs was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). Within earlier stage PBC, the incidence of severe TEAEs was higher for compensated OCA-treated subjects compared to proposed SmPC indicated population OCA-treated subjects. In the proposed SmPC indicated population, the majority of TEAEs were mild or moderate across treatment groups. With the exception of pruritus, individual PTs of severe TEAEs occurred in ≤ 2 subjects.

Severe Gastrointestinal Disorders

In comparison to the overall population, the incidence rate of the severe PTs of oesophageal varices haemorrhage, abdominal pain, melaena, and ascites was generally balanced in the proposed SmPC indicated population:

- Oesophageal varices haemorrhage (none in the OCA group and 1.5% in the placebo group)
- Abdominal pain (1.2%) in the OCA group and 1.5% in the placebo group.
- Melaena and ascites (none across treatment groups)

Within the proposed SmPC indicated population, the only severe TEAE that occurred at a higher incidence in OCA-treated subjects (2.5%) compared to placebo-treated subjects (none) was vomiting. The severe TEAE of vomiting was assessed by the Investigator as unlikely, or not related to investigational product.

Infections and infestations

Severe PTs of peritonitis bacterial and sepsis were not observed in the proposed SmPC indicated population. In the overall population, the incidence rate was 1.2% for both events in the OCA group and none in the placebo group. In the proposed SmPC indicated population, the incidence of severe PT of

urinary tract infection was low and was higher in the OCA-treated subjects (2.5%) compared to placebo-treated subjects (none).

Hepatobiliary Disorders

Severe PTs of hepatic cirrhosis or hepatic failure were not observed in the proposed SmPC indicated subgroup. In the overall population, the incidence rate for both events was 1.2% in the OCA group and 0.6% in the placebo group.

Acute Respiratory Failure

In the overall population, 2 (1.2%) subjects in the OCA group had severe TEAEs of acute respiratory failure: 1 subject was in the proposed SmPC indicated population and 1 subject was in the proposed SmPC contraindicated population. Both severe TEAEs of acute respiratory failure led to death and were considered not related or unlikely related to investigational product by the Investigator.

- One female subject with PBC in the proposed SmPC indicated and compensated populations died of acute respiratory failure, in the setting of Stage 4 B-cell lymphoma with tumour lysis syndrome, on 10 Sep 2016 (Study Day 317), approximately 10 months after the initiation of OCA. Investigational product was withdrawn in response to the events of lymphoma and AKI with the last dose administered on 20 Aug 2016 (Study Day 296). The death was considered not related to investigational product by the Investigator.
- One male subject with PBC in the proposed SmPC contraindicated and compensated populations died of lower respiratory tract infection, with underlying influenza A and hospital acquired pneumonia, on 09 Feb 2017 (Study Day 183), approximately 6 months after the initiation of OCA. The subject's last dose of investigational product was on 15 Dec 2016 (Study Day 127). The death was considered unlikely related to investigational product by the Investigator.

Severe Back Pain

In the overall population, 2 (1.2%) subjects in the OCA group had severe TEAEs of back pain: 1 subject was in proposed SmPC indicated population and 1 subject was in the contraindicated population. Both severe TEAEs of back pain were assessed by the Investigator as not related to investigational product.

Severe Cerebrovascular Accident and TTP

In the overall population, 2 (1.2%) subjects in the OCA group experienced severe TEAEs of TTP and 1 (1.2%) subject each in the OCA group of the proposed SmPC indicated and proposed SmPC contraindicated populations experienced a severe TEAE of cerebrovascular accident. Of note, 2 events of TTP in 2 subjects in the OCA group were captured in the SMQ search criteria for both CV and renal TEAEs. However, since the underlying pathophysiology for TTP is not related to atherosclerotic mechanisms, the TTP cases are discussed under renal TEAEs.

- A female subject with PBC in proposed SmPC indicated population reported a serious TEAE of TTP on 06 Jun 2016 (Study Day 111), approximately 4 months after the initiation of OCA. The patient began rifampicin approximately 3 months after the initiation of OCA, and it was ongoing at the time of the event. Investigational product was initially interrupted and later withdrawn in response to the event. The peak creatinine documented following the diagnosis of TTP was 1.5 mg/dl. The event was considered resolved with sequelae (plasmapheresis [as needed]) on 09 Jul 2016 (Study Day 144). The Investigator assessed the event of TTP as severe and not related to investigational product.
- One female subject with PBC in proposed SmPC indicated population reported serious TEAEs of TTP and cerebrovascular accident on 10 Oct 2019 (Study Day 441), approximately 1 year and 3 months after the initiation of OCA. While the subject was in the proposed SmPC indicated

population when she began OCA, she had an elastography score of 16.5 kPa measured on 29 Jan 2019 (Study Day 187) which may be outside of the proposed population description. The subject presented to the emergency department several months later for evaluation and admitted to the intensive care unit with the diagnosis of sub-acute stroke (serious TEAESI of cerebrovascular accident) and subsequently confirmed a diagnosis of TTP with disintegrin and metalloproteinase with thrombospondin motifs activity noted at 2%. Investigational product was withdrawn in response to the events of cerebrovascular accident and TTP. The event of cerebrovascular accident was considered resolved on 26 Oct 2019 (Study Day 457) and TTP was considered resolved on 04 Dec 2019 (Study Day 496). Both events were considered severe and unlikely related to investigational product.

Examining the two cases of TTP that occurred in subjects receiving OCA, 1 had ongoing treatment with rifampicin at the time of the event. Rifampicin has a reported association with TTP (Hamad 2020, Fahal 1992, Gupta 2005). The second subject with TTP was likely idiopathic, which is consistent with current understanding (Joly 2017).

Table 101: Study 747-302 - Summary of Severe Treatment-Emergent Adverse Events in ≥2 Overall OCA-treated Subjects by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

System Organ Class, n (%) Preferred Term	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Severe TEAE	65 (39.2)	86 (51.2)	18 (48.6)	22 (68.8)	47 (36.4)	64 (47.1)	22 (32.4)	37 (45.7)	43 (43.9)	49 (56.3)
Skin and subcutaneous tissue disorders	16 (9.6)	51 (30.4)	5 (13.5)	8 (25.0)	11 (8.5)	43 (31.6)	9 (13.2)	26 (32.1)	7 (7.1)	25 (28.7)
Pruritus	15 (9.0)	51 (30.4)	5 (13.5)	8 (25.0)	10 (7.8)	43 (31.6)	8 (11.8)	26 (32.1)	7 (7.1)	25 (28.7)
Gastrointestinal disorders	15 (9.0)	23 (13.7)	6 (16.2)	7 (21.9)	9 (7.0)	16 (11.8)	3 (4.4)	7 (8.6)	12 (12.2)	16 (18.4)
Oesophageal varices haemorrhage	3 (1.8)	4 (2.4)	1 (2.7)	1 (3.1)	2 (1.6)	3 (2.2)	1 (1.5)	0	2 (2.0)	4 (4.6)
Abdominal pain upper	1 (0.6)	3 (1.8)	1 (2.7)	2 (6.3)	0	1 (0.7)	0	1 (1.2)	1 (1.0)	2 (2.3)
Ascites	1 (0.6)	3 (1.8)	1 (2.7)	1 (3.1)	0	2 (1.5)	0	0	1 (1.0)	3 (3.4)
Abdominal pain	2 (1.2)	2 (1.2)	0	1 (3.1)	2 (1.6)	1 (0.7)	1 (1.5)	1 (1.2)	1 (1.0)	1 (1.1)
Diarrhoea	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	0	1 (1.0)	2 (2.3)
Melaena	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Vomiting	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Infections and infestations	5 (3.0)	11 (6.5)	1 (2.7)	5 (15.6)	4 (3.1)	6 (4.4)	2 (2.9)	4 (4.9)	3 (3.1)	7 (8.0)
Urinary tract infection	0	3 (1.8)	0	1 (3.1)	0	2 (1.5)	0	2 (2.5)	0	1 (1.1)
Peritonitis bacterial	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Sepsis	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	0	0	2 (2.3)
Hepatobiliary disorders	4 (2.4)	10 (6.0)	2 (5.4)	4 (12.5)	2 (1.6)	6 (4.4)	0	1 (1.2)	4 (4.1)	9 (10.3)
Hepatic cirrhosis	1 (0.6)	2 (1.2)	0	0	1 (0.8)	2 (1.5)	0	0	1 (1.0)	2 (2.3)
Hepatic failure	1 (0.6)	2 (1.2)	1 (2.7)	1 (3.1)	0	1 (0.7)	0	0	1 (1.0)	2 (2.3)
Nervous system disorders	12 (7.2)	9 (5.4)	1 (2.7)	3 (9.4)	11 (8.5)	6 (4.4)	6 (8.8)	4 (4.9)	6 (6.1)	5 (5.7)
Cerebrovascular accident	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)

System Organ Class, n (%) Preferred Term	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
General disorders and administration site conditions	4 (2.4)	7 (4.2)	3 (8.1)	3 (9.4)	1 (0.8)	4 (2.9)	1 (1.5)	2 (2.5)	3 (3.1)	5 (5.7)
Fatigue	3 (1.8)	2 (1.2)	3 (8.1)	1 (3.1)	0	1 (0.7)	0	0	3 (3.1)	2 (2.3)
Injury, poisoning and procedural complications	7 (4.2)	6 (3.6)	2 (5.4)	3 (9.4)	5 (3.9)	3 (2.2)	4 (5.9)	2 (2.5)	3 (3.1)	4 (4.6)
Fall	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders	4 (2.4)	6 (3.6)	0	3 (9.4)	4 (3.1)	3 (2.2)	0	2 (2.5)	4 (4.1)	4 (4.6)
Acute respiratory failure	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)
Blood and lymphatic system disorders	3 (1.8)	5 (3.0)	3 (8.1)	1 (3.1)	0	4 (2.9)	0	3 (3.7)	3 (3.1)	2 (2.3)
Anaemia	1 (0.6)	3 (1.8)	1 (2.7)	1 (3.1)	0	2 (1.5)	0	1 (1.2)	1 (1.0)	2 (2.3)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Musculoskeletal and connective tissue disorders	1 (0.6)	3 (1.8)	0	1 (3.1)	1 (0.8)	2 (1.5)	0	1 (1.2)	1 (1.0)	2 (2.3)
Back pain	0	2 (1.2)	0	1 (3.1)	0	1 (0.7)	0	1 (1.2)	0	1 (1.1)

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics
TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

Adverse events were coded using MedDRA Version 24.0.

For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Sources: 747-302 CSR Table 14.3.1.4.1; 747-302, Ad Hoc 76.1, Ad Hoc 76.2

Assessment of the MAH's response

A summary of severe TEAEs in ≥ 2 overall OCA-treated subjects by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), as requested, is provided. In addition, these events are presented for the new proposed SmPC indicated, and proposed SmPC contraindicated populations. Not unexpectedly, these data show that the incidence of severe TEAEs was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than in subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). Within earlier stage PBC, contrary to the MAH's claim, the incidence of severe TEAEs was roughly similar for compensated OCA-treated subjects and for the newly proposed SmPC indicated population OCA-treated subjects overall (47.1% vs 45.7%, respectively) and this was the case for the majority of severe individual TEAEs. The only exception is a numerical decrease in the incidence of severe GI TEAEs (11.8% vs 8.6% for compensated per current SmPC or proposed SmPC, respectively) and hepatobiliary disorders (4.4% vs 1.2%), of uncertain meaning. Nevertheless, even in the mildest PBC population, as defined by the newly proposed indication, there is an increased risk of severe TEAEs in OCA treated patients vs placebo treated patient overall (45.7%OCA vs 32.4%placebo), mostly driven by TEAEs like pruritus (32.1%OCA vs 11.8%placebo), GI disorders (8.6% vs 4.4%), infections (4.9% vs 2.9%), and hepatobiliary disorders (1.2% OCA vs 0 placebo).

Issue solved. The information requested has been provided. Even if a more benign safety profile is observed in a milder subset of the PBC population, this is a non-prespecified, data driven analysis, and as such it should be interpreted with caution.

Question 12

Renal AESIs were also reported more frequently in patients treated with OCA, both for the overall safety population (17 (10.1%) subjects in the OCA and 13 (7.8%) subjects in the placebo groups, with acute kidney injury reported by 3.0 % in OCA vs 1.2% in placebo treated

patients), and for the subset of patients with compensated disease (8.8% OCA-treated and 6.2% placebo-treated patients experienced a renal AESI, with acute kidney injury reported by 2.2% in OCA and 1.6% in placebo treated patients). In addition, it has been reported that exposure to OCA was associated with a small reduction in estimated glomerular filtration rate (eGFR) in a NASH clinical study. The higher incidence of renal events in patients treated with OCA regardless of the severity of the underlying liver disease is worrisome. Please discuss.

Summary of the MAH's response

Renal TEAESIs

The MAH evaluated renal TEAESIs in OCA-treated subjects from Study 747-302 and post-marketing data. From the totality of these analyses, the MAH concluded there is no increased risk of acute kidney injury (AKI) in the proposed SmPC indicated population.

- Study 747-302: The incidence of AKI in the proposed SmPC indicated population was lower compared to the overall and compensated populations. The PT of AKI was reported in 1 subject in the OCA group, which was considered not related to investigational product by the Investigator.
 - Upon subject-level review, the majority of subjects with the renal TEAESIs had serum creatinine levels within normal ranges.
- Ocaliva Postmarketing Data: Cumulatively, from over 35,000 patient-years exposure from marketing experience, there has been no increased risk of AKI.

Mean eGFR

No clinically significant changes overtime or across treatment groups were observed with respect to eGFR or serum creatinine in 3 long-term, double-blinded, placebo-controlled studies in patients with liver fibrosis due to NASH (Study 747-303, FLINT, and 2001).

Similar results were observed in Study 747-302. Within 4 years of treatment, no clinically significant changes in mean eGFR values over time or across treatment groups were observed with respect to eGFR in the overall population, as well as in the compensated and proposed SmPC indicated populations. Interpretation of data at later timepoints (Month 48 and beyond) was limited due to fewer observations in each treatment group.

Study 747-302: Renal TEAESIs

Renal TEAESIs are summarized overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 102. A listing of subjects with treatment-emergent AKI is presented in Table 103.

The incidence of renal TEAESIs was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). Within earlier stage PBC, the incidence of renal TEAESIs was higher for compensated OCA-treated subjects compared to proposed SmPC indicated OCA-treated subjects. In the proposed SmPC indicated population, with the exception of TTP, individual renal TEAESIs occurred in 1 subject each.

Renal TEAESIs were defined as events included in the following broad SMQs: acute renal failure, chronic kidney disease, proteinuria, renovascular disorders, or tubulointerstitial diseases.

The following groups were coded under renal TEAESI and represent a heterogeneous group of conditions with different mechanisms of change or injury:

Groups	Preferred Term
Kidney-related • Impaired function • Infection • Other	Renal failure, acute kidney injury, proteinuria, leukocyturia, urinary tract infection, hyperkalaemia, renal tumour
Endocrine, Liver, or Kidney-related	Hyponatraemia, hypoalbuminaemia
Haematology/Immunology-related	Thrombotic thrombocytopenic purpura
Diabetes-related	Diabetic nephropathy

Acute Kidney Injury

The incidence of AKI in the proposed SmPC indicated population was lower compared to the overall and compensated populations. Except for 1 subject all subjects who experienced a renal TEAESI of AKI were in the proposed SmPC contraindicated population (4 [4.6%] subjects in the OCA group and 2 [2.0%] subjects in the placebo group). The subject in the proposed SmPC indicated population who had an AKI is briefly discussed below. The Investigator considered the event as a non-serious TEAE and not related to investigational product.

- One female subject with PBC was referred to the emergency room on 20 Aug 2016 (Study Day 296) for evaluation of moderate left upper quadrant abdominal pain (non-serious AE). On 23 Aug 2016 (Study Day 299), the subject was hospitalized with the diagnosis of Stage 4 B-cell lymphoma (SAE) with renal/breast/lung/central nervous system involvement. The metastatic disease was thought to have originated from the right kidney. On the same day, the subject was diagnosed reported to have with "acute kidney injury" on the basis of an elevated serum urea level but otherwise normal renal function tests (note: urea is commonly elevated in metastatic lymphoma patients). Investigational product was withdrawn in response to the events of lymphoma and acute kidney injury (AKI), with the last dose administered on 20 Aug 2016 (Study Day 296). The Investigator assessed the event of lymphoma as severe and AKI as moderate in severity. On 03 Sept 2016 (Study Day 310), the subject completed the first cycle of chemotherapy (R-EPOCH). On 05 Sep 2016 (Study Day 312), the subject was transferred to the intensive care unit as she developed acute hypoxemic respiratory failure (SAE) and subsequently intubated due to worsening hypoxia and respiratory distress on 09 Sep 2016 (Study Day 316). Additional diagnoses were tumour lysis syndrome, and pancytopenia with neutropenia. The subject's family decided to pursue comfort care and the subject was extubated and died due to the event of acute respiratory failure on the same day. The events of lymphoma, AKI, and the fatal event of acute respiratory failure were all considered not related to investigational product by the Investigator.

Other Renal TEAESIs

With the exception of TTP, all other renal TEAESIs in OCA-treated subjects were mild to moderate in severity. The renal TEAESIs of TTP in the proposed SmPC indicated population are briefly discussed below. None of the cases were considered related to investigational product.

- One female subject presented to hospital with confusion and a syncope having been severely thrombocytopenic for at least 27 days prior to the presentation. The TEAE of TTP was diagnosed on 06 Jun 2016 (Study Day 111), approximately 4 months after the initiation of OCA. The patient began rifampicin approximately 3 months after the initiation of OCA, and it was ongoing at the time of the event. Investigational product was initially interrupted and later withdrawn in response to the event. The peak creatinine documented following the diagnosis of TTP was mildly

elevated at 1.5 mg/dL (reference range: 0.6-1.3). The subject was treated with steroids, plasmapheresis and Rituximab. The event was considered resolved with sequelae (plasmapheresis [as needed]) on 09 Jul 2016 (Study Day 144). The Investigator assessed the event of TTP as severe and not related to investigational product.

- One female subject tPBC reported serious TEAEs of cerebrovascular accident and TTP on 10 Oct 2019 (Study Day 441), approximately 1 year and 3 months after the initiation of OCA. While the subject was programmatically assigned to the proposed SmPC indicated population upon initiation of OCA, elastography score of 16.5 kPa was measured on 29 Jan 2019 (Study Day 187). On 10 Oct 2019 (Study Day 441) the subject presented to the emergency department for evaluation and was admitted to the intensive care unit with the diagnosis of sub-acute stroke (serious TEAE of cerebrovascular accident) and subsequently a confirmed diagnosis of TTP with disintegrin and metalloproteinase with thrombospondin motifs activity noted low at 2%. Investigational product was withdrawn in response to the events of cerebrovascular accident and TTP. The event of cerebrovascular accident was considered resolved on 26 Oct 2019 (Study Day 457) and TTP was considered resolved on 04 Dec 2019 (Study Day 496). Both events were considered severe and unlikely related to investigational product.

Examining the two cases of TTP that occurred in subjects receiving OCA, 1 had ongoing treatment with rifampicin at the time of the event. Rifampicin has a reported association with TTP (Hamad 2020, Fahal 1992, Gupta 2005). The second subject with TTP was likely idiopathic, which is consistent with current understanding (Joly 2017).

One event of renal failure was reported in 1 OCA-treated subject (non-serious) and one event of diabetic nephropathy (non-serious) in the proposed SmPC indicated population. These events were considered mild and not related to investigational product by the Investigator.

