EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) No 726/2004

Invented name: Ocaliva

INN: obeticholic acid

Procedure number: Ocaliva EMEA/H/A-20/1531/C/004093/0045

Note:

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

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1. Information on the procedure

At the time of the granting of the marketing authorisation (MA) of Ocaliva, uncertainty remained as to the extent to which the observed changes in laboratory parameters (levels of alkaline phosphatase and bilirubin) correlated with clinical outcomes. The conduct of study 747-302 (also COBALT) was imposed in order to alleviate this uncertainty.

In October 2023, the CHMP considered as part of a variation procedure submitted to request the switch from a conditional to a full MA (EMEA/H/C/004093/II/0038) that study 747-302 had failed to demonstrate the clinical benefit of Ocaliva across the spectrum of PBC patients. In this context, the CHMP further considered that the risk minimisation measures proposed by the MAH, including the restriction of indication to patient with less severe disease, were considered insufficient. The CHMP considered that the 747-302 study results indicated a lack of efficacy and concerning safety profile the CHMP raised serious concerns as to whether the benefit of Ocaliva still outweighed its risks.

On 12 October 2023, the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Ocaliva and to issue a recommendation on whether its marketing authorisation should be maintained, varied, suspended, or revoked.

2. Scientific discussion

2.1. Introduction

Ocaliva contains the active substance obeticholic acid (OCA), a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine which is thought to be a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol and increasing transport of bile acids out of the hepatocytes.

Ocaliva was granted a conditional marketing authorisation (CMA) in the European Union (EU) in December 2016, 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. This initial approval was mainly based on results from the phase 3, randomised, double blind, placebo-controlled, parallel-group study 747-301 (also called POISE), showing superiority to placebo on the primary endpoints (percentage of patients reaching alkaline phosphatase and bilirubin levels below predefined cut-off values).

At the time of the granting of the marketing authorisation (MA), uncertainty remained as to the extent to which the observed changes in those laboratory parameters correlated with clinical liver outcomes. In order to alleviate this uncertainty, the marketing authorisation holder (MAH) was requested to conduct and submit the results of study 747-302 (also COBALT), 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. In addition, in order to investigate the uncertainties related to the lack of data in a population with more advances liver disease, the MAH was requested to 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.

The exact wording of the specific obligations (SOBs) was the following:

- Interventional study 747-302: *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.*
- *Interventional study 747-401: 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.*

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 to the CHMP at the time.

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 (e.g. Child-Pugh Class B or C) or a prior decompensation event, a variation was submitted to contraindicate Ocaliva in those patients (EMEA/H/C/004093/II/0030), and study 747-401 was prematurely terminated. Study 747-302 was also prematurely terminated.

In December 2022, the MAH submitted the final results from studies 747-302 and 747-401 in a type II variation requesting the switch of the type of marketing authorisation from CMA to a full MA (EMEA/H/C/004093/II/0038). Final results from the long-term safety extension (LTSE) of study 747-301 together with results of three real-world evidence studies were also included in this variation application as supportive information.

In October 2023, the CHMP considered that study 747-302 had failed to demonstrate the clinical benefit of Ocaliva across the spectrum of PBC patients and considered the request to switch to a full MA not acceptable. In this context, the CHMP further considered that the proposed risk minimisation measures, including the restriction of indication to patient with less severe disease, proposed by the MAH, were insufficient. Considering that the 747-302 study results indicated a lack of efficacy and concerning safety profile the CHMP raised serious concerns as to whether the benefit of Ocaliva still outweighed its risks in its authorised indication.

In view of the above, the EC initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product Ocaliva (obeticholic acid). The EC requested the Agency/CHMP to give its opinion by June 2024 on whether the marketing authorisation for this product should be maintained, varied, suspended, or revoked.

In the context of the present Article 20 referral, the CHMP considered all available data, including the two SOB studies, study 747-401 and study 747-302, the phase 2 studies 747-201 and 747-202 together with the pivotal study 747-301 (which supported the CMA), including its long-term safety extension (747-301-LTSE), as well as additional results from real-world evidence (RWE) study 747-405 and from three other supportive RWE studies.

A summary of the most relevant efficacy information is included below.

Table 1. Overview of Key Efficacy Data Submitted

Study ID and design / reference	Key objectives / endpoints	Population	Inclusion/ exclusion criteria	Treatment	Main results
747-302 Phase 3b/4 double-blind, randomized, placebo-controlled, multicentre study (also COBALT)	Primary Assess the effect of OCA on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint of death, liver transplant, model of end stage liver disease (MELD)≥15, uncontrolled ascites, or hospitalisation for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis. Secondary Assess the effect of OCA on the following: • time to first occurrence of each of the individual components in group 1 of the expanded primary endpoint (for FDA) • 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. • time to first occurrence of each of the individual components of the expanded primary endpoint (for FDA) • time to occurrence of liver-related death. • progression to cirrhosis • time to occurrence of hepatocellular carcinoma (hcc)	Planned 428 subjects Randomised 334 (168 subjects in the OCA group and 166 subjects in the placebo group)	Key Inclusion Criteria Eligible subjects were ≥18 years at the time of enrolment who had a definite or probable diagnosis of PBC (consistent with American Association for the Study of Liver Diseases [AASLD] and European Association for the Study of the Liver [EASL] Practice Guidelines [Lindor 2009, EASL 2009]), defined as having ≥2 of the following 3 diagnostic factors: • History of elevated ALP levels for at least 6 months • Positive antimitochondrial antibody (AMA) titre, or if AMA negative or low titre (≤1:80), PBC-specific antibodies (anti-GP210 and/or anti-SP100) and/or antibodies against the major M2 components (PDC-E2, and/or 2-oxo-glutaric acid dehydrogenase complex) • Liver biopsy consistent with PBC (collected at any time prior to screening) Subjects satisfied the criteria of a mean total bilirubin >ULN and ≤5x ULN and/or a mean ALP >3x ULN and took UDCA for at least 12 months (stable dose for ≥3 months) prior to Day 0 or were not taking UDCA (no UDCA for ≥3 months). Key Exclusion Criteria Subjects were excluded from participation if they had clinical complications of PBC or clinically significant (CS) hepatic decompensation including a history of liver transplant,	OCA 5-mg and OCA 10-mg tablets Placebo tablets	Primary results Time to First Occurrence of Primary Outcome Event (ITT Population): HR (95% CI) 1.01 (0.68, 1.51)

	• disease progression via the liver biochemistry and markers of inflammation and fibrosis • liver-