- One female subject with PBC and a history of pruritus, initiated OCA study treatment on 13 Jan 2017. The subject's serum creatinine at baseline on 12 Jan 2018 was 0.87 mg/dL (reference range: 0.51 – 0.96 mg/dL). On 23 Feb 2018 (D42), the subject experienced an episode of severe pruritus and was maintained rifampicin, phenobarbital, and cholestyramine with the addition of bezafibrate. On 11 Jul 2018 (D180), a serum creatinine value of 0.92 mg/dL was reported for the subject a MELD score of 6.4. Approximately 8 months after the initiation of OCA, the subject discontinued study treatment on 21 Aug 2018 (D221), the same day she was admitted for a planned liver transplantation due to intractable pruritus. On 03 Sept 2018 (D234), the subject underwent a successful liver transplantation without complication and was initiated on treatments with tacrolimus, mycophenolate mofetil, sulfamethoxazole/trimethoprim, valganciclovir hydrochloride, prednisone, and magnesium hydroxide. Subsequently, an event of renal failure was recorded on 17 Sept 2018 (D248) having discontinued bezafibrate treatment shortly before on 14 Sept 2018 (D245). At the onset of the renal failure event, the subject reported the concurrent AEs of anaemia, chills, constipation, diarrhoea, and oral candidiasis. The subject remained on hydrochlorothiazide, tacrolimus, and sulfamethoxazole through the event of renal failure. On 18 Oct 2018 (D279), a peak serum creatinine value of 1.20 mg/dL (reference range: 0.51 – 0.96 mg/dL) was reported. The subject withdrew from the study 18 Oct 2018 (D279).
- One male subject with PBC and a history of pruritus, type 1 diabetes mellitus (insulin dependent), and hypertension (on hydrochlorothiazide since 2006) initiated OCA study treatment on 05 Dec 2016. Serum creatinine at baseline on 02 Dec 2016 was 1.02 mg/dL (reference range: 0.67 – 1.17 mg/dL). On 12 Dec 2016 the subject was reported to have a moderate increase in blood pressure determined by the investigator to be unlikely related to study treatment and the subject was initiated on amlodipine the same day after discontinuing hydrochlorothiazide on 11

Dec 2016. Due to excessive pain of the cervical and thoracic spine, the subject initiated celecoxib and diclofenac sodium on 30 Nov 2017 before discontinuing these therapies on 10 Dec 2017. On 07 April 2018 the subject initiated ibuprofen and pseudoephedrine for acute frontal sinusitis before discontinuing these therapies on 07 May 2018. The subject was administered diclofenac sodium and meloxicam transiently in for spine pain in Aug 2018. On 11 Sept 2019, the subject had a serum creatinine level of 1.22 mg/dL (reference range: 0.67 – 1.17 mg/dL). Subsequently, the subject experienced an event of mild diabetic nephropathy on 09 Dec 2019, which the investigator determined was not related to study treatment. The subject had insulin-dependent type 1 diabetes mellitus at the time of study enrollment per reported medical history (unknown onset date). The presence of proteinuria was not provided. On 09 Dec 2019, the subject had a serum creatinine level of 1.28 mg/dL (reference range: 0.67 – 1.17 mg/dL). The subject was administered meloxicam for spine pain in Sept 2019. Peak serum creatinine was observed on 17 Dec 2020 of 1.54 mg/dL. The subject discontinued study treatment on 01 Dec 2021 due to study termination by the MAH.

Table 102: Study 747-302 - Renal Treatment-Emergent AESIs in ≥1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=123	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Subjects with at least 1 Renal TEAE	13 (7.8)	17 (10.1)	5 (13.5)	5 (15.6)	8 (6.2)	12 (8.8)	4 (5.9)	8 (9.9)	9 (9.2)	9 (10.3)
Acute kidney injury	2 (1.2)	5 (3.0)	0	2 (6.3)	2 (1.6)	3 (2.2)	0	1 (1.2)	2 (2.0)	4 (4.6)
Hypoalbuminaemia	1 (0.6)	4 (2.4)	1 (2.7)	3 (9.4)	0	1 (1.7)	0	1 (1.2)	1 (1.0)	3 (3.4)
Hyponatremia	1 (0.6)	2 (1.2)	0	2 (6.3)	1 (0.8)	0	1 (1.5)	0	0	2 (2.3)
Proteinuria	0	2 (1.2)	0	0	0	2 (1.5)	0	1 (1.2)	0	1 (1.1)
Thrombotic thrombocytopenic purpura	0	2 (1.2)	0	0	0	2 (1.5)	0	2 (2.5)	0	0
Diabetic nephropathy	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Haematuria	2 (1.2)	1 (0.6)	1 (2.7)	0	1 (0.8)	1 (0.7)	0	0	2 (2.0)	1 (1.1)
Hyperkalaemia	1 (0.6)	1 (0.6)	1 (2.7)	0	0	1 (0.7)	0	0	1 (1.0)	1 (1.1)
Leukocyturia	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Renal failure	1 (0.6)	1 (0.6)	1 (2.7)	0	0	1 (0.7)	0	1 (1.2)	1 (1.0)	0

MedDRA=Medical Dictionary for Regulatory Activities; OCA=oxetacetic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

Adverse events were coded using MedDRA Version 24.0.

For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2

Table 103: Study 747-302 – Listing of Treatment-Emergent Acute Kidney Injury by Baseline Disease Stage (Safety Population [N=334])

Preferred Term: Acute Kidney Injury						
Subject ID	IP	Baseline Disease Stage 1 / Stage 2	Serious	Severity	Relatedness	Onset Day / Stop Date or Day of Death
207007	OCA 5 mg	Proposed SmPC Indicated /Compensated	No	Moderate	Not related	23 Aug 2016/ 10 Sep 2016 (death date)
227002	OCA 5 mg	Proposed SmPC Contraindicated /Compensated	Yes	Mild	Not related	26 Jul 2016/ 29 Jul 2016 (resolved)
313002	OCA 5 mg	Proposed SmPC Contraindicated /Compensated	Yes	Severe	Unlikely	16 Dec 2016/Ongoing at time of subject's death (09 Feb 2017)
119006	OCA 5 mg	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	14 Aug 2016/ongoing
207003	OCA 10 mg	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	06 Oct 2015/ 08 Oct 2015
166001	Placebo	Proposed SmPC Contraindicated /Compensated	No	Mild	Unlikely	24 May 2017/ongoing
194002	Placebo	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	28 Apr 2019/12 Sep 2019

IP=investigational product; OCA=obeticolic acid; SmPC=Summary of Product Characteristics

Source: 747-302 CSR, Table 14.3.1.10.1, Listing 16.2.7.1, Listing 16.2.4.1

Table 103: Study 747-302 – Listing of Treatment-Emergent Acute Kidney Injury by Baseline Disease Stage (Safety Population [N=334])

Preferred Term: Acute Kidney Injury					
IP	Baseline Disease Stage 1 / Stage 2	Serious	Severity	Relatedness	Onset Day / Stop Date or Day of Death
OCA 5 mg	Proposed SmPC Indicated /Compensated	No	Moderate	Not related	23 Aug 2016/ 10 Sep 2016 (death date)
OCA 5 mg	Proposed SmPC Contraindicated /Compensated	Yes	Mild	Not related	26 Jul 2018/ 28 Jul 2018 (resolved)
OCA 5 mg	Proposed SmPC Contraindicated /Compensated	Yes	Severe	Unlikely	16 Dec 2016/Ongoing at time of subject's death (09 Feb 2017)
OCA 5 mg	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	14 Aug 2017/ongoing
OCA 10 mg	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	06 Oct 2015/ 08 Oct 2015
Placebo	Proposed SmPC Contraindicated /Compensated	No	Mild	Unlikely	24 May 2017/ongoing
Placebo	Proposed SmPC Contraindicated /Decompensated	No	Moderate	Not related	28 Apr 2019/12 Sep 2019

IP=investigational product; OCA=obeticholic acid; SmPC=Summary of Product Characteristics
Source: 747-302 CSR, Table 14.3.1.10.1, Listing 16.2.7.1, Listing 16.2.4.1

Renal TEAESI events in the proposed SmPC indicated population are presented in Table 104. Renal events are not uncommon in patients with advanced chronic liver disease. These patients are predisposed due to the profound haemodynamic changes that occur in cirrhosis with developing and established portal hypertension. It is therefore important to analyse the renal events (AESI) that manifested as renal impairment (elevated serum creatinine/decreased eGFR). The most common causes for renal impairment in cirrhotic patients are: 1) AKI due to hypovolaemia (e.g., variceal haemorrhage or diuretics) or due to medications that impair renal blood flow (NSAIDs, ARBs, ACEi) and 2) hepatorenal syndrome (type 1 and type 2), which is related to portal hypertension and hypoperfusion of the kidneys. This highlights the importance of considering the effects of factors on renal hemodynamics that alter the ability of the kidneys to function at full capacity and the scenario of injury of renal cells.

As previously discussed, the etiology of TTP is one of an enzyme deficiency within endothelial cells that causes diffuse small vessel thrombosis. This is clinically different from the presence of white cells in the urine and red cells in the urine (leukocyturia and hematuria) which arguably while part of a class that is grouped with other events that are associated with the kidneys can also results from infection in the bladder and other issues related to the collecting system. Table 104 presents the individual terms with creatinine to reflect the baseline and peak following the event so that the multiple etiologies (in terms of mechanism such as infection and organ such as kidney or collecting system) may be considered.

The majority of the renal TEAESIs that occurred in the proposed SmPC indicated population occurred when serum creatinine levels were within normal ranges. A total of 5 total subjects had abnormal serum creatinine values at the time of the renal TEAESI (3 subjects in the OCA group and 2 subjects in the placebo group). Of the 3 subjects in the OCA group, 1 subject experienced renal failure after liver transplantation while on anti-rejection medication, 1 subject had renal impairment due to the

development of TTP, and 1 subject had a pre-existing condition of insulin-dependent Type 1 diabetes mellitus.

Table 104: Study 747-302 – Listing of Treatment-Emergent Renal Adverse Events of Special Interest in the Proposed SmPC Indicated Population

Subject ID	Study Treatment	Date of Onset (Study Day)	Renal AESI Preferred Term	Serum Creatinine (mg/dL) at Time of Renal AESI (Study Day)	Normal Serum Creatinine at Time of Renal AESI (Y/N)	Abnormal Serum Creatinine at Any Point While on Study (Y/N)	Peak Serum Creatinine (mg/dL) (Study Day)	MAH Clinical Comments
164005	OCA	10Oct2019 (441)	TTP	0.59 (496)	Y	N	0.76 (365)	Without renal impairment
166004	OCA	25Aug2018 (773)	Hypo-albuminemia	0.62 (811)	Y	N	0.77 (1737)	2* liver disease not renal
207007	OCA	23Aug2016 (299)	AKI	0.89 (264)	Y	N	0.95 (91)	SAE of lymphoma (Day 299) with normal RFTs
219002	OCA	30Nov2020 (1483)	Proteinuria	0.64 (1483)	Y	N	0.79 (769)	Concomitant Ibuprofen
319002	OCA	15Jan2019 (461)	Leukocyturia	0.8 (461)	Y	N	0.86 (-45)	Likely 2* UTI
272003	OCA	17Sep2018 (248)	Renal failure	1.20 (279)	N	Y	1.20 (279)	Renal failure event with high serum creatinine occurred after liver transplant (Ltx on Day 234) under anti-rejection medications
309013	PBO	04Aug2018 (179)	UTI	0.8 (188)	Y	N	0.80 (188)	-
117005	OCA	06Jun2016 (111)	TTP	1.5 (111)	N	Y	1.35 (84)	Renal impairment 2* to development of TTP
178001	PBO	21Dec2017 (484)	Bone cyst	0.78 (378)	Y	Y	0.98 (1575)	-
178006	OCA	09Dec2019 (1100)	Diabetic Nephropathy	1.28 (1100)	N	Y	1.54 (1474)	Pre-existing Type 1 diabetes

Table 104: Study 747-302 – Listing of Treatment-Emergent Renal Adverse Events of Special Interest in the Proposed SmPC Indicated Population

Study Treatment	Date of Onset (Study Day)	Renal AESI Preferred Term	Serum Creatinine (mg/dL) at Time of Renal AESI (Study Day)	Normal Serum Creatinine at Time of Renal AESI (Y/N)	Abnormal Serum Creatinine at Any Point While on Study (Y/N)	Peak Serum Creatinine (mg/dL) (Study Day)	MAH Clinical Comments
OCA	10Oct2019 (441)	TTP	0.59 (496)	Y	N	0.76 (365)	Without renal impairment
OCA	25Aug2018 (773)	Hypo-albuminemia	0.62 (811)	Y	N	0.77 (1737)	2* liver disease not renal
OCA	23Aug2016 (299)	AKI	0.89 (264)	Y	N	0.95 (91)	SAE of lymphoma (Day 299) with normal RFTs
OCA	30Nov2020 (1483)	Proteinuria	0.64 (1483)	Y	N	0.79 (769)	Concomitant Ibuprofen
OCA	15Jan2019 (461)	Leukocyturia	0.8 (461)	Y	N	0.86 (-45)	Likely 2* UTI
OCA	17Sep2018 (248)	Renal failure	1.20 (279)	N	Y	1.20 (279)	Renal failure event with high serum creatinine occurred after liver transplant (Ltx on Day 234) under anti-rejection medications
PBO	04Aug2018 (179)	UTI	0.8 (188)	Y	N	0.80 (188)	-
OCA	06Jun2016 (111)	TTP	1.5 (111)	N	Y	1.35 (84)	Renal impairment 2* to development of TTP
PBO	21Dec2017 (484)	Bone cyst	0.78 (378)	Y	Y	0.98 (1575)	-
OCA	09Dec2019 (1100)	Diabetic Nephropathy	1.28 (1100)	N	Y	1.54 (1474)	Pre-existing Type 1 diabetes

Subject ID	Study Treatment	Date of Onset (Study Day)	Renal AESI Preferred Term	Serum Creatinine (mg/dL) at Time of Renal AESI (Study Day)	Normal Serum Creatinine at Time of Renal AESI (Y/N)	Abnormal Serum Creatinine at Any Point While on Study (Y/N)	Peak Serum Creatinine (mg/dL) (Study Day)	MAH Clinical Comments
219012	PBO	29Sep2021 (1609)	Blood creatinine increased	1.21 (1609)	N	N	1.21 (1609)	UGIB and hypovolaemia
452002	PBO	29Jul2019 (502)	UTI	1.33 (548)	N	Y	1.82 (1360)	Pre-existing elevation of serum creatinine

AESI=adverse events of special interest; AKI=acute kidney injury; IP=investigational product; Ltx=liver transplant; OCA=obeticholic acid; PBO=placebo; RFT=renal function test; SmPC=Summary of Product Characteristics; TTP=Thrombotic thrombocytopenic purpura; UGIB=upper gastrointestinal bleeding; UTI=urinary tract infection
Source: 747-302 CSR, Table 14.3.1.10.1, Listing 16.2.7.1, Listing 16.2.4.1, data on file

Study Treatment	Date of Onset (Study Day)	Renal AESI Preferred Term	Serum Creatinine (mg/dL) at Time of Renal AESI (Study Day)	Normal Serum Creatinine at Time of Renal AESI (Y/N)	Abnormal Serum Creatinine at Any Point While on Study (Y/N)	Peak Serum Creatinine (mg/dL) (Study Day)	MAH Clinical Comments
PBO	29Sep2021 (1609)	Blood creatinine increased	1.21 (1609)	N	N	1.21 (1609)	UGIB and hypovolaemia
PBO	29Jul2019 (502)	UTI	1.33 (548)	N	Y	1.82 (1360)	Pre-existing elevation of serum creatinine

AESI=adverse events of special interest; AKI=acute kidney injury; IP=investigational product; Ltx=liver transplant; OCA=obeticholic acid; PBO=placebo; RFT=renal function test; SmPC=Summary of Product Characteristics; TTP=Thrombotic thrombocytopenic purpura; UGIB=upper gastrointestinal bleeding; UTI=urinary tract infection
Source: 747-302 CSR, Table 14.3.1.10.1, Listing 16.2.7.1, Listing 16.2.4.1, data on file

Study 747-302: Renal Function Biochemical Analysis

Mean (SE) eGFR values over time for each study visit are summarized for the overall population in Figure 40. Mean values and mean (SE) change from baseline in eGFR are presented in Table 105 by overall and baseline disease severity for the safety population at Baseline, Month 3, Month 12, Month 24, Month 36, and Month 48.

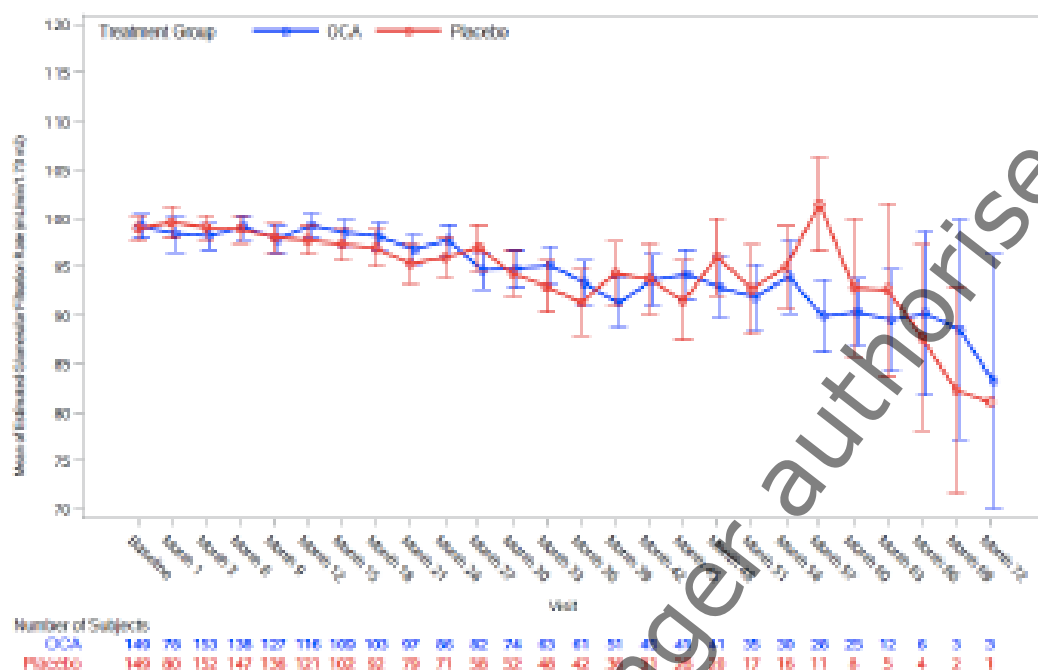
Within the first 4 years of treatment, no clinically significant changes over time or across treatment groups were observed with respect to eGFR in the overall population, as well as based on disease severity.

Shifts from baseline to post-baseline visits in chronic kidney disease stage are summarized for the overall population in Table 106, Month 3, Month 12, Month 24, Month 36, and Month 48. The majority of subjects in both placebo and OCA groups were CKD stage 1 at baseline, with approximately 20% of subjects in both groups CKD stage 2 at baseline. No subjects were CKD stage 3b, 4, or 5 at baseline.

Within the first 4 years of treatment, no clinically significant shifts over time in CKD stage were observed in either treatment group.

Interpretation of data at later timepoints (Month 48 and beyond) is limited due to fewer observations in each treatment group.

Figure 40: Study 747-302 – Mean (SE) eGFR Over Time (Safety Population)



Source: 747-302, Ad hoc 78.1

Table 105: Study 747-302 – Summary of eGFR (Safety Population [N=334])

Visit Statistic	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Baseline (mL/min)										
n	149	149	51	28	118	121	66	74	83	75
Mean (SE)	98.939 (1.266)	99.134 (1.256)	97.478 (2.081)	98.706 (2.784)	99.323 (1.439)	99.233 (1.411)	99.463 (1.815)	98.748 (1.936)	98.523 (1.764)	99.514 (1.617)
Month 3 (mL/min)										
n	152	153	32	31	120	122	63	74	89	79
Mean (SE)	99.043 (1.255)	98.115 (1.335)	99.439 (2.540)	99.431 (2.660)	98.937 (1.443)	97.781 (1.535)	97.926 (1.975)	97.324 (1.980)	99.833 (1.628)	98.857 (1.809)
n	144	143	29	28	115	115	63	70	81	73
Change from Baseline (Mean [SE])	-0.500 (0.631)	-0.024 (0.462)	0.259 (1.441)	0.842 (1.410)	-0.441 (0.560)	-0.235 (0.462)	-1.408 (0.910)	-0.655 (0.635)	0.562 (0.614)	0.582 (0.666)
Month 12 (mL/min)										
n	121	116	23	17	98	99	49	59	72	57
Mean (SE)	97.721 (1.465)	99.243 (1.333)	100.311 (2.429)	98.362 (3.873)	97.113 (1.716)	99.394 (1.421)	98.085 (2.356)	100.561 (1.632)	97.474 (1.881)	97.878 (2.122)
n	106	105	18	16	88	89	47	54	59	51
Change from Baseline (Mean [SE])	-0.708 (0.676)	-0.293 (0.659)	-0.245 (2.296)	-0.445 (2.558)	-0.802 (0.673)	-0.266 (0.637)	-0.751 (0.903)	-0.236 (0.829)	-0.673 (0.985)	-0.353 (1.043)
Month 24 (mL/min)										
n	71	86	9	10	62	76	30	46	41	40
Mean (SE)	95.947 (2.018)	97.753 (1.571)	97.879 (4.637)	101.280 (4.999)	95.667 (2.221)	97.289 (1.657)	97.104 (2.948)	99.302 (1.916)	95.100 (2.773)	95.971 (2.557)
n	59	86	5	9	54	67	29	42	30	34

Visit Statistic	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	FBO N=166	OCA N=168	FBO N=37	OCA N=32	FBO N=129	OCA N=136	FBO N=68	OCA N=81	FBO N=98	OCA N=87
Change from Baseline (Mean [SE])	-2.253 (1.021)	-1.500 (0.988)	-4.730 (5.862)	-1.821 (5.682)	-2.024 (0.997)	-1.457 (0.856)	-2.286 (1.577)	-1.827 (1.216)	-2.222 (1.333)	-1.096 (1.637)
Month 36 (mL/min)										
n	42	61	3	7	39	54	20	31	22	30
Mean (SE)	91.307 (3.438)	93.335 (2.246)	93.205 (1.958)	100.247 (7.510)	91.161 (3.702)	92.439 (2.344)	90.902 (5.984)	96.596 (2.899)	91.675 (3.818)	89.965 (3.387)
n	36	53	3	7	33	46	22	28	17	25
Change from Baseline (Mean [SE])	-6.744 (2.638)	-5.010 (1.633)	1.858 (6.688)	-1.198 (9.038)	-7.526 (2.796)	-5.590 (1.355)	-12.129 (4.441)	-5.160 (1.822)	-0.726 (1.771)	-4.882 (2.840)
Month 48 (mL/min)										
n	20	41	0	3	20	38	9	22	11	19
Mean (SE)	96.035 (3.947)	92.857 (3.139)	NA	111.098 (2.653)	96.035 (3.947)	91.417 (3.271)	93.554 (6.207)	94.582 (3.570)	93.066 (17.455)	90.895 (5.445)
n	17	34	0	3	17	31	8	19	9	15
Change from Baseline (Mean [SE])	-8.061 (3.476)	-4.493 (2.310)	NA	12.913 (10.392)	-8.061 (3.476)	-6.178 (2.161)	-12.704 (6.438)	-3.081 (3.333)	-3.934 (2.980)	0.051 (2.791)

eGFR=estimated Glomerular Filtration Rate; OCA=obeticholic acid; FBO=placebo; PH=evidence of portal hypertension; SE=standard error; SmPC=Summary of Product Characteristics

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302, Ad hoc 78.1, Ad hoc 78.2, Ad hoc 78.5

Table 106: Shift from Baseline in Stages of Chronic Kidney Disease (CKD)

	Placebo N=166						OCA N=168					
	Baseline CKD Stage						Baseline CKD Stage					
	1	2	3a	3b	4/5	Total	1	2	3a	3b	4/5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Month 3												
1	106 (73.6)	4 (2.8)	0	0	0	110 (76.4)	99 (69.2)	6 (4.2)	0	0	0	105 (73.4)
2	6 (4.2)	25 (17.4)	0	0	0	31 (21.5)	10 (7.0)	23 (16.1)	2 (1.4)	0	0	35 (24.5)
3a	1 (0.7)	0	1 (0.7)	0	0	2 (1.4)	0	0	2 (1.4)	0	0	2 (1.4)
3b	0	0	1 (0.7)	0	0	1 (0.7)	0	0	1 (0.7)	0	0	1 (0.7)
4/5	0	0	0	0	0	0	0	0	0	0	0	0
Total	113 (78.5)	29 (20.1)	2 (1.4)	0	0	144	109 (76.2)	29 (20.3)	5 (3.5)	0	0	143
Month 12												
1	75 (70.8)	6 (5.7)	0	0	0	81 (76.4)	76 (72.4)	7 (6.7)	0	0	0	83 (79.0)
2	8 (7.5)	14 (13.2)	0	0	0	22 (20.8)	9 (8.6)	12 (11.4)	0	0	0	21 (20.0)
3a	0	1 (0.9)	0	0	0	1 (0.9)	0	1 (1.0)	0	0	0	1 (1.0)
3b	0	0	2 (1.9)	0	0	2 (1.9)	0	0	0	0	0	0
4/5	0	0	0	0	0	0	0	0	0	0	0	0
Total	83 (78.3)	21 (19.8)	2 (1.9)	0	0	106	85 (81.0)	20 (19.0)	0	0	0	105
Month 24												
1	37 (62.7)	5 (8.5)	0	0	0	42 (71.2)	54 (71.1)	6 (7.9)	0	0	0	60 (78.9)
2	8 (13.6)	8 (13.6)	0	0	0	16 (27.1)	5 (6.6)	11 (14.5)	0	0	0	16 (21.1)
3a	0	0	1 (1.7)	0	0	1 (1.7)	0	0	0	0	0	0
3b	0	0	0	0	0	0	0	0	0	0	0	0
4/5	0	0	0	0	0	0	0	0	0	0	0	0

	Placebo N=166						OCA N=168					
	Baseline CKD Stage						Baseline CKD Stage					
	1	2	3a	3b	4/5	Total	1	2	3a	3b	4/5	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	45 (76.3)	13 (22.0)	1 (1.7)	0	0	59	59 (77.6)	17 (22.4)	0	0	0	76
Month 36												
1	22 (61.1)	2 (5.6)	0	0	0	24 (66.7)	33 (62.3)	4 (7.5)	0	0	0	37 (69.8)
2	5 (13.9)	5 (13.9)	0	0	0	10 (27.8)	7 (13.2)	6 (11.3)	0	0	0	13 (24.5)
3a	0	0	0	0	0	0	1 (1.9)	2 (3.8)	0	0	0	3 (5.7)
3b	0	0	1 (2.8)	0	0	1 (2.8)	0	0	0	0	0	0
4/5	0	1 (2.8)	0	0	0	1 (2.8)	0	0	0	0	0	0
Total	27 (75.0)	8 (22.2)	1 (2.8)	0	0	36	41 (77.4)	12 (22.6)	0	0	0	53

Stage 1=normal (GFR >90 mL/min); Stage 2=mild CKD (GFR 60 to 89 mL/min); Stage 3A=moderate CKD (GFR 45-59 mL/min); Stage 3b=moderate CKD (GFR 30-44 mL/min); Stage 4=severe CKD (GFR 15 to 29 mL/min); Stage 5=End Stage CKD (GFR <15 mL/min)
Note: CKD stage was evaluable for 298 subjects with eGFR measurements at baseline.
Source: 747-302, Ad hoc 78.4

Ocaliva Post-marketing Data: Renal PTs

OCA was granted accelerated approval under the trade name Ocaliva by the US FDA on 27 May 2016, and received conditional approval by the European Commission on 12 Dec 2016, by Health Canada on 24 May 2017, and is now approved in 43 countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years. No increased risk of renal events has been observed in the post-marketing setting.

Cumulatively, since marketing approval in 2016, 204 renal reports which included 279 renal events have been reported. The most frequent adverse events reported were PTs of blood creatinine abnormal (26), renal failure (25), AKI (23), renal impairment (13), glomerular filtration rate abnormal (11), blood creatinine increased (11), and blood urea abnormal (11).

Nine renal cases with a fatal outcome were reported. All except 2 of these cases were assessed as not related or unlikely related to Ocaliva, and the remaining 2 cases which were assessed as related to Ocaliva were both from patients with advanced PBC disease who would now be contraindicated per the current SmPC.

Assessment of the MAH's response

The higher incidence of renal events in patients treated with OCA regardless of the severity of the underlying liver disease is worrisome, and the Company was requested to discuss on this finding. In response, the Company presented renal TEASIs in OCA-treated subjects in Study 747-302 by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), proposed SmPC and proposed contraindicated populations, changes in renal function over a 4-year period in the same study, as well as post-marketing data. According to the Company, none of the NASH studies showed a decrease in eGFR over time while on OCA treatment.

Contrary to the Company's claim, the incidence of renal TEASIs remains rather consistent across OCA-treated subjects in the overall study population (10.1%), and in subjects with earlier stage PBC both compensated (per current SmPC) (8.8%) and proposed SmPC indicated (9.9%), but it is lower than in decompensated subjects currently contraindicated per SmPC (15.6%). It is also noted that systematically, the incidence of renal TEASIs, including renal events that manifest as renal impairment, is numerically higher in OCA treated group vs placebo-groups regardless of the PBC population analysed, i.e., the overall study population or any of the restricted subsets of milder PBC subjects. A partial analysis of the renal TEASIs, restricted to the newly proposed restricted PBC target population, indicate that in most of these events there were no parallel changes in creatinine levels or eGFR decline over time. However, in 5 out these 12 cases, changes in renal function parameters were observed (3 OCA vs 2 placebo). In any case, focusing the discussion of renal events to those occurring only in a small portion of the actual studied population does not help to assess the safety concern properly. Indeed, overall data provided do not allow excluding the potential role of OCA in the

observed increased incidence of renal TEASIs. Furthermore, given the differences in exposure, actual incidence of the events corrected by exposure time might have contributed to the interpretation of the phase 3 data. In this context, post marketing data provided do not alleviate the concern. Since marketing approval in 2016, 204 renal reports which included 279 renal events have been reported and the most frequent adverse events reported were PTs of blood creatinine abnormal (26), renal failure (25), AKI (23), renal impairment (13), glomerular filtration rate abnormal (11), blood creatinine increased (11), and blood urea abnormal. Nine renal cases with a fatal outcome were reported. All except 2 of these cases were assessed as not related or unlikely related to Ocaliva, and the remaining 2 cases which were assessed as related to Ocaliva were both from patients with advanced PBC disease who would now be contraindicated per the current SmPC.

In conclusion, based on the existing evidence a possible association between OCA treatment and the occurrence of renal TEASI events, including severe, serious, and fatal events, cannot be ruled out. Incidence rates adjusted by exposure time for the relevant renal TEASI events should be provided. A discussion, on the need to update current information in the SmPC Sections 4.4 and 4.8, and a proposal, is requested.

Issue not solved, but not further followed up within this procedure. Incidence rates adjusted by exposure time for the relevant renal TEASI events were not provided. Based on the overall evidence available, a discussion on the need to update current information in the SmPC Sections 4.4 and 4.8, and a proposal may be needed.

Question 13

When discussing the incidence of liver transplant and deaths events (adjudicated by an Hepatic Outcome Committee, HSAC), the information provided is quite confusing given the number of analyses conducted and lack of tabulated results, but all point into the same direction: a total of 60 liver transplants and deaths in patients overall were retrospectively adjudicated in a blinded manner by the HSAC (ITT population=32 (19.0%) subjects OCA vs 28 (16.9%) placebo, considered possibly treatment related in 12.5% OCA vs 3.6% placebo), less than half occurred in patients with decompensated liver disease (26), and the remaining 34 occurred in patients with compensated disease (20 in OCA vs 14 in placebo). This is considered a matter of major concern, given that the aim of OCA treatment is just the opposite, to prevent these clinical outcomes. The MAH is invited to provide these results, tabulated, for the overall study population, for the subset of patients with compensated disease and also for patients with decompensated conditions, and discuss on the clinical relevance of these findings in the compensated population bearing in mind that the demonstrated benefit of OCA treatment is limited to ALP reductions. The appropriateness of the current risk minimization measures deserves further discussion in view of these results. Further, the MAH should explain the differences observed in the incidence of liver transplant and deaths adjudicated events between the safety population and the ITT population.

Summary of the MAH's response

The MAH recognizes the significant imbalance in liver transplant and death events in Study 747-302. In the proposed SmPC indicated population: 7 subjects had a liver transplant, and 4 subjects had an all-cause death (11 total events) in the OCA group; 1 subject had a liver transplant and 1 subject had an all-cause death (2 total events) in the placebo group.

A comprehensive evaluation of liver transplant and death events in the 11 OCA-treated subjects and 2 placebo subjects was performed to assess the potential increased risk with OCA:

- Of the 11 subjects in the OCA group, a total of 1 subject had an event that was considered

possibly related to investigational product by an independent, blinded adjudication by an HSAC. Based on an ultrasound showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suspicion (or suggestion) one subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

- The remainder of liver transplant and death events within proposed SmPC indicated population were adjudicated as unlikely related to investigational product.
- Upon subject-level review of Study 747-302, the majority of liver transplants and all-cause death events in the proposed SmPC indicated population had alternate diagnoses/comorbidities.
- The incidence of liver transplants and deaths in the placebo group from Study 747-302 was substantially lower than any of the other non-OCA treated groups from real world datasets. Meanwhile, the liver transplant and death event rates were consistent across real world datasets.
 - Real-world evidence (RWE) datasets
 - Over 35,000 patient-years of Ocaliva postmarketing exposure in PBC

Based on totality of assessments, the MAH concludes that the rate of liver transplant and death events in Study 747-302 was not consistent with postmarketing and real-world datasets, previous PBC studies, and external control studies.

Study 747-302: Blinded Adjudication by HSAC

All liver transplant and death events were adjudicated in an independent, blinded manner by HSAC. Adjudicated liver transplants and deaths by blinded HSAC causality assessment are summarized in overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 107.

The incidence of liver transplant and deaths was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). The incidence of liver transplants and deaths was higher for OCA-treated subjects in the compensated population (20 subjects) compared to OCA-treated subjects in the proposed SmPC indicated population (11 subjects).

In the compensated (indicated per current SmPC) population, there were 20 subjects in the OCA group (13 liver transplants and 7 all-cause deaths) and 14 subjects in the placebo group (7 liver transplants and 7 all-cause deaths).

In the proposed SmPC indicated population, there were a total of 11 subjects in the OCA group (7 subjects had a liver transplant and 4 subjects had an all-cause death); and a total of 2 subjects in the placebo group (1 subject had a liver transplant and 1 subject had an all-cause death).

The majority of the liver transplants and deaths in the proposed SmPC indicated population were considered unlikely related to investigational product by the HSAC. Upon additional subject-level review, the majority of the subjects with a liver transplant or death in the proposed SmPC indicated population had alternate underlying diseases and/or causes which may have contributed to the outcome. A listing of liver transplant and all-cause deaths in subjects in the proposed SmPC indicated population is presented in Table 108.

One subject in the OCA group had a liver transplant that was considered possibly related to investigational product by the HSAC. Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion that the subject had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

The remainder of liver transplant and death events within the proposed SmPC indicated population were adjudicated as unlikely related to investigational product by the HSAC.

- One female subject with AMA negative PBC and a medical history of alcohol use disorder and severe chronic pancreatitis with endocrine and exocrine pancreatic insufficiency, underwent an allogenic liver transplant on 13 Feb 2020 (Study Day 639), approximately 1 year and 3 months after the discontinuation of OCA. There was an ultrasound prior to study initiation with significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, suggesting that the subject may have had portal hypertension at baseline and would have been contraindicated per proposed SmPC. Investigational product had been permanently discontinued approximately 6 months after the initiation due to mild ALT and AST elevation. Rifampicin was a concomitant medication at that time. Liver transplantation was performed due to progressive deterioration in synthetic liver function. Liver transplantation was challenging with severe fibrotic changes of the biliary tree and the retroperitoneum suspicious of primary sclerosing cholangitis ("absurd intraabdominal conditions" as per surgical theatre report). Explant histology was not available

Table 107: Summary of Liver Transplants or Deaths (All-cause) by Overall and Baseline Disease Stage (ITT Population [N=334])

	Overall		Current SmPC				Proposed SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=87
Liver Transplants or Deaths (All-cause)	28	32	14	13	15	20	2	11	27	22
Highly Likely Drug Related	0	0	0	0	0	0	0	0	0	0
Probable Drug Related	0	0	0	0	0	0	0	0	0	0
Possibly Related	1 (3.6)	4 (12.5)	1 (7.1)	1 (8.3)	0	3 (15.0)	0	1 (9.1)*	1 (3.8)	3 (14.3)
Unlikely Related	27 (96.4)	28 (87.5)	13 (92.9)	11 (91.7)	14 (100.0)	17 (85.0)	2 (100)	10 (90.9)	25 (95.2)	18 (85.7)
Insufficient Information	0	0	0	0	0	0	0	0	0	0
Liver Transplants										
Possibly Related	1	4	1	1	0	3	0	1	1	3
Unlikely Related	17	18	13	6	7	10	1	6	16	10
Deaths (All-cause)										
Possibly Related	0	0	0	0	0	0	0	0	0	0
Unlikely Related	11	13	3	4	7	7	1	4	9	8
Liver-related death										
Unlikely Related	4	3	1	1	3	2	0	1	4	2
Non-liver-related death										
Unlikely Related	7	10	2	3	4	5	1	3	5	6

PBO=placebo; OCA=obeticholic acid; SmPC=Summary of Product Characteristics

* Based on an ultrasound prior to study initiation showing significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, there is a suggestion Subject 272004 had portal hypertension at baseline and would have been contraindicated per proposed SmPC.

Note: All liver transplant and death events were independently adjudicated in a blinded manner by a Hepatic Safety Adjudication Committee, which were comprised of experts with relevant adjudication experience; they were not involved in the study as investigators, DMC members, or consultants.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

Source: 747-307 CTR Table 14.4.3, Data on file

Table 108: Listing of Liver Transplant and Deaths (All-Cause) in Subjects in the Proposed SmPC (N=149)

Tmt	Outcome	HSAC Causality/ Drug Relatedness	Duration Study Drug (days)	Study Day at Onset of Outcome (days)	Time from End of Treatment to Outcome (days)	MAH Clinical Comments on Review
Liver Transplant						
Placebo / commercial OCA	Liver Transplant	Unlikely	269	1078	810	BL: CP-5A, total bilirubin 1.5 mg/dL, thrombocytopenia, TE 15 kPa – evidence of portal hypertension at BL, stable blood test on commercial OCA, discontinued by Investigator in 2019, OLTx Dec 2021
OCA	Liver Transplant	Unlikely	221	234	13	BL: CP-5A, OLTx for pruritus with normal synthetic liver function, MELD 6.4, explant histology shows “no acute or chronic cholestasis and no sclerosis around bile ducts”
OCA	Liver Transplant	Possible	199	639	440	BL: CP-5A, comorbidities including alcohol use disorder, chronic pancreatitis with endocrine and exocrine dysfunction, OLTx: “completely stenotic biliary tree ? PSC”; There was an ultrasound prior to study initiation with significant splenomegaly and an endoscopy report which was equivocal for oesophageal varices, suggesting Subject 272004 may have had portal hypertension at baseline and would have been contraindicated per proposed SmPC.
OCA	Liver Transplant	Unlikely	667	812	145	BL: CP-6A, decline in synthetic liver function
OCA	Liver Transplant	Unlikely	434	823	389	BL: CP-6A, total bilirubin 2.5-3.5 mg/dL, ALP ~1000 U/L
OCA	Liver Transplant	Unlikely	593	1356	763	BL: CP-5A, Explant histology: sarcoidosis
OCA	Liver Transplant	Unlikely	611	1412	801	BL: CP-5A, TE 14 kPa, total bilirubin ~2mg/dL, gradual deterioration of synthetic liver function
OCA	Liver Transplant	Unlikely	912	1580	668	BL: CP-6A, hx of ulcerative colitis, TE 30.4 kPa, total bilirubin 2.1

Non-liver Related Death						
Placebo	Cardiorespiratory Arrest	Unlikely	379	512	133	BL: CP-5A, death after gradual deterioration at home
OCA	Acute Respiratory Failure	Unlikely	299	317	18	BL: CP-5A, death after first cycle of chemotherapy for stage 3 B-cell lymphoma R kidney
OCA	Subdural hematoma	Unlikely	221	618	397	BL: CP-6A, subdural haematoma after fall with mass effect
OCA	Multi-organ Failure	Unlikely	223	887	664	BL: CP-5A, pseudomembranous colitis, acute renal impairment, iatrogenic pneumothorax, ARDS
Liver-Related Death						
OCA	Liver-Related Death	Unlikely	889	937	48	BL: CP-5A, splenomegaly, multiple variceal haemorrhages with hypotension and associated cerebral ischaemia

BL=baseline, CP=Child-Pugh Score, F=Female, M=Male, Tmt=treatment

UK PBC, Global PBC, Komodo, Italian PBC Datasets

Due to significant bias observed in Study 747-302, particularly in the placebo group (i.e., functional unblinding, informative censoring, and initiation of rescue therapy while on study), the interpretation of liver transplant and death event rates in Study 747-302 may be of limited value; differential dropout rates were observed between the treatment groups, with more subjects in the placebo group initiating PBC rescue therapy while on study. However, it was important to thoroughly evaluate the observed imbalance in liver transplant and death rates in Study 747-302. The MAH undertook 2 additional analyses to investigate this imbalance:

1. A comparison of the placebo group in the proposed SmPC indicated population in Study 747-302 real-world non-OCA treated patients with PBC, to understand the observed event rate relative to the known natural history of PBC.
2. An analysis of liver transplants in the US transplant registry before and after launch of commercial OCA, as the observed significant imbalance in liver transplants associated with OCA would manifest as increased transplants in the real world.

The first analysis compared the observed liver transplant and death event rates in the placebo group in the proposed SmPC indicated population with non-OCA treated patients with PBC from real world datasets:

- Study 747-301 (POISE) external controls: UK PBC (>6900 patients) and Global PBC (>6000 patients) registries
- Study 747-405 (HEROES) fully real-world analysis: Komodo Health claims database (>100,000 patients)
- RECAPITULATE fully real-world analysis: Consolidated Italian PBC Registry

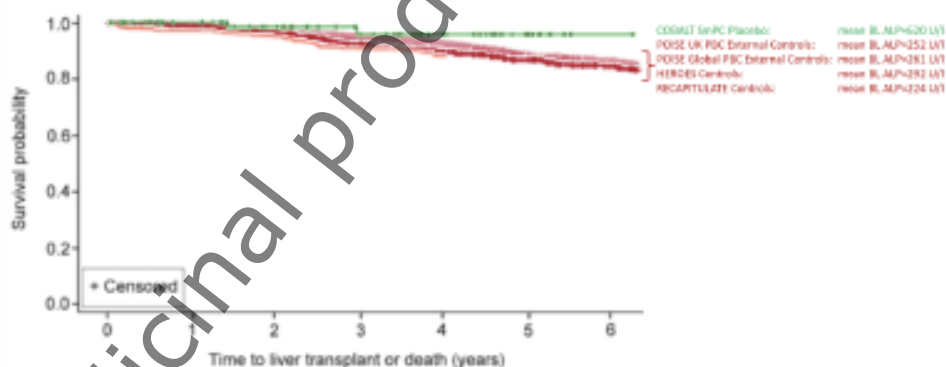
The eligibility criteria were similar across Study 747-302 and external control and real-world analyses, but it is important to note that enrolled subjects in Study 747-302 had more advanced disease at baseline. Mean ALP levels at baseline in the placebo group in proposed SmPC indicated population in Study 747-302 (620 U/L) was more than twice the baseline mean ALP levels of any of the other non-OCA treated groups (224 U/L to 292 U/L).

Time to death or liver transplant in the placebo group of the proposed SmPC indicated population in Study 747-302 and non-OCA treated patients with PBC from external controls (UK PBC and Global PBC), Study 747-405, and RECAPITULATE are shown in Figure 41.

- Despite having more advanced disease, the incidence of liver transplants and deaths in the placebo group from Study 747-302 was substantially lower than any of the other non-OCA treated groups from real world datasets. Meanwhile, the liver transplant and death event rates were consistent across the non-OCA treated groups.
- None of the liver transplants and/or deaths in the placebo group from Study 747-302 occurred in the first year. However, liver transplants and/or deaths in the non-OCA treated groups from real world datasets had approximately 10-times the event rate at 6 years versus the placebo group from Study 747-302.

In comparison to the non-OCA treated patients with PBC from real-world datasets, the liver transplants and death event rate in the placebo group of Study 747-302 is epidemiologically and medically implausible considering that the subjects enrolled had more advanced disease at baseline.

Figure 41: Time to Death or Liver Transplant Analysis in the Placebo Group in Study 747-302 (Proposed SmPC Indicated Population) and non-OCA Treated Groups from Multiple Real-world Datasets



ALP=Alkaline Phosphatase; OCA=obeticholic acid; SmPC=Summary of Product Characteristics

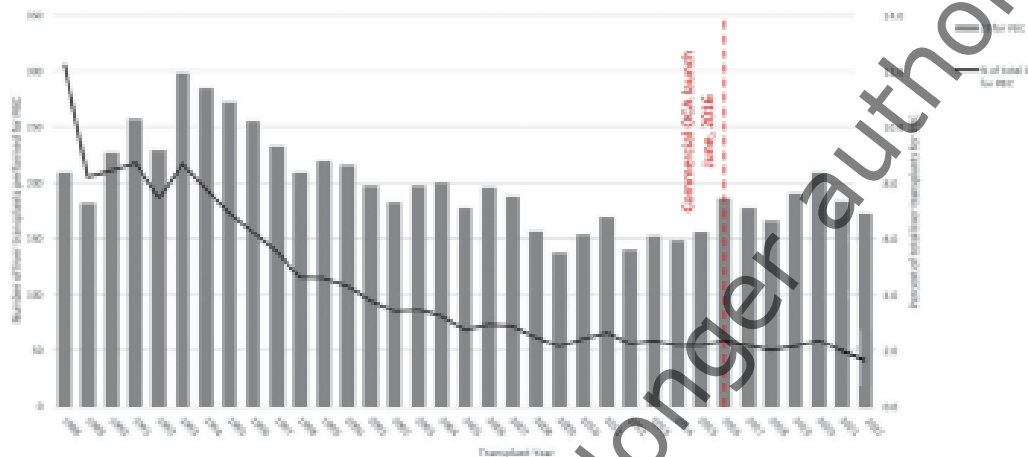
Note: Study 747-302 (COBALT) is in green. Study 747-301 (POISE) external controls from UK PBC and Global PBC, Study 747-405 (HEROES), and RECAPITULATE are in red.

The second analysis compared the number of liver transplants performed in patients with PBC before and after the launch of commercial OCA in the real world setting to investigate if there was an increased risk of liver transplants after the launch of commercial OCA.

The number of liver transplants and the percentage of total liver transplants in patients with PBC before and after the launch of commercial OCA in the US from the comprehensive Organ Procurement and Transplant Network national registry is shown in Figure 42.

Ocaliva was approved in the US in May 2016. In 2015, there were 7127 total liver transplants in patients with PBC in the US. The total number of liver transplants increased to 7811 in 2016, and steadily increased to 9234 by 2021. There was no clear increase in liver transplants in patients with PBC after OCA commercial launch in Jun 2016, despite the number of OCA-treated patients increasing to over 3500 per year, with >30,000 years of accumulating post-marketing treatment exposure during that period. Remarkably, the percentage of liver transplants associated with PBC has decreased slightly overtime.

Figure 42: Organ Procurement and Transplant Network: Liver Transplants in Patients with PBC by Year Before and After Launch of Commercial Ocaliva



LT=liver transplant; OCA=obeticholic acid; PBC=primary biliary cholangitis

In summary, the observed imbalance in liver transplants and deaths in Study 747-302 was not valid and reflected significant bias, particularly in favor of the placebo group.

- The liver transplants and death event rates observed in the placebo group in Study 747-302 did not reflect the high event rates seen in real-world analyses, which was consistent in multiple larger datasets.
- The liver transplant event rates observed in the OCA group in Study 747-302 was not consistent with the rates seen over time in a comprehensive liver transplant national registry. Remarkably, the percentage of liver transplants associated with PBC has decreased slightly over time despite the increasing number of patient-exposure years of OCA in the post-marketing setting.

Ocaliva Post-marketing Data: Liver Transplants and Liver-related Deaths

OCA was granted accelerated approval under the trade name Ocaliva by the US FDA on 27 May 2016, and received conditional approval by the European Commission on 12 Dec 2016, by Health Canada on 24 May 2017, and is now approved in 43 countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years.

No increased risk of liver transplant or deaths has been observed in the post-marketing setting.

Cumulatively, since marketing approval in 2016, 47 fatal reports due to hepatic events have been reported, and the majority were reported from patients who would now be contraindicated by the current SmPC. Cumulatively, 33 reports of liver transplants (31 with PT of liver transplant, and 2 with PT of liver transplant rejection) have been reported.

Analysis Populations in Study 747-302

All subjects were included in the efficacy and safety analyses using the ITT population and safety population, respectively. Both the ITT and safety populations included all randomized subjects who received any amount of investigational product (N=334). The ITT population was the primary population used for efficacy analyses. The safety population was the primary population used for safety analyses. Only treatment-emergent events were included (i.e., following exposure to the investigational product or within 30 days after the discontinuation of investigational product) in the safety analyses.

Of note, 2 deaths (one subject in the OCA group and one in the placebo group; both subjects were in the proposed SmPC contraindicated population at baseline) occurred after the subjects had withdrawn from the study, without providing explicit consent for continued collection of clinical outcome data. These events were inadvertently reported in the clinical database. These were excluded from the analyses following the study protocol and ICH/GCP principles (i.e., data collected/reported outside of the protocol requirements without subject consent).

Assessment of the MAH's response

In Study 747-302 a total of 60 liver transplants and deaths in the overall safety population were retrospectively adjudicated in a blinded manner by the HSAC (32 [19.0%] subjects OCA vs 28 [16.9%] placebo, considered possibly treatment related in 12.5% OCA vs 3.6% placebo). Less than half occurred in patients with decompensated liver disease (26), and the remaining 34 occurred in patients with compensated disease (20 in OCA vs 14 in placebo) per current SmPC. However, the numerical imbalance in OCA and placebo treated groups is observed across all the PBC groups analysed: overall safety population, compensated vs contraindicated per current SmPC, compensated vs contraindicated for newly proposed restricted indication. Indeed, these events are evenly distributed between compensated vs decompensated subsets per current SmPC. Not unexpectedly, a stricter definition of mild PBC, as it is now proposed, reduces the number of these events in the compensated subset (13 compensated vs 47 contraindicated per newly proposed SmPC), though still 13 events of disease progression to transplant or death are observed in an otherwise less advanced PBC population and mostly in OCA treated subjects (11 vs 2 placebo).

In the overall safety PBC population, a total of 24 death events (11 placebo vs 13 OCA) were observed. All death events were considered unlikely related to the investigational treatment. Of them, most were non-liver related. Death events deemed likely related to treatment occurred numerically higher in OCA-treated group, regardless of the PBC disease severity. A total of 38 liver transplant events (18 placebo vs 20 OCA) were reported, most of them were unlikely related to treatment. Numbers are limited and differences purely numerical, but these differences remain in the milder PBC subset where 4 events of liver transplant were observed in OCA vs 1 in placebo. This is considered a matter of concern.

The Company claims that the observed imbalance in liver transplants and deaths in Study 747-302 was not valid and reflected significant bias, particularly in favour of the placebo group, given that the event rates observed in the placebo group in Study 747-302 did not reflect the high event rates seen in real-world analyses. In addition, it is claimed that the liver transplant event rates observed in the OCA group in Study 747-302 was not consistent with the rates seen over time in a comprehensive liver transplant national registry. However, the evidence showing an increased incidence of liver transplant and death events in OCA vs placebo treated subjects across the spectrum of PBC populations analysed has been generated in a randomised, double blind, placebo-controlled trial, with central adjudication of these events. Given the heterogeneity in the PBC disease progression or maybe also differences in local transplant practices, differences with external cohorts are not unexpected, but do not serve as sound evidence to invalidate the RCT outcomes. Furthermore, it is uncertain to what extent the high rates of pruritus (new or worsening) associated to OCA treatment, often moderate-severe and potentially

refractory to available treatments, might have contributed to the higher-than-expected rates of liver transplant events in OCA treated group, but this would not alleviate the concern. It is also uncertain if differences in exposure might explain to some extent the observed differences, the MAH should further comment.

Finally, since marketing approval in 2016, 47 fatal reports due to hepatic events have been reported, and the majority were reported from patients who would now be contraindicated by the current SmPC. Cumulatively, 33 reports of liver transplants (31 with PT of liver transplant, and 2 with PT of liver transplant rejection) have been reported. According to the Company, no increased risk of liver transplant or deaths has been observed in the post-marketing setting. However, bearing in mind that these events are expected during this progressive condition, the low post marketing reports are not unexpected nor reassuring at all.

The existing concern remains. Even if less events are observed in a milder subset of the PBC population, these results should be interpreted with caution. Final acceptability will be a matter of benefit-risk assessment.

Issue not solved, to be further followed up within the appropriate procedure.

Question 14

The incidence of cholecystitis/cholelithiasis TEAEs was 5.4% in both treated groups, but a higher incidence of cholelithiasis-related events was seen in the OCA treated group. For the compensated subset, a similar pattern was seen: 5.1% OCA-treated and 6.2% placebo-treated patients experienced a cholecystitis/cholelithiasis TEAEs. Of these, 4 patients reported cholecystitis/cholelithiasis SAEs (3 patients in the OCA group: 2 patients with cholelithiasis and 1 patient with bile duct stone; 1 patient in the placebo group with cholecystitis). The MAH is invited to present comparative tabulated results of these cholelithiasis-related TEAE for the overall safety population vs decompensated vs compensated patients, and discuss if a higher incidence should be expected in patients with a more advance disease.

Summary of the MAH's response

The MAH assessed the frequency of events between OCA and placebo in the overall, compensated (indicated per current SmPC), and decompensated (contraindicated per current SmPC) populations. Given the subjects in these various groups have more advanced PBC disease and many of which are now contraindicated, the MAH has explored a more appropriate population that maximizes the benefit:risk profile. Therefore, the MAH has now proposed a revised SmPC population to contraindicate patients with compensated cirrhosis with evidence of portal hypertension (PH) and/or hepatic decompensation at baseline.

The incidence of cholecystitis/cholelithiasis TEAEs was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations) in Study 747-302.

In addition, the MAH evaluated cholecystitis/cholelithiasis TEAEs in post-marketing data and found no increased risk with OCA.

Study 747-302: Cholecystitis/cholelithiasis TEAEs

Cholecystitis/cholelithiasis TEAEs and serious cholecystitis/cholelithiasis TEAEs are summarized by overall, decompensated (contraindicated per current SmPC), compensated (indicated per current SmPC), the proposed SmPC indicated, and proposed SmPC contraindicated populations in Table 109.

Cholecystitis/cholelithiasis TEAESIs were defined by Gallbladder related disorders narrow SMQ and Gallstone related disorders narrow SMQ.

The incidence of cholecystitis/cholelithiasis TEAESIs was higher in OCA-treated subjects with more advanced stage PBC (i.e., proposed SmPC contraindicated or decompensated [contraindicated per current SmPC] populations) than subjects with earlier stage PBC (i.e., proposed SmPC indicated or compensated [indicated per current SmPC] populations). Within earlier stage PBC, the incidence of cholecystitis/cholelithiasis TEAESIs was higher for compensated OCA-treated subjects compared to OCA-treated subjects in the proposed SmPC indicated population.

In the proposed SmPC indicated population, 3 (3.7%) subjects in the OCA group and 1 (1.5%) subject in the placebo group reported a cholecystitis/cholelithiasis TEAESI. Cholelithiasis was the only PT reported across treatment groups. All cholecystitis/cholelithiasis TEAESIs were considered not related to investigational product by the Investigator and were mild to moderate in severity.

Of these, 1 OCA-treated subject in the proposed SmPC indicated population reported a serious TEAESI:

- One female PBC subject in the proposed SmPC indicated population reported a serious TEAESI of cholelithiasis on 16 Dec 2019 (Study Day 1133), approximately 3 years and 1 month after initiation of OCA. The subject had a history of gallbladder stones and was hospitalized for an elective laparoscopic assisted cholecystectomy due to cholelithiasis. The event of cholelithiasis was considered resolved on 17 Dec 2019 (Study Day 1134). The Investigator and the MAH assessed the event of cholelithiasis as moderate in severity and unlikely related to the investigational product.

In addition, 1 OCA-treated subject in the proposed SmPC indicated population reported a serious TEAESI of cholelithiasis that was not treatment-emergent (i.e., after 30 days of permanently discontinuing investigational product), which was considered possibly related by the Investigator. The event was assessed as moderate in severity and resolved after an elective laparoscopic cholecystectomy was performed.

Table 109: Study 747-302 - Cholecystitis/Cholelithiasis Treatment-Emergent AESIs in ≥1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

Preferred Term, n (%)	Overall		Current SmPC				Proposed SmPC			
	PBO N=166	OCA N=168	Decompensated (Contraindicated)		Compensated (Indicated)		Indicated		Contraindicated	
			PBO N=37	OCA N=32	PBO N=129	OCA N=136	PBO N=68	OCA N=81	PBO N=98	OCA N=69
Subjects with ≥1 Cholecystitis/Cholelithiasis TEAE of Special Interest	9 (5.4)	9 (5.4)	1 (2.7)	2 (6.3)	8 (6.2)	7 (5.1)	1 (1.5)	3 (3.7)	8 (8.2)	6 (6.9)
Cholelithiasis	4 (2.4)	7 (4.2)	0	1 (3.1)	4 (3.1)	6 (4.4)	1 (1.5)	3 (3.7)	3 (3.1)	4 (4.6)
Hyperplastic cholecystopathy	0	2 (1.2)	0	0	0	2 (1.5)	0	0	8 (8.2)	2 (2.3)
Bile duct stone	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Cholecystitis acute	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)
Biliary colic	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0
Cholecystitis	3 (1.8)	0	1 (2.7)	0	2 (1.6)	0	0	0	3 (3.1)	0
Cholecystitis chronic	1 (0.6)	0	0	0	1 (0.8)	0	0	0	1 (1.0)	0
Subjects with ≥1 Cholecystitis/Cholelithiasis Serious TEAE of Special Interest	2 (1.2)	3 (1.8)	1 (2.7)	1 (3.1)	1 (0.8)	2 (1.5)	0	1 (1.2)	2 (2.0)	2 (2.3)
Cholelithiasis	0	1 (0.6)	0	0	0	1 (0.7)	0	1 (1.2)	0	0
Bile duct stone	0	1 (0.6)	0	0	0	1 (0.7)	0	0	0	1 (1.1)
Cholecystitis	2 (1.2)	0	1 (2.7)	0	1 (0.8)	0	0	0	2 (2.0)	0
Cholecystitis acute	0	1 (0.6)	0	1 (3.1)	0	0	0	0	0	1 (1.1)

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence of portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event.
TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.
Adverse events were coded using MedDRA Version 24.0.
For each row category, a subject with two or more adverse events in that category was counted only once for the subject total.
Percentages were based on number of subjects in the Safety Population within each treatment group.
The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.
The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.
Source: 747-302 CSR, Table 14.3.1.10.1, Table 14.3.1.10.1.1, Table 14.3.1.10.1.2; 747-302, Ad hoc 62, Ad hoc 62.1, Ad hoc 62.1

Ocaliva Post-marketing Data: Cholecystitis/cholelithiasis PTs

OCA was granted accelerated approval under the trade name Ocaliva by the US FDA on 27 May 2016, and received conditional approval by the European Commission on 12 Dec 2016, by Health Canada on 24 May 2017, and is now approved in 43 countries for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA. As of May 2023, the estimated cumulative global patient-years exposure from marketing experience is over 35,000 patient-years.

No increased risk of cholecystitis/cholelithiasis events has been observed in the post-marketing setting. Cumulatively, since marketing approval in 2016, 99 reports which included 131 Gallbladder disorder events have been reported. The most frequent adverse events reported were PTs of cholelithiasis (37), cholecystectomy (28), gallbladder disorder (10), cholangitis (9), cholecystitis (7), bile duct stenosis (7), and bile duct stone (7). Two cases with a fatal outcome were reported, both cases were assessed as not related to Ocaliva, and one was from a patient with advanced disease who would now be contraindicated per the current SmPC and one for whom baseline status before initiating Ocaliva is unknown.

Assessment of the MAH's response

The Company has provided the requested data. The MAH assessed the frequency of events between OCA and placebo in the overall, compensated (indicated per current SmPC), and decompensated (contraindicated per current SmPC) populations, as well as in the newly proposed revised SmPC indicated vs contraindicated populations (i.e. patients with compensated cirrhosis with evidence of portal hypertension (PH) and/or hepatic decompensation at baseline). The incidence of cholelithiasis TEAEs events in the overall safety population was 7 (4.2%) OCA vs 4 (2.4%) placebo, including 3 SAEs OCA vs 1 in placebo. A clear reduction of the cholelithiasis/cystitis events is only seen in the milder compensated subset of PBC (newly proposed), mostly at the expenses of a reduction in cholecystitic events. Nevertheless, in the proposed SmPC indicated population, still the incidence of cholecystitis/cholelithiasis

TEAESI remains numerically higher in OCA treated patients (3 (3.7%) OCA vs 1 (1.5%) subject in the placebo group), one of these being a SAEs in OCA. During the clinical pharmacology studies, one patient experienced two SAEs of cholelithiasis and acute cholecystitis while on OCA treatment, considered treatment related by the investigator. Although these events are not unexpected in PBC subjects, it appears that OCA treatment might slightly increase the incidence of these events. Postmarketing data further support this assumption. Cumulatively, since marketing approval in 2016, 99 reports which included 131 gallbladder disorder events have been reported. The most frequent AEs reported were PTs of cholelithiasis (37), cholecystectomy (28), gallbladder disorder (10), cholangitis (9), cholecystitis (7), bile duct stenosis (7), and bile duct stone (7). Two cases with a fatal outcome were reported, both cases were assessed as not related to Ocaliva, and one was from a patient with advanced disease who would now be contraindicated per the current SmPC and one for whom baseline status before initiating Ocaliva is unknown.

Thus, even if a more benign safety profile is seen in a milder newly subset of the PBC population, results should be interpreted with caution given the limitations of the analyses conducted as outlined previously. An increased risk is seen consistently, acceptability of the increased risk including further SmPC amendments will be a matter of benefit-risk assessment.

Issue partially solved, but not further pursued within this procedure.

Question 15

The safety of OCA in special populations deserved further discussion, particularly, safety data in the elderly population should be provided and any relevant differences with previous observations will need to be discussed. The same would apply for patients with renal impairment, bearing in mind the increased risk for renal events during OCA treatment.

Summary of the MAH's response

Safety Data in the Elderly Population

Of the 334 subjects in the safety population of Study 747-302, 54 (16.2%) were ≥ 65 years and 2 (0.6%) were > 75 years. Both subjects > 75 years were randomized to placebo, thus, analyses are presented by "age at time of enrollment" for the < 65 years and ≥ 65 years subgroups only. The frequency of AESIs between OCA and placebo by age subgroup was analyzed for the overall and proposed SmPC indicated populations in Table 110.

Overall Population

For the overall population, the age distribution in the placebo group was similar as that of OCA-treated subjects (140 subjects < 65 years of age and 26 to 28 subjects were ≥ 65 years of age). Although the disparity in the overall number of subjects between the age subgroups precludes major conclusions, a review of AESIs by baseline age subgroup did not indicate any meaningful differences and trends across the subgroups appeared to be generally similar.

There were more OCA-treated subjects ≥ 65 years of age with a cardiovascular disorder TEAE compared with subjects < 65 years of age (18% and 8%, respectively); this pattern was also observed in placebo-treated subjects (8% and 4%, respectively). Similarly, more OCA-treated subjects ≥ 65 years of age had a renal TEAE compared with subjects < 65 years of age (21% and 8%, respectively); this pattern was also observed in placebo-treated subjects (15% and 6%, respectively). This pattern for higher incidence of cardiovascular and renal disorders in the ≥ 65 years group suggests these are likely age-related observations as opposed to treatment-related. All other AESIs (pruritus, hepatic disorders, cholecystitis/cholelithiasis and dyslipidemia) were similar between subjects < 65 years of age compared with subjects ≥ 65 years of age although, the small number ≥ 65 years subjects preclude definitive

conclusions.

Proposed SmPC Indicated Population

The age distribution in the placebo group was similar as that of OCA-treated subjects for the ≥65 years subgroup (10 to 11 subjects) and (140 subjects <65 years of age and 26 to 28 subjects were ≥65 years of age), but slightly higher for OCA-treated subjects compared to placebo subjects (71 vs 57) in the <65 years subgroup. Similar trends in AESIs were observed in the proposed SmPC indicated population compared to the overall population though the small number of subjects in the proposed SmPC indicated population (10 to 11 subjects) precludes definitive conclusions. Of note, the 3 CV events in OCA-treated subjects in the ≥65 years subgroup were thrombosis related events (thrombosis, TTP, venous thrombosis), no MACE event was reported in any OCA-treated subject in this subgroup.

Table 110: Study 747-302 Treatment-Emergent Adverse Events of Special Interest by Age Subgroup and Overall and Proposed SmPC Indicated Population (Safety Population [N=334])

AESI Preferred Term	AESIs Occurring in >1 OCA-Treated Subjects in the ≥65 Years Subgroup*							
	Overall				Proposed SmPC Indicated			
	<65 years		≥65 years		<65 years		≥65 years	
	PBO N=140	OCA N=140	PBO N=26	OCA N=28	PBO N=57	OCA N=71	PBO N=11	OCA N=10
Pruritus	75 (53.6)	111 (79.3)	11 (42.3)	22 (78.6)	28 (49.1)	58 (81.7)	5 (45.5)	9 (90.0)
Pruritus	74 (52.9)	110 (78.6)	11 (42.3)	22 (78.6)	27 (47.4)	57 (80.3)	5 (45.5)	9 (90.0)
Hepatic*	82 (58.6)	68 (48.6)	15 (57.7)	12 (42.9)	25 (43.9)	20 (28.2)	4 (36.4)	2 (20.0)
Ascites	15 (10.7)	15 (10.7)	6 (23.1)	3 (10.7)	2 (3.5)	1 (1.4)	1 (9.1)	0
Varices oesophageal	22 (15.7)	17 (12.1)	6 (23.1)	3 (10.7)	4 (7.0)	3 (4.2)	2 (18.2)	1 (10.0)
Blood bilirubin increased	22 (15.7)	18 (12.9)	3 (11.5)	2 (7.1)	1 (1.7)	4 (5.6)	1 (9.1)	0
International normalised ratio increased	2 (1.4)	2 (1.4)	0	2 (7.1)	0	1 (1.4)	0	1 (10.0)
Portal hypertensive gastropathy	6 (4.3)	12 (8.6)	1 (3.8)	1 (3.6)	0	3 (4.2)	0	0
Cardiovascular	5 (3.6)	11 (7.9)	2 (7.7)	5 (17.9)	2 (3.5)	2 (2.8)	0	3 (30.0)
Myocardial infarction	0	1 (0.7)	0	1 (3.6)	0	0	0	0
Thrombophlebitis	0	0	0	1 (3.6)	0	0	0	0
Thrombosis	0	0	0	1 (3.6)	0	0	0	1 (10.0)
Thrombotic thrombocytopenic purpura	0	1 (0.7)	0	1 (3.6)	0	1 (1.4)	0	1 (10.0)
Venous thrombosis	0	0 (0.0)	0	1 (3.6)	0	0	0	1 (10.0)
Renal	9 (6.4)	11 (7.9)	4 (15.4)	6 (21.4)	2 (3.5)	6 (8.5)	2 (18.2)	2 (20.0)
Acute kidney injury	1 (0.7)	3 (1.4)	1 (3.8)	3 (10.7)	0	0	0	1 (10.0)
Haematuria	1 (0.7)	0	1 (3.8)	1 (3.6)	0	0	0	0
Hyperkalaemia	1 (0.7)	0	0	1 (3.6)	0	0	0	0

AESI Preferred Term	AESIs Occurring in >1 OCA-Treated Subjects in the ≥65 Years Subgroup*							
	Overall				Proposed SmPC Indicated			
	<65 years		≥65 years		<65 years		≥65 years	
	PBO N=140	OCA N=140	PBO N=26	OCA N=28	PBO N=57	OCA N=71	PBO N=11	OCA N=10
Hypoalbuminaemia	1 (0.7)	3 (2.1)	0	1 (3.6)	0	1 (1.4)	0	0
Hyponatraemia	0	1 (0.7)	1 (3.8)	1 (3.6)	0	0	1 (9.1)	0
Thrombotic thrombocytopenic purpura	0	1 (0.7)	0	1 (3.6)	0	1 (1.4)	0	1 (10.0)
Cholecystitis/Cholelithiasis	9 (6.4)	7 (5.0)	0	2 (7.1)	1 (1.8)	3 (4.2)	0	0
Cholecystitis acute	0	0	0	1 (3.6)	0	0	0	0
Cholelithiasis	4 (2.9)	6 (4.3)	0	1 (3.6)	1 (1.8)	3 (4.2)	0	0
Hyperplastic cholecystopathy	0	1 (0.7)	0	1 (3.6)	0	0	0	0
Dyslipidaemia	9 (6.4)	5 (3.6)	0	1 (3.6)	3 (5.3)	3 (4.2)	0	1 (10.0)
Low density lipoprotein increased	0	1 (0.7)	0	1 (3.6)	0	1 (1.4)	0	1 (10.0)

AESI=adverse events of special interest; OCA=obeticholic acid; PBO=placebo; PH=evidence of portal hypertension; SmPC=Summary of Product Characteristics

* For hepatic disorders, AESIs occurring in >2 overall OCA-treated subjects in the ≥65 years subgroup are presented

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

Source: 747-302, Ad hoc 106, Ad hoc 106.1

Safety Data by Renal Impairment

As shown in Table 111, the majority of subjects had normal renal status at baseline as defined by a normal creatinine and estimated glomerular filtration rate (eGFR). CKD stage distribution at baseline was 69% stage 1, 20% stage 2, and 2% stage 3. Subjects with hepatorenal syndrome (type I or II) or Screening (visit 1 or 2) serum creatinine >2 mg/dL (178 µmol/L) were excluded from the study, thus, no subjects enrolled were CKD stage 4 or 5 at baseline. Given only 2% of the population was stage 3, the safety analyses are summarized by stage 1 and stage 2/3 subgroups.

Within each subgroup (stage 1 vs stage 2/3), baseline distribution in the placebo group was similar as that of OCA-treated subjects for both the overall and proposed SmPC indicated population.

Table 111: Summary of Subjects by CKD Stage (Safety Population N=334)

CKD Stage	Placebo	OCA	Total
Stage 1			
ITT Population	n=117	n=114	n=231
Proposed SmPC Indicated Population	n=50	n=55	n=105
Stage 2			
ITT Population	n=30	n=30	n=60
Proposed SmPC Indicated Population	n=15	n=15	n=30
Stage 3			
ITT Population	n=2	n=5	n=7
Proposed SmPC Indicated Population	n=1	n=4	n=5
Stage 2/3			
ITT Population	n=32	n=35	n=67
Proposed SmPC Indicated Population	n=16	n=19	n=35

Note: Cutoff values for CKD stages - Stage 1: eGFR (mL/min/1.73 m²) ≥ 90; Stage 2: 60 ≤ eGFR (mL/min/1.73 m²) < 89; Stage 3: 30 ≤ eGFR (mL/min/1.73 m²) < 59.

Note: CKD stage was only evaluable for 298 subjects with eGFR measurements at baseline.

Source: 747-302, Ad hoc 107, Ad hoc 107.1

AESI data by baseline CKD stage are summarized in Table 112 for the overall and proposed SmPC indicated population.

Although the disparity in the overall number of subjects between the subgroups precludes major conclusions, a review of AESIs by baseline CKD subgroup did not indicate any obvious differences for the overall and trends across the subgroups appeared to be generally similar.

As expected, there were more renal disorder TEAEs reported in subjects with more advanced chronic kidney disease (CKD stage 2/3), both in the OCA-treated and the placebo-treated groups than in subjects with a more preserved glomerular filtration rate (CKD stage 1): OCA: 7% and 6%, respectively and placebo-treated: 9% and 4%, respectively.

In proposed SmPC indicated population, there was no clear pattern for any TEAESIs across treatment groups and no AKIs reported in subjects with CKD Stage 2/3.

Table 112: Study 747-302 - AESIs in >1 Overall OCA-treated Subject by Preferred Term by Overall and Baseline Disease Stage (Safety Population [N=334])

AESI Preferred Term	AESIs Occurring in >1 OCA-Treated Subjects							
	Overall				Proposed SmPC Indicated			
	CKD Stage 1		CKD Stage 2/3		CKD Stage 1		CKD Stage 2/3	
	PBO N=117	OCA N=114	PBO N=32	OCA N=35	PBO N=50	OCA N=55	PBO N=16	OCA N=19
Pruritus	60 (51.3)	92 (80.7)	13 (40.6)	27 (77.1)	26 (52.0)	47 (85.5)	5 (31.3)	15 (78.9)
Pruritus	59 (50.4)	91 (79.8)	13 (40.6)	27 (77.1)	25 (50.0)	46 (83.6)	5 (31.3)	15 (78.9)
Hepatic*	69 (59.0)	55 (48.2)	13 (40.6)	17 (48.6)	23 (46.0)	15 (27.3)	4 (25.0)	6 (31.6)
Blood bilirubin increased	17 (14.5)	15 (13.2)	5 (15.6)	5 (14.3)	6 (12.0)	4 (7.3)	1 (6.3)	0
Varices oesophageal	19 (16.2)	14 (12.3)	4 (12.5)	3 (8.6)	5 (10.0)	3 (5.5)	1 (6.3)	1 (5.3)
Ascites	12 (10.3)	12 (10.5)	5 (15.6)	5 (14.3)	2 (4.0)	0	1 (6.3)	1 (5.3)
Portal hypertensive gastropathy	4 (3.4)	8 (7.0)	0	4 (11.4)	0	1 (1.8)	0	1 (5.3)
Hepatic cirrhosis	6 (5.1)	6 (5.3)	1 (3.1)	3 (8.6)	3 (6.0)	1 (1.8)	0	0
Jaundice	6 (5.1)	5 (4.4)	1 (3.1)	1 (2.9)	2 (4.0)	4 (7.3)	0	0
Blood alkaline phosphatase increased	4 (3.4)	4 (3.5)	0	0	2 (4.0)	0	0	0
Hepatic encephalopathy	6 (5.1)	4 (3.5)	3 (9.4)	2 (5.7)	0	1 (1.8)	0	0
Oesophageal varices haemorrhage	4 (3.4)	4 (3.5)	1 (3.1)	1 (2.9)	2 (4.0)	0	0	0
Alanine aminotransferase increased	4 (3.4)	3 (2.6)	1 (3.1)	0	2 (4.0)	1 (1.8)	0	0
Aspartate aminotransferase increased	4 (3.4)	3 (2.6)	0	0	2 (4.0)	1 (1.8)	0	0
Drug induced liver injury	0	3 (2.6)	0	1 (2.9)	0	1 (1.8)	0	1 (5.3)
Hepatic Mass	1 (0.9)	3 (2.6)	1 (3.1)	0	0	0	0	0
Portal hypertension	1 (0.9)	3 (2.6)	1 (3.1)	0	1 (2.0)	1 (1.8)	0	0
Hepatic enzyme increased	4 (3.4)	2 (1.8)	0	0	4 (8.0)	2 (3.6)	0	0
Hepatic fibrosis	1 (0.9)	2 (1.8)	0	0	0	0	0	0

AESI Preferred Term	AESIs Occurring in >1 OCA-Treated Subjects							
	Overall				Proposed SmPC Indicated			
	CKD Stage 1		CKD Stage 2/3		CKD Stage 1		CKD Stage 2/3	
	PBO N=117	OCA N=114	PBO N=32	OCA N=35	PBO N=50	OCA N=55	PBO N=16	OCA N=19
Hepatomegaly	0	2 (1.8)	0	0	0	0	0	0
Hyperbilirubinaemia	9 (7.7)	2 (1.8)	0	2 (5.7)	0	1 (1.8)	0	1 (5.3)
International normalised ratio increased	2 (1.7)	0	0	4 (11.4)	0	0	0	2 (10.5)
Hepatic failure	4 (3.4)	1 (0.9)	0	2 (5.7)	0	0	0	0
Cardiovascular	5 (4.3)	10 (8.8)	0	3 (8.6)	2 (4.0)	3 (5.5)	0	2 (10.5)
Cerebrovascular accident	1 (0.9)	2 (1.8)	0	0	0	1 (1.8)	0	0
Subarachnoid haemorrhage	0	2 (1.8)	0	0	0	0	0	0
Renal	5 (4.3)	7 (6.1)	3 (9.4)	6 (17.1)	2 (4.0)	5 (9.1)	2 (12.5)	2 (10.5)
Hypoalbuminaemia	0	3 (2.6)	1 (3.1)	0	0	1 (1.8)	0	0
Acute kidney injury	0	0	0	3 (8.6)	0	0	0	0
Cholecystitis/ Cholelithiasis	5 (4.3)	5 (4.4)	3 (9.4)	3 (8.6)	0	2 (3.6)	1 (6.3)	1 (5.3)
Cholelithiasis	3 (2.6)	4 (3.5)	1 (3.1)	2 (5.7)	0	2 (3.6)	1 (6.3)	1 (5.3)
Dyslipidaemia	6 (5.1)	4 (3.5)	0	0	2 (4.0)	3 (5.5)	0	0
Low density lipoprotein increased	0	2 (1.8)	0	0	0	2 (3.6)	0	0

MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; PH=evidence portal hypertension; SmPC=Summary of Product Characteristics; TEAE=Treatment-Emergent Adverse Event

TEAE was any event starting on or after the initiation of the investigational product and within 30 days of last dose of the investigational product, or any event already present prior to first dose that worsens in intensity following exposure to the investigational product. Events after initiation of commercial OCA were excluded.

Adverse events were coded using MedDRA Version 24.0.

For each row category, a subject with two or more adverse events in that category was counted only once for the subject count.

Percentages were based on number of subjects in the Safety Population within each treatment group.

The proposed SmPC indicated population included subjects who had not experienced PH or decompensation at baseline. The proposed SmPC contraindicated population included subjects who had not experienced PH and/or decompensation at baseline.

* For hepatic disorders, AESIs occurring in >2 OCA-Treated Subjects in the ≥65 years subgroup are presented

Note: CKD stage was evaluated for 298 subjects with eGFR measurements at baseline.

Source: 747-302, Ad hoc 107, Ad hoc 107.1

Assessment of the MAH's response

The Company was requested to present and discuss the safety profile of OCA in the elderly population. No information on the overall incidence of TEAEs, serious & severe TEAEs, AE leading to discontinuation and leading to death have been provided. Thus, no conclusion can be drawn on the toxicity/tolerability of OCA treatment in the elderly population. This should be provided, including a discussion on whether a more toxic and/or less tolerated safety profile would be expected in ≥65 years subjects.

Instead, the Company has presented tabulated data of the incidence of TEASIs both in the overall safety population and in the newly proposed indicated subset by “age at time of enrolment” for the <65 years and ≥65 years subgroups only. A total of 54 (16.2%) out of the 334 subjects included in Study 747-302 were ≥65 years and 2 (0.6%) were >75 years (but these two were assigned to placebo). As expected, higher incidences of cardiovascular disorder TEAEs and renal TEAEs were observed in subjects ≥65 years, both in placebo and OCA treated groups. For the remaining TEAEs of pruritus, hepatic, cholecystitis/cholelithiasis, and lipid disorders, similar incidences to those seen in adult subjects are observed. These results should be interpreted with caution given the low number of ≥65 years subjects, which preclude definitive conclusions. Similar trends in AESIs are noted for the proposed SmPC indicated population compared to the overall safety population, though the numbers are too limited (10 subjects in placebo vs 11 in OCA) to firmly conclude.

Safety in subjects with renal impairment at baseline was also analysed. The majority of subjects had normal renal status at baseline: CKD stage distribution was 69% stage 1, 20% stage 2, and 2% stage 3. CKD stage 4 or 5 at baseline were excluded. Given only 2% of the population was stage 3, the safety analyses are summarized by stage 1 and stage 2/3 subgroups. Again, information has only been provided for the AESIs, and not the overall safety profile. This should be provided. The analysis of AESIs by renal CKD stage at baseline show a similar pattern, with one relevant exception: a higher incidence of renal events in CKD Stage 2/3 subjects (9.4% placebo vs 17.1% OCA) was noted. This is not unexpected. Even if numbers are limited to firmly conclude, the risk of higher renal events in patients with CKD Stage 2 should be reflected in the SmPC Section 4.8, as well as the lack of data in subjects with more severe renal impairment.

Issue not solved, to be further pursued within the appropriate procedure. The Company did not present the overall incidence of TEAEs, serious & severe TEAEs, AE leading to discontinuation and leading to death, tabulated as for the TEASIs events (for the overall safety population and the newly proposed indication by age and by renal CKD stage), including a discussion on whether a more toxic and/or less tolerated safety profile would be expected in ≥65 years subjects or in subjects with CKD Stage 2/3 which may become of relevance in the appropriate follow up procedure assessing the Benefit / Risk of the product this may include proposed updates to the SmPC (including 4.8).

RWE

Question 16

The external comparator analyses cannot serve as a replacement of the negative results from the placebo controlled study and are considered purely exploratory. Despite this, the MAH is requested to discuss why such remarkable differences are observed between the placebo-controlled study and the RWE in order to better elucidate the value of these data.

Summary of the MAH's response

The Marketing Authorisation Holder (MAH) agrees that the real-world evidence (RWE) is not a “replacement” for Study 747-302. Instead, the MAH believes that a series of MAH-supported and independent studies provide consistent evidence of clinically meaningful obeticholic acid (OCA) benefit in improving transplant-free and event-free survival in patients living with primary biliary cholangitis (PBC) with inadequate response or intolerant to ursodeoxycholic acid (UDCA), and should be included as part of Committee for Medicinal Products for Human Use's (CHMP's) assessment of obeticholic acid (OCA) benefit:risk.

As discussed in Question 8, there was significant treatment crossover in both the placebo and OCA-treated groups in 747-302. In the placebo group, there is evidence that crossover was the result of functional unblinding associated with high ALP levels, which was associated with initiation of commercial

PBC treatments, which proved effective in lowering ALP. Conversely, 65% of OCA-treated subjects discontinued therapy before experiencing a clinical event. This degree of crossover makes it impossible to conduct meaningful intent-to-treat (ITT) analyses, as subject treatment status was largely discordant with randomized treatment assignment. The inverse probability censored weighting (IPCW) analysis referenced by the CHMP, as well as the analyses of the US Food and Drug Administration (FDA) endpoint, all showed similar moderate benefit (HR=0.80 to 0.84), but all remain subject to bias that would compromise the magnitude of treatment effect.

Due to the lack of feasibility of Study 747-302, and the understanding that further randomized controlled trials would be equally infeasible, the MAH undertook multiple real-world studies to assess the effect of OCA on clinical outcomes including death, liver transplant, and hepatic decompensation. These studies demonstrated consistent reductions (58% to 71%) in the relative risk of serious clinical events for PBC patients treated with OCA, a substantial benefit that should be considered in the overall assessment of benefit:risk. These studies included:

1. Study 747-405, fully real-world using the Komodo Health US claims database
2. Study 747-302, OCA-treated versus external controls from Komodo Health
3. Study 747-301, long-term safety extension (LTSE) versus external controls from the Global-PBC registry
4. Study 747-301, LTSE versus external controls from the United Kingdom (UK) PBC registry

As shown in Table 113, the treatment effects across these studies are stable: HRs ranged from 0.29 to 0.40 for time-to-death and liver transplant; and from 0.30 to 0.42 for death, liver transplant or hepatic decompensation. In addition to these MAH-supported studies, an independent Italian study group independently conducted a fully real-world time-to-event study of OCA-treated patients from the combined Italian PBC registries versus external controls from Global PBC. Results from this independent study were consistent with those of the MAH-supported studies demonstrating an HR=0.32 for risk of death and liver transplant, and HR=0.33 for risk of death, liver transplant, or hepatic decompensation (Gentilucci 2023).

A relative risk reduction of 58% to 71% in serious clinical events of all-cause death, liver transplants, and hepatic decompensation offers strong support that OCA treatment provides a clinically meaningful and significant benefit to appropriately treated PBC patients with a positive benefit:risk, not replacing but supplementing Study 747-302.

Table 113: Real-world Studies Show Consistent Statistically Significant and Clinically Meaningful Reductions in Death, Liver Transplant and Hepatic Decompensation in Patients Treated with OCA

Study Data Source	Population	Endpoint	Events	HR (95% CI)
Study 747-301 (LTSE) with External Control ¹ OCA-treated: POISE RCT+LTSE (N=209) External Control: GLOBAL PBC registry (N=1391)	Compensated PH with complications excluded	Death and LT	OCA-treated=2.4% Controls=10.0%	0.29 (0.10, 0.83)
		Death, LT, hepatic decomp	OCA-treated=7.7% Controls=15.4%	0.42 (0.21, 0.85)
Study 747-301 (LTSE) with External Control ¹ OCA-treated: POISE RCT+LTSE (N=209) External Control: UK PBC registry (N=2135)	Compensated PH with complications excluded	Death and LT	OCA-treated=2.4% Controls=13.2%	0.30 (0.12, 0.75)
Study 747-405 ² OCA-treated: Komodo Health claims (N=403) Control: Komodo Health claims (N=4174)	Compensated PH with complications excluded	Death and LT	OCA-treated=0.5% Controls=2.9%	0.30 (0.00, 0.96)
		Death, LT, hepatic decomp	OCA-treated=2.0% Controls=7.9%	0.37 (0.14, 0.75)
Study 747-302 EC ³ OCA-treated: COBALT RCT (N=168) External Control: Komodo Health claims (N=1051)	Decompensated 19.0% OCA 22.0% External Controls Clinical Evidence of PH: 48.9% OCA 54.6% External Controls	Death and LT	OCA-treated=6.4% Controls=13.7%	0.40 (0.18, 0.90)
		Death, LT, hepatic decomp	OCA-treated=10.1% Controls=21.5%	0.39 (0.22, 0.69)
RECAPITULATE ⁴ OCA-treated: Consolidated Italian PBC registry (N=437) External Control: GLOBAL PBC registry (N=831)	Compensated PH with complications: >28% OCA Unknown Controls	Death and LT	Not Reported	0.32 (0.15, 0.66)
		Death, LT, hepatic decomp		0.33 (0.20, 0.54)

EC=External Control; HR=hazard ratio; LT=liver transplant; LTSE=long-term safety extension; OCA=obeticholic acid; PBC=primary biliary cholangitis;

PH=portal hypertension; RCT=randomized controlled trial; UK=United Kingdom

Note: Death and liver transplant endpoint is highlighted.

¹ Murillo Perez 2022

² Brookhart 2022

Each of these studies is described below to allow CHMP to better evaluate the diversity of populations and design, and consistency of results across studies.

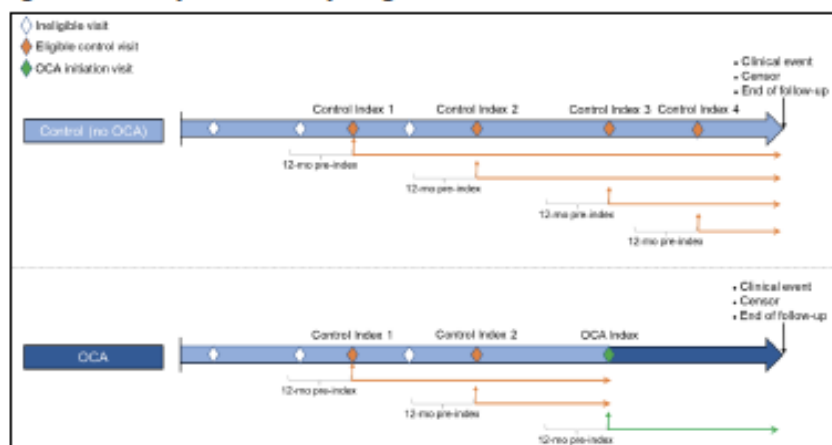
Study 747-405

Study Design

Study 747-405 was a nested trial emulation study (Hernán 2008, Danaei 2013, Brookhart 2015; Figure 43). The study utilized the Komodo Health claims database, with >100,000 patients diagnosed with PBC, merged through Datavant tokenization with LabCorp and Quest Diagnostics laboratory data, Organ Procurement and Transplantation Network (OPTN) transplant data, and Social Security Disability Insurance Program (SSDI)+national obituary search death data. The study utilized 747-301 eligibility criteria and was designed to replicate the results observed in the 747-301 open-label extension with an external controls outcomes study.

The treatment group included patients with PBC who initiated OCA. The control group allowed OCA-eligible, but not OCA-treated patients, to contribute an index for each eligible visit. Eligibility was determined based on inclusion criteria for Study 747-301 as originally designed. Study 747-405 tested the hypothesis that treatment with OCA would increase event-free survival (progression to death, liver transplant, or hepatic decompensation) relative to comparable OCA-eligible but non-OCA-treated control patients.

Figure 43: Study 747-405: Study Design Schematic



Mo=month; OCA=obesticholic acid

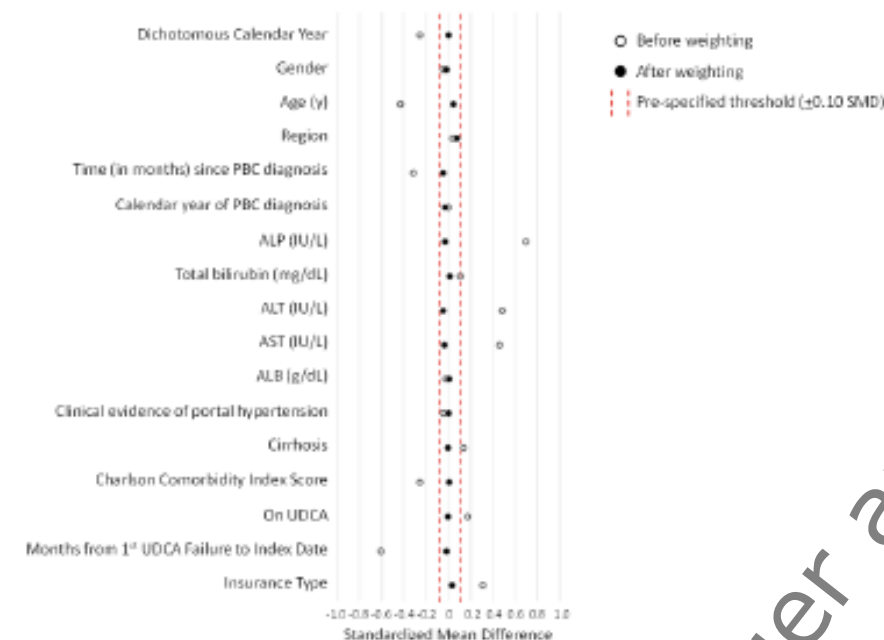
To ensure balance between the OCA-treated and non-OCA-treated groups, propensity scores were generated using a logistic regression model, predicting treatment as the outcome (for predictor variables, see Figure 44). The propensity scores were used to generate standardized morbidity ratio weights, applied to controls. A standardized mean difference of +0.10 was prespecified as indicative of adequate balance on baseline variables.

The primary efficacy analysis was an as-treated analysis, censoring OCA-treated patients 90-days after OCA discontinuation or upon the initiation of fibrates; and censoring control patients at initiation of commercial treatments (OCA, fibrates, or UDCA if patients were not treated with UDCA at baseline). Cox regression and log-rank test assessed time to the composite outcome. Secondary efficacy analyses assessed treatment impact on components of the composite. Sensitivity analyses included ITT analyses removing censoring; sub-group analyses to examine consistency of effect by patients and disease characteristics; and quantitative bias analyses.

Results

After applying Study 747-301 eligibility criteria, 4535 patients contributed 12,399 control index dates, and 432 patients contributed an OCA index. After weighting, all standardized mean differences were within the pre-specified +0.10 threshold (Figure 44). Groups were well balanced after weighting: >90% female; mean age, 56 years; UDCA use=73%; total bilirubin=0.7 mg/dL; and ALP=292 U/L to 294 U/L (Table 114).

Figure 44: Study 747-405: Standardized Mean Differences Before and After Weighting



ALB=albumin; PBC=primary biliary cholangitis; SMD=standardized mean difference; UDCA=ursodeoxycholic acid; y=year

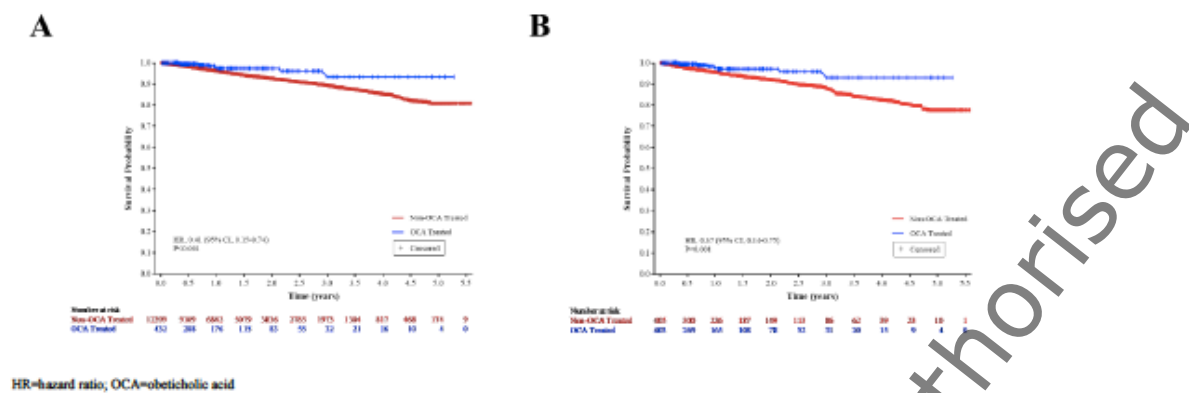
Table 114: Study 747-405: Baseline Variables Before and After Weighting

	Non-OCA		OCA
	Unweighted	SMR-weighted	
Eligible patients	4535	4174	403
Indexes, n	12,400	405.4	403
Female, %	90.2	91.1	91.6
Age, years	61.1±11.7	58.2±2.4	56.2±10.6
US Region, %			
South	44.0	43.4	46.2
West	24.0	26.2	24.1
Northeast	22.2	20.9	20.3
Midwest	9.7	9.5	9.4
Insurance, %			
Commercial	45.0	48.2	48.1
Medicaid	13.3	18.7	18.1
Medicare	24.5	14.4	14.9
Self-insured/exchanges	15.9	16.6	16.9
Other	1.3	2.1	2.0
TB, mg/dL	0.7±0.4	0.7±0.5	0.7±0.5
ALP, U/L	198.2±102.9	294.7±29.0	292.1±154.4
ALT, U/L	34.7±28.2	52.7±8.7	51.5±41.2
AST, U/L	35.5±23.2	49.6±6.9	48.8±34.0
Albumin, mg/dL	4.1±0.4	4.1±0.1	4.1±0.3
PLT, counts/mL blood (1000)	243.2±91.4	252.2±19.0	249.7±94.9
On UDCA at index, %	63.8	72.7	72.5
Months from UDCA failure to index	7.3±13.5	1.2±0.6	1.1±3.8
Portal HTN, %	24.8	23.4	23.6
Cirrhosis, %	43.1	50.5	50.4
Charlson comorbidity score	3.7±2.7	3.0±0.4	3.0±2.3

HTN=hypertension; OCA=obeticolic acid; PLT=platelets; SMR=standardized morbidity ratio; TB= total bilirubin; UDCA=ursodeoxycholic acid; US=United States

There were 8 events in the OCA arm and 32 in the weighted control (HR=0.37; 95% CI 0.14, 0.75; $p<0.001$; Figure 45). Evidence of benefit was observed for each component of the composite endpoint: death (2.0 events vs 9.4 events; HR=0.38; 95% CI 0.00, 1.26); liver transplant (0 events vs 2.5 events; HR cannot be calculated when events=0); and hepatic decompensation (6.0 events vs 23.0 events; HR=0.37; 95% CI 0.09, 0.85).

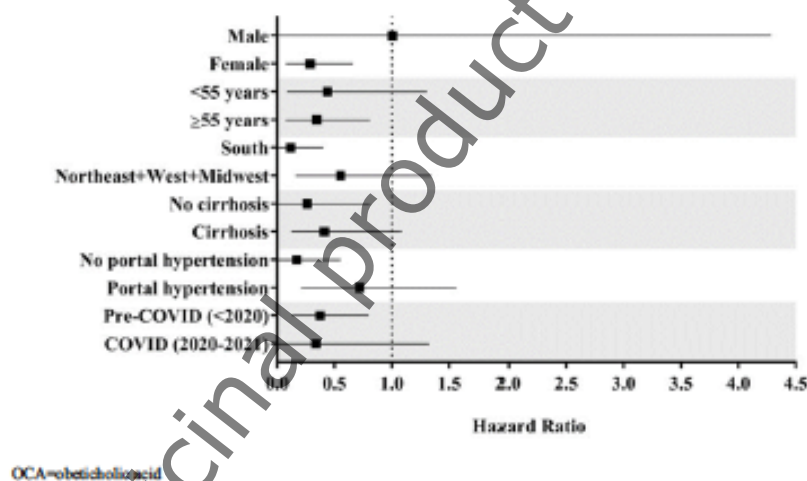
Figure 45: Study 747-405: Kaplan-Meier Curves of Time to Primary Endpoint for OCA-Treated vs Non-OCA Treated Patient - Unweighted (A) and Weighted (B)



Subgroup analyses by sex, age, region, baseline cirrhosis, baseline hypertension, and time period (pre/post-COVID) demonstrated evidence of benefit in all subgroups except for the male sex, which had only 31 patients in the OCA treatment group (Figure 46). ITT analyses in which OCA patients were not censored after OCA discontinuation or fibrate initiation demonstrated statistically significant benefit (HR=0.59; 95% CI 0.337, 0.995); ITT analyses that also did not censor control patients at initiation of commercial PBC treatments found an effect of similar magnitude (HR=0.64; 95% CI 0.378, 1.048).

Quantitative bias analyses demonstrated that the observed treatment effect was robust even in the face of significant potential confounding. Evidence of benefit was eliminated only if a potential confounder was present in 50% of the population, the benefit was at the low range of the 95% CI for the primary efficacy effect (HR, 0.75), and the confounder was strongly associated with the outcome (HR <0.50).

Figure 46: Study 747-405: Subgroup Analysis of Time to Primary Endpoint for OCA-Treated vs Non-OCA-Treated Patients



Conclusion

This study demonstrated a statistically significant and clinically meaningful 63% reduction in relative risk for death, liver transplant, and hepatic decompensation. The observed effect was robust across endpoint components, patient subgroups (with the exception of the male sex), when an ITT approach was taken, and in quantitative bias analyses that demonstrate benefit even in the face of significant confounding.

Study 747-301 Open Label Extension with External Controls

Study Design

Study 747-301 (POISE) was a randomized double-blind, placebo-controlled Phase 3 study examining the

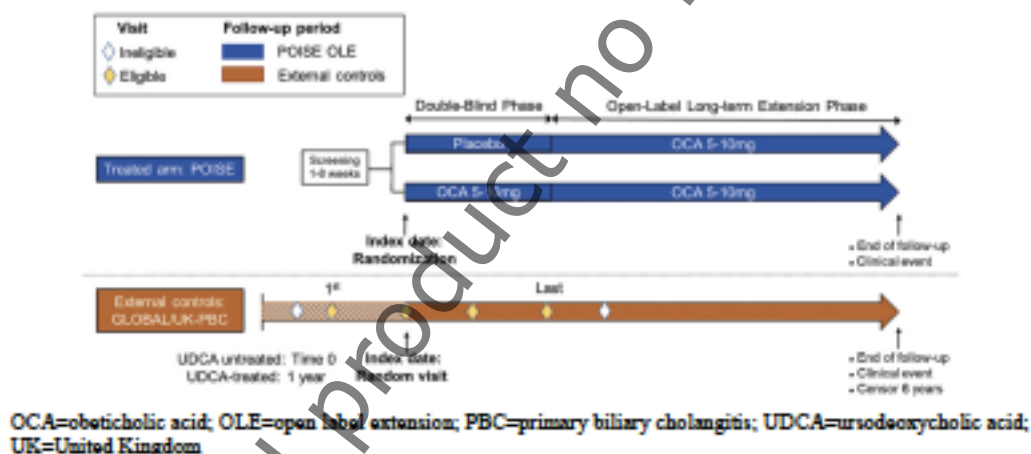
effect of OCA-treatment on a surrogate endpoint: ALP <1.67x ULN with a >15% reduction from baseline ALP level and bilirubin <ULN at 12 months. After 12 months, subjects randomized to OCA continued treatment and subjects randomized to placebo crossed over to OCA-treatment, with an open-label observation period of up to 5 additional years.

Two external control groups were created, one from the Global PBC registry and one from the UK PBC registry. The Global PBC registry includes 6484 non-OCA-treated patients with PBC recruited from 17 liver centres across 8 countries in Europe and North America between September 2012 and August 2016. The UK PBC registry includes more than 6900 non-OCA-treated patients with PBC recruited from 161 UK centres between February 2008 and December 2020.

The 747-301 LTSE external control study was designed and executed before the release of the FDA draft guidances governing the use of real-world data. As such, it does not meet several of the requirements in the guidances, e.g., pre-submission of the protocol to the Agency. The MAH believes that, though the study does not meet guidance specifications, it is a well-designed, scientifically rigorous study.

The external control group was created by identifying each study visit on which a registry patient met POISE inclusion/exclusion criteria (Figure 47). A random visit was selected between first and last eligible visit (inclusive) and served as the index visit, the equivalent of the randomization date for the OCA-treated subjects in POISE. Baseline patient characteristics were established at index, and patients were followed for events from index date forward. The study tested the hypothesis that treatment with OCA would increase transplant-free survival (progression to death or liver transplant) relative to comparable external controls.

Figure 47: Design of Study 747-301 Open Label Extension with External Controls



To ensure balance between the OCA-treated subjects in POISE and non-OCA-treated external controls, a logistic regression, with treatment group as outcome and demographic, laboratory, disease state and treatment variables as predictors, was used to generate propensity scores (for predictor variables, see Figure 48). The propensity scores were used to generate inverse probability of treatment weights (IPTW), applied to OCA-treated patients and controls. IPTW were truncated at 10 and stabilized. A standardized mean difference of +0.25 was prespecified as indicative of adequate balance on baseline variables.

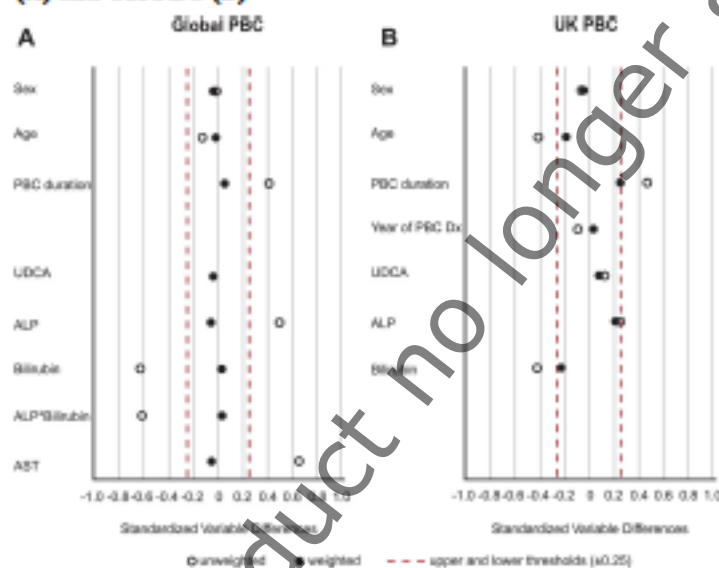
The primary efficacy analysis was ITT. A Cox regression and log-rank test assessed time to the composite outcome. Events during the first 6 months were excluded in the primary analysis to ensure early events were not due to residual differences in baseline disease state. A sensitivity analysis was conducted which included these events. Secondary efficacy analyses assessed treatment impact on time to a composite endpoint of death, liver transplant, or hepatic decompensation only using the Global PBC cohort. Sensitivity analyses included running the primary efficacy analysis with first and last eligible visit as index date and modifying the analysis to control only for treatment group, or to enter baseline variables

as covariates in the Cox regression, as opposed to using IPTW. A subgroup analysis was run on patients with and without baseline cirrhosis. A third sensitivity analysis examined biomarkers during the first year for patients randomized to placebo, versus untreated controls, to test for the possibility that selection bias resulted in the placebo group who were healthier than external controls.

Results

Of the 4922 patients in the Global PBC registry, 1381 met POISE inclusion criteria, with 6702 qualifying visits. Of the 6543 patients in the UK PBC registry, 2135 patients met POISE inclusion criteria, with 8331 qualifying visits. After weighting, all standardized mean differences were within the pre-specified +0.25 threshold for the Global PBC external control (Figure 48). In the UK PBC controls, ALT was sufficiently imbalanced after weighting that it was removed from the logistic and propensity score and entered as a covariate in the Cox regression. Though PBC duration was slightly outside the prespecified range (standardized variable difference=0.259), it was not included as an additional covariate.

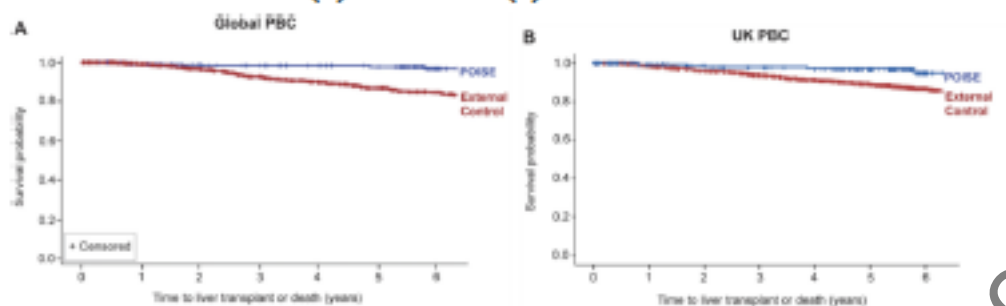
Figure 48: Standardized Mean Differences Before and After Weighting for Global PBC (A) and UK PBC (B)



Dx=diagnosis; OCA=obeticholic acid; PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid; UK=United Kingdom

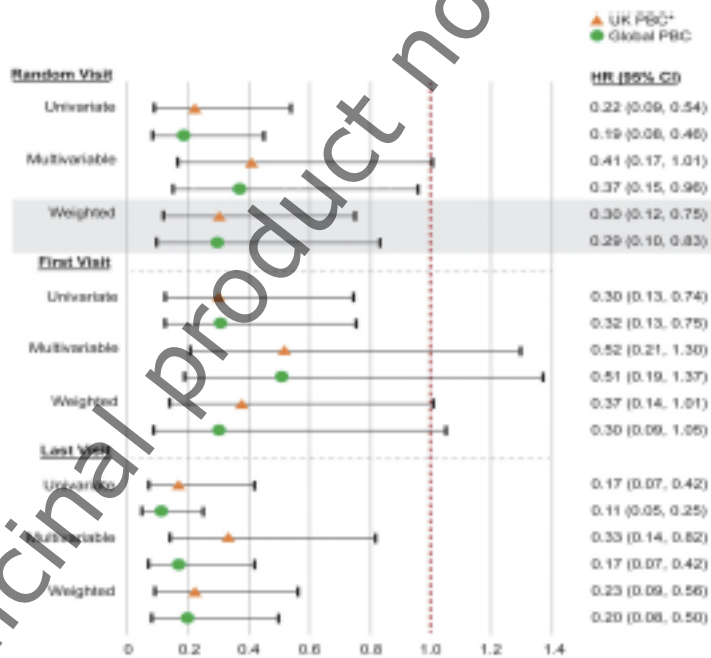
During the 6-year follow-up, there were 5 composite events (2 liver transplantations and 3 deaths) in 209 OCA-treated subjects in POISE (2.4%). There were 135 events (51 liver transplantations and 84 deaths) in 1381 patients in the Global PBC external control (10.0%; HR=0.29; 95% CI 0.10, 0.83; p=0.02; Figure 49A). There were 281 events (119 liver transplantations and 162 deaths) in 2135 patients in the UK-PBC controls (13.2%; HR=0.30; 95% CI 0.12, 0.75; p<0.01; Figure 49B). There were 16 events of death, liver transplantations, or hepatic decompensation in 209 OCA-treated subjects in POISE (7.7%) versus 212 events in 1381 patients in the Global PBC external control (15.4%; HR=0.42; 95% CI 0.21, 0.85; p=0.02).

Figure 49: Kaplan-Meier Curves of Time to Primary Endpoint for OCA-Treated Subjects in POISE vs Weighted Non-OCA Treated External Controls in Global PBC (A) and UK PBC (B)



Treatment benefit was observed regardless of whether first, random or last eligible visit was used as index, and was observed regardless of the analytic technique used to balance baseline covariates (Figure 50). Treatment benefit was observed in patients with cirrhosis (HR=0.20; 95% CI 0.03, 1.22) and without cirrhosis (HR=0.31; 95% CI 0.09,1.04). Results did not change appreciably when events that occurred in the first 6 months after index were not excluded (Global PBC HR=0.26; 95% CI 0.09, 0.74; UK-PBC HR= 0.25; 95% CI 0.10, 0.60).

Figure 50: Hazard Ratios for Death or Liver Transplantation for POISE vs Global PBC and UK PBC in Univariate, Multivariable, and Weighted Cox Regressions for Random Index Date, First Qualifying Visit Date, and Last Qualifying Visit Date



HR=hazard ratio; OCA=obeticholic acid; PBC=primary biliary cholangitis; UK=United Kingdom

When change from baseline ALP, total bilirubin, and AST were compared in the placebo group from Study 747-301 in first 12 months after randomization, versus the external controls first 12 months after index, all biomarkers numerically favoured the external control groups, with the exception of bilirubin in the UK-PBC control group (Table 115). Thus, the data did not support the hypothesis of selection bias in which the placebo group was healthier than the external controls.

Table 115: Change in ALP, Bilirubin, and ALT From Baseline to 12 Months for Patients Randomized to Placebo in the POISE Double-Blind and Patients in Global PBC and UK-PBC External Controls

Variable	Change from Baseline to Month 12 (ULN), mean (95 % CI)		
	ALP	Bilirubin	AST
POISE placebo	-0.08 (-0.53 to 0.23)	0.07 (-0.04 to 0.16)	-0.04 (-0.28 to 0.26)
GLOBAL PBC	-0.26 (-0.72 to 0.12)	0.00 (-0.18 to 0.13)	-0.08 (-0.34 to 0.12)
Variable	ALP	Bilirubin	ALT
POISE placebo	0.07 (-0.34 to 0.48)	0.04 (-0.13 to 0.20)	-0.10 (-0.11 to 0.31)
UK PBC	-0.29 (-0.9 to 0.80)	0.10 (0.03 to 0.16)	-0.23 (-0.31 to -0.15)

PBC=primary biliary cholangitis; UK=United Kingdom

Conclusion

This study demonstrated a statistically significant and clinically meaningful 70% to 71% reduction in relative risk for death and liver transplant, and 58% reduction in relative risk for death, liver transplant, and hepatic decompensation (i.e., serious clinical events). The observed effect was robust regardless of whether first, last, or random index was selected, and regardless of the statistical approach used to address confounding. The results were not consistent with the hypothesis of selection bias in favour of the external control.

Study 747-302 with External Controls

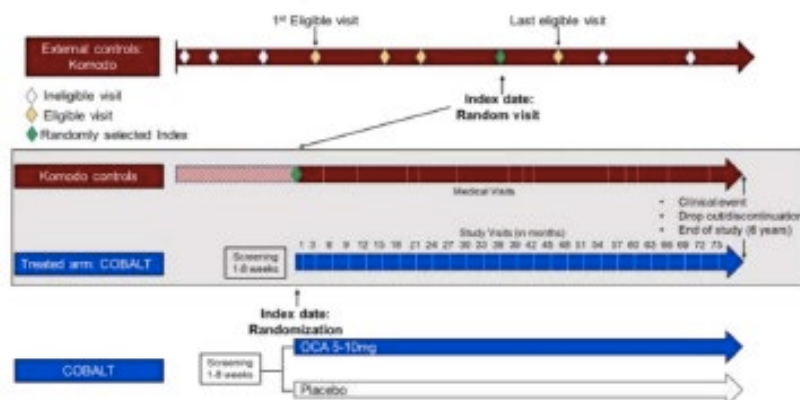
Study Design

Study 747-302 was a randomized double-blind, placebo-controlled Phase 3b/4 confirmatory outcomes trial examining the effect of OCA-treatment on event-free survival. Study 747-302 enrolled subjects with advanced PBC. After the trial was discontinued, a second expanded endpoint was created to include clinical evidence of portal hypertension with or without decompensation and became conditional on disease status at baseline.

In anticipation that the trial might prove infeasible, an external control group was created to allow for alternative means of efficacy evaluation. The study utilized the Komodo Health claims database, with >100,000 patients diagnosed with PBC, merged through Datavant tokenization with LabCorp and Quest Diagnostics laboratory data, OPTN transplant data, and SSDI+national obituary search death data. The protocol and statistical analysis plan were developed after the 2021 RWE draft guidances were released and were pre-submitted to the FDA. While the study was executed before the 2023 FDA draft guidance on external controls, after careful review the MAH believes the study was conducted in a manner consistent with that guidance.

The EC group was created by identifying each study visit on which a registry patient met 747-302 inclusion/exclusion criteria (Figure 51). A random visit was selected from all eligible visits and served as the index visit, the equivalent of the randomization date for the OCA-treated subjects in 747-302. Baseline patient characteristics were established at index, and patients were followed for events from index date forward. The study tested the hypothesis that treatment with OCA would increase event and transplant-free survival (progression to death or liver transplant) relative to comparable external controls.

Figure S1: Design of Study 747-302 with External Controls



OCA=obeticholic acid

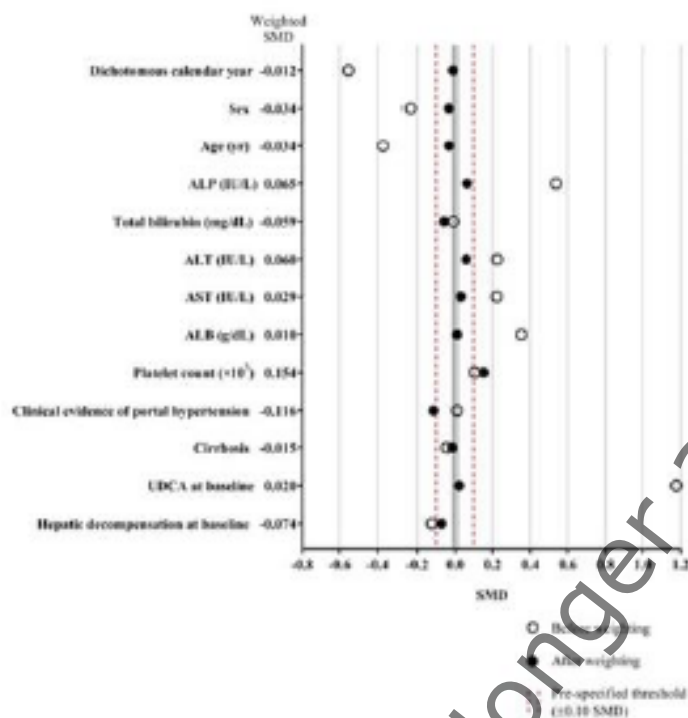
To ensure balance between the OCA-treated patients in 747-302 and non-OCA-treated external controls, a logistic regression, with treatment group as outcome and demographic, laboratory, disease state and treatment variables as predictors, was used to generate propensity scores (for predictor variables, see Figure 52). The propensity scores were used to standardized morbidity ratios (SMRs), applied to external controls. A standardized mean difference of +0.10 was prespecified as indicative of adequate balance on baseline variables. In addition to the external control group, a group of patients initiating OCA in the Komodo was created, using the same 747-302 eligibility criteria and SMR weighting approach.

The primary efficacy analysis was an as-treated analysis, censoring OCA-treated patients 90-days after OCA discontinuation; and censoring control patients at initiation of commercial treatments (OCA, fibrates, or UDCA if patients were not treated with UDCA at baseline). A Cox regression and log-rank test assessed time to the composite outcome. The SAP required that analyses needed to be powered at 0.70. Only the FDA expanded endpoint analysing the full population met this threshold (0.76), though the 747-302 protocol version 6 approached the threshold (0.65). Both analyses are presented.

Results

There were 168 subjects randomized to OCA treatment in the 747-302 trial and were included in the external control analysis. There were 1051 external controls in the Komodo health database who met 747-302 eligibility criteria (Table 116). After weighting, the OCA-treated arm and external controls were well balanced; however, platelet count, and clinical evidence of portal hypertension fell just outside of the prespecified ± 0.10 standardized mean difference (SMD) threshold (0.15 and -0.12, respectively) and were included as covariates in the Cox regression model (Figure 52).

Figure 52: Study 747-302 EC: Standardized Mean Differences Before and After Weighting



ALB=albumin; EC=external control; OCA=obeticholic acid; SMD=standardized mean difference; UDCA=ursodeoxycholic acid; yr=year

Table 116: Study 747-302 EC: Baseline Variables

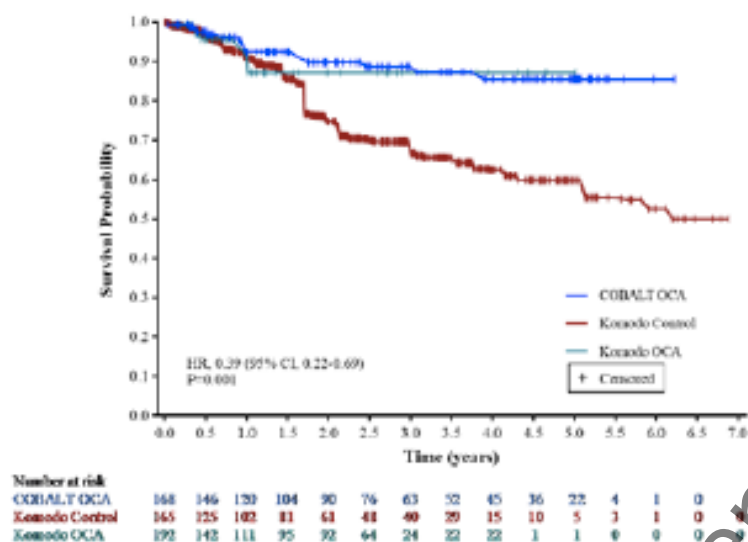
	747-302		Komodo	
	Placebo (n=166)	OCA (n=168)	Untreated control (unweighted n=1051) (weighted n=165)	OCA treated (unweighted n=61) (weighted n=192)
Age, y				
Mean (SD)	53.9 (10.4)	53.4 (10.3)	53.8 (5.2)	57.0 (16.4)
Sex, n (%)				
Female	149 (89.8)	151 (89.9)	146.5 (88.8)	174.5 (90.9)
Race, n (%)				
White	143 (86.1)	146 (86.9)	-	-
Black or African American	2 (1.2)	2 (1.2)	-	-

	747-302		Komodo	
	Placebo (n=166)	OCA (n=168)	Untreated control (unweighted n=1051) (weighted n=165)	OCA treated (unweighted n=61) (weighted n=192)
Asian	9 (5.4)	11 (6.5)	-	-
American Indian or Alaska Native	2 (1.2)	1 (0.6)	-	-
Multiple races	1 (0.6)	4 (2.4)	-	-
Not reported	9 (5.4)	4 (2.4)	-	-
Baseline/index laboratory value, mean (SD)				
ALP, U/L	499.3 (294.5)	481.3 (276.7)	463.8 (104.4)	441.5 (447.3)
TB, mg/dL	1.7 (0.8)	1.6 (0.8)	1.6 (0.5)	1.6 (1.2)
ALT, U/L	84.0 (50.2)	81.5 (51.9)	77.1 (35.9)	78.5 (70.6)
AST, U/L	81.9 (36.3)	81.1 (41.1)	79.1 (35.8)	85.3 (84.2)
ALB, g/dL	3.96 (0.40)	4.00 (0.41)	4.00 (0.20)	4.06 (0.80)
Platelets x1000 μ L	197.2 (102.6)	209.9 (101.8)	194.8 (37.3)	200.1 (138.0)
Disease history at baseline, n (%)				
Decompensation	37 (22.3)	32 (19.0)	36.3 (22.0)	50.9 (26.5)
Portal hypertension	98 (59.0)	82 (48.8)	90.1 (54.6)	95.4 (49.7)
Use of UDCA, n (%)				
At baseline/index	147 (88.6)	147 (87.5)	143.2 (86.8)	159.7 (83.2)
Ever used	163 (98.2)	161 (95.8)	162 (100)	192 (100)
Never	3 (1.8)	7 (4.2)	0	0

ALB=albumin; EC=external control; OCA=obeticholic acid; TB=total bilirubin; UDCA=ursodeoxycholic acid

For the 747-302 protocol version 6 endpoint analysis of all subjects (Figure 53), there were 17 events (10.1%) in the 747-302 OCA group and 35.4 events (21.5%) in external controls (HR=0.39; 95% CI 0.22, 0.69; $p<0.001$). The primary difference in events vs the ITT analysis was due to censoring OCA-treated patients 90 days after OCA discontinuation: 31 of 48 OCA-treated subjects were censored prior to the composite endpoint. There was a similar percentage of events (7 events, 10.0%) in the Komodo OCA-treated group as in the 747-302 OCA-treated group.

Figure 53: Kaplan-Meier Curves of Time to Protocol Version 6 Endpoint for OCA-Treated Subjects in 747-302 vs Weighted Non-OCA Treated External Controls: All Subjects

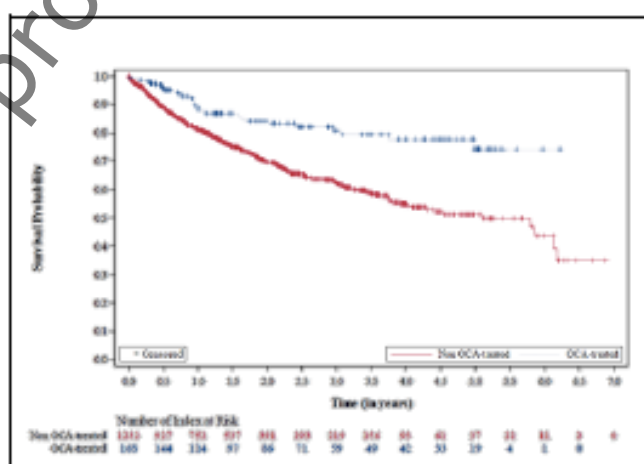


HR=hazard ratio; OCA=obeticholic acid

For the FDA expanded endpoint, in the analysis of all patients, there were 28 events among 168 patients (16.7%) in the 747-302 OCA group and 45.5 endpoints among 164.9 patients (27.6%) in external controls (HR=0.48; 95% CI 0.30, 0.77; Figure 54).

This study demonstrated a statistically significant and clinically meaningful 61% reduction in relative risk for death, liver transplant and hepatic decompensation among all patients enrolled in the study. The event rate among OCA-treated patients in 747-302 and comparable OCA-treated patients in Komodo were nearly identical. The observed effect was similar for the FDA endpoint among all patients, with a 52% reduction in relative risk of progression to death, liver transplant, hepatic decompensation, or portal hypertension.

Figure 54: Kaplan-Meier Curve of Time to FDA Expanded Endpoint for OCA-Treated Subjects in 747-302 vs Weighted Non-OCA Treated External Controls:



FDA=Food and Drug Administration; OCA=obeticholic acid

RECAPITULATE

Study Design

RECAPITULATE was a fully real-world observational study comparing OCA-treated patients with PBC from

the consolidated Italian PBC registry to OCA-eligible but non-OCA-treated patients with PBC from the Global PBC registry. The consolidated Italian PBC registry included OCA-treated patients with PBC from the Italian PBC Registry; Club Epatologi Ospedalieri (CLEO); Associazione Italiana Gastroenterologie Endoscopisti Digestivi Ospedalieri (AIGO) PBC Task Force; Sicilian PBC Network; PBC Project Piemonte-Liguria-Valle D'Aosta. The Global PBC registry included non-OCA-treated patients who met the same study inclusion/exclusion criteria.

Inclusion criteria included: age ≥ 18 years; PBC diagnosis per European Association for the Study of the Liver (EASL) guidelines; taking UDCA for at least 12 months or intolerant to UDCA; ALP $\geq 1.5 \times$ ULN and/or 1 mg/dL $<$ total bilirubin < 2 mg/dL; treated with OCA for at least 6 months. Exclusion criteria included: Child-B or Child-C classification; previous decompensation event. The Global PBC cohort also excluded patients with hepatic comorbidities: hepatitis C; active hepatitis; primary sclerosing cholangitis; alcoholic liver disease. Patients in the Italian registries had an OCA-initiation index dates from 2016 through 2021. Patients in the Global PBC controls had index dates between 2000 and 2016, and 1 date was randomly selected from eligible index dates as the control index.

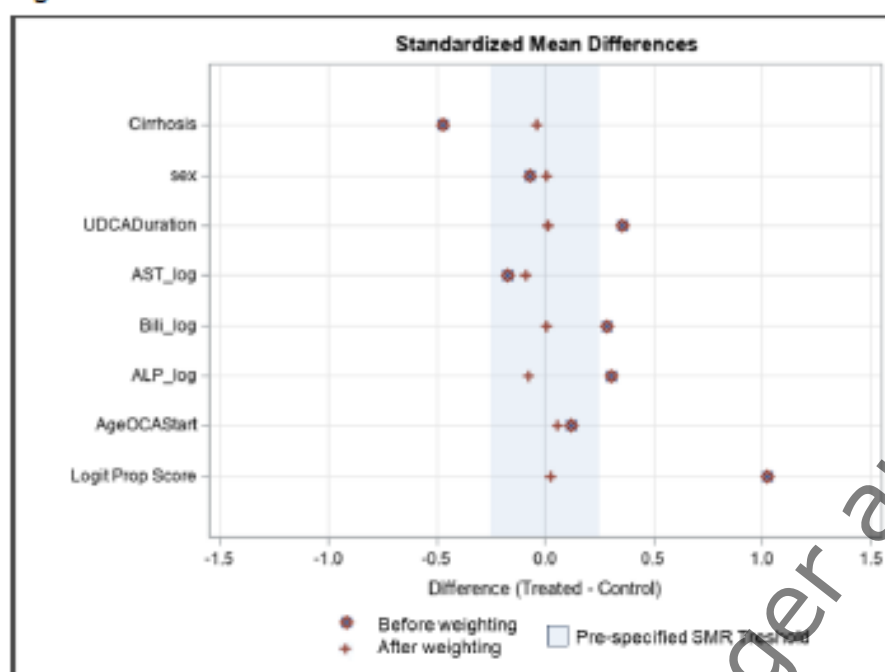
To ensure balance between the OCA-treated and non-OCA-treated groups, a logistic regression, with treatment group as outcome and demographic, laboratory, disease state and treatment variables as predictors, was used to generate propensity scores (for predictor variables, see Figure 55). The propensity scores were used to generate standardized morbidity ratio weights, applied to controls. A standardized mean difference of $+0.25$ was prespecified as indicative of adequate balance on baseline variables.

The primary efficacy analysis was an ITT analysis. Cox regression and log-rank test assessed the effect of OCA-treatment on time to death or liver transplant. The secondary efficacy analyses assessed the effect of OCA-treatment on time to death, liver transplant, or hepatic decompensation.

Results

After applying eligibility criteria, there were 437 patients in the OCA-treated Italian cohort and 831 controls patients from Global PBC. After weighting, all standardized mean differences were within the pre-specified $+0.25$ threshold (Figure 55) and groups were well balanced on all variables (Table 117).

Figure 55: RECAPITULATE Standardized Mean Differences



OCA=obeticolic acid; Prop=propensity; SMR=standard mean ratio; UDCA=ursodeoxycholic acid

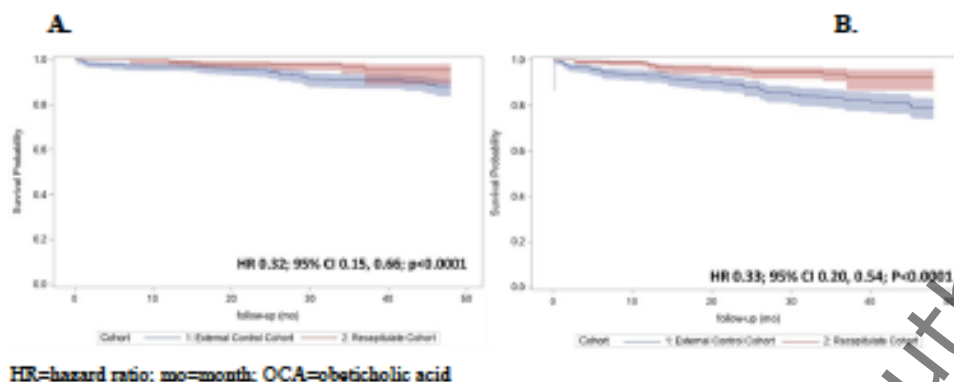
Table 117: RECAPITULATE: Baseline Variables Before and After Weighting

N	Global PBC Controls		Italian OCA-treated
	Before Weighting	After Weighting	
	831		437
Sex, female	756 (91%)	88%	386 (88%)
UDCA	623 (75%)	98%	428 (98%)
Duration of UDCA treatment, years	4.2 (4-4.4)	7 (3.3-11.4)	7 (2-12)
Age at index, years	56.5 (8.2)	57.2 (8.6)	57.7 (10.8)
Cirrhosis	125 (15%)	33%	148 (34%)
ALP/ULN at baseline	1.45 (1.6-2.6)	2.2 (1.6-3.7)	2.0 (1.7-2.9)
ALT/ULN at baseline	1.2 (0.7-1.9)	1.2 (0.7-1.8)	1.1 (0.8-1.7)
AST/ULN at baseline	1.3 (0.9-1.9)	1.2 (0.9-1.9)	1.1 (0.8-1.6)
Total Bilirubin/ULN at baseline	0.6 (0.4-1.1)	0.8 (0.5-1.2)	0.7 (0.5-1)

OCA=obeticolic acid; PBC=primary biliary cholangitis; UDCA=ursodeoxycholic acid

There was a statistically significant improvement in time to death or liver transplant for OCA-treated patients versus non-OCA-treated controls (HR=0.32; 95% CI 0.15, 0.66; $p<0.0001$) Figure 56. There was a similar statistically significant improvement in time to death, liver transplant or hepatic decompensation for OCA-treated patients versus non-OCA-treated controls (HR=0.33; 95% CI 0.20, 0.54; $p<0.0001$).

Figure 56: RECAPITULATE: Kaplan-Meier Curves of Time to Death or Liver Transplant (A) or Time to Death, Liver Transplant or Hepatic Decompensation (B) for OCA-Treated vs Weighted Non-OCA Treated Patients



Conclusion

This study, conducted independently from the MAH, used methods similar to those used in the MAH-supported studies. The 68% reduction in relative risk of death or liver transplant, and 67% reduction in relative risk of death, liver transplant or hepatic decompensation are very similar to the effects observed in the MAH-supported studies.

Summary of Real-world Evidence

CHMP wrote: "...the MAH is requested to discuss why such remarkable differences are observed between the placebo controlled study and the RWE in order to better elucidate the value of these data."

Evidence of efficacy needs to be replicable across populations, consistent across patient subgroups, robust in the face of varying study designs and analytic approaches and observed regardless of the scientific organization conducting the study. The real-world studies presented used data from the treatment arms of 2 randomized controlled trials (including 1 long-term safety extension), 1 global and 2 European PBC registries, and a large US claims database supplemented with outcomes data from a national transplant and death registry. The populations varied from early to late in PBC disease progression. The designs differed from external controls to fully real-world; from random selection of control index dates to nested trial emulation allowing all eligible index dates to be included. IPTWs and SMRs were used to balance treatment groups at baseline. Endpoints included transplant-free survival and event-free survival, as well as their individual components. Numerous sensitivity analyses were conducted. The studies were conducted in collaboration with the MAH, and independently.

The treatment effects, summarized in Table 113, are remarkably consistent. Across studies, HRs ranged from 0.29 to 0.40 for time-to-death and liver transplant; and from 0.30 to 0.42 for death, liver transplant, or hepatic decompensation. The size of the treatment effects were consistent for each component of the composite endpoint (death, liver transplant, and hepatic decompensation), i.e., the effects were not driven by a single component. The observed effects demonstrated treatment benefit in all studied subgroups, with the exception of male patients in Study 747-405 (in which the sample size was extremely small).

The event rates in OCA-treated patients are very similar across studies, with slightly higher events in patients with more advanced PBC. The events rates in untreated patients were nearly superimposable for patients early in disease, and higher for patients with more progressed disease. Event rates increased as the endpoint was expanded from transplant-free survival to event-free survival adding hepatic decompensation, to event-free-survival adding hepatic decompensation and portal hypertension. These details are important for 2 reasons:

1. The data “behave” in a way that demonstrates a high level of construct validity. For example, if sicker patients had lower observed event rates than healthier patients, one could legitimately question the validity of the data.
2. The data demonstrate that the course of PBC disease is highly predictable, both for untreated patients and OCA-treated patients.

These 58% to 71% reductions in the relative risk of serious clinical events of all-cause death, liver transplants, and hepatic decompensation offer strong support that OCA treatment provides a clinically meaningful and significant benefit to appropriately treated PBC patients with a positive benefit:risk. We believe that CHMP should consider these results, in addition to those from 747-302, in their evaluation.

Conclusions

There are several reasons why the partial and fully real-world analyses differ from those of the clinical trial. Prior to the submission of the original MAA, the original MAH sought Follow-up Protocol Assistance from CHMP on the design of Study 747-302 (EMA/CHMP/SAWP/290154/2014). Many of the potential issues that both the MAH and CHMP raised and discussed have become apparent during the study’s execution:

- Recruiting subjects on placebo in a rare disease trial, which was then exacerbated owing to the COVID-19 pandemic
- Maintaining subjects on placebo once commercial drug became available
- An inability to expand recruitment to countries where the product was not commercially available, largely owing to the COVID-19 pandemic
- The majority of subjects included in Study 747-302 have advanced disease and are no longer indicated in the SmPC

In addition, patients with PBC can easily monitor their disease progression, as ALP is part of standard routine blood chemistry panels. The MAH has also been informed by some investigators that they felt it was unethical to maintain subjects on investigational product who experienced disease progression when effective commercial treatment was available. Some subjects randomized to placebo who progressed subsequently crossed over to active treatment, which lowered their event rates. In the OCA-treated group, 65% of events occurred in subjects who had discontinued treatment, increasing events in that group. Therefore, the effect size was compromised, and ITT analyses prohibit taking this bias into account.

Putting all of these issues together, the MAH believes that significant bias has, unfortunately, influenced the results in Study 747-302.

The original MAH highlighted their concerns with Study 747-302 during their interactions with CHMP during the Annual Renewals in 2019, 2020 and 2021 and sought Scientific Advice in 2021 to directly address the issues. Discussions also took place with FDA, who suggested expanding the endpoint in the study, thereby improving power, resulting in an improved hazard ratio. Similarly, when IPCW was applied to the primary analysis to reduce bias, the hazard ratio improved and indicated benefit. However, residual bias remained, compromising treatment effect.

The real-world studies that have been undertaken on behalf of the MAH and also, separately, by an independent group, utilized various techniques described in the reports to minimize bias. The PBC patients in these studies are reflective of those who have been prescribed Ocaliva since its approval in 2016 and the MAH believes represent the true treatment effect. That treatment benefit is consistent across study populations, patient subgroups, study design and analysis, and was maintained throughout extensive sensitivity analyses. Combining the results seen with both the randomised control study, with

all its flaws, and the real-world studies makes it possible to conclude that it is reasonable to conclude that there is a positive benefit:risk for Ocaliva for those PBC patients for whom there are no other treatment options.

Assessment of the MAH's response

The MAH's initial comment that the real-world evidence (RWE) is not a "substitute" for the 747-302 study is welcomed. However, the MAH has provided a number of complementary analyses and their conclusions are consistent not only in supporting the benefit-risk assessment of OCA, but also in overcoming the results of the randomised comparisons from the conducted trials.

The discussion on the potential bias (and/or its uncertainty) due to crossover has been addressed in the answer to question 8. There are still uncertainties about the frequency and timing of discontinuation of treatment, study visits and the trial, and in fact, the results do not suggest an overall higher rate in the placebo group, but quite the opposite. This further supports the view that the IPCW analysis can only be considered as a post-hoc exploratory analysis for hypothesis generation, where a treatment policy strategy was predefined as the primary analysis in the 747-302 failed trial. This analysis cannot be considered more important than the prespecified confirmatory analysis, and in fact, despite being more in the MAH's expected positive direction, it was still very far from statistical significance (HR [95%CI]: 0.82 [0.53, 1.27]).

Overall, all analyses provided based on RWE were quite more positive, and some of them showed statistical significance in favour of OCA. Notably, some of the MAH's comments are aimed at justifying the invalidity of the placebo test group, which is also the basis for justifying the use of external controls. This has been discussed in several previous questions, in particular it has been extensively addressed in answer to question 1. In essence, the regulatory assessment has concluded that despite the fact that the current estimation of the treatment effect might be confounded to some extent, should this occur it would be in both treatment arms and not just in placebo. Therefore, any post-hoc external comparison to overcome the failed trial results is invalid, especially as the RWE results are very far from the results of a randomised comparison. Furthermore, in contrast to the trial, MELD could not be assessed in the EC comparison as a measure of baseline balance and as a component of the primary endpoint, and notably, patients were censored at the occurrence of an ICE, which was handled in the trial using the treatment policy strategy for the primary assessment.

Finally, propensity score methods are useful tools for balancing for prognostic factors, but unlike randomisation, they only allow adjustment for known and measured factors, so that they will never overcome the effect of randomisation. The MAH states that the treatment effects were remarkably consistent, but the divergence from the trial results only points out that there is a remarkable divergence due to the lack of a randomised comparison and that there is a very high risk of residual confounding in the baseline balance and during the follow-up. As a result of this, the risk-benefit assessment of OCA in the treatment of PBC will be mainly based on the results of the trials, and the RWE is considered only as complementary and exploratory with a much lower level of evidence than the trial results.

Conclusion

Issue not further pursued.

13. 2nd Request for supplementary information to be addressed in the oral explanation

Major objections

1. The confirmatory study 747-302 has failed to demonstrate the clinical benefit of OCA treatment in reducing the risk of relevant clinical outcomes in patients with PBC, regardless of liver disease severity. The absence of improvement of liver histology further corroborates these findings. The results submitted from the external control studies/analyses, based on RWD, are not considered a sound piece of evidence valid to counterbalance for the negative results of a RCT. Consequently, the SOB#1, aimed to address the main efficacy uncertainty at the time of granting a CMA, i.e. to what extent those changes in biochemical parameters correlate with a risk reduction in relevant clinical liver outcomes in PBC patients and thus, the actual benefit of OCA treatment is not demonstrated. Therefore, this type II variation requesting a switch from CMA to a full MA is not approvable, and the proposed amendments of the SmPC (including also a restriction of the indication) cannot be agreed with in view of the concerns raised on the demonstration of efficacy and safety in the whole target population.

14. Oral explanation

The MAH addressed the Major objection in an oral explanation to the CHMP reiterating largely previous argumentation that the failure of study 742-302 could be explained by bias also referring to results generated in RWE studies. The MAH agreed that the switch from a conditional to a full marketing authorisation is not approvable at present and proposed a registry study as a follow up specific obligation, a drug utilisation study and the implementation of further risk minimisation measures to maintain the benefit risk balance positive within this CMA. The oral explanation did not change the CHMPs negative opinion on the outcome of this variation procedure as outlined in the assessment report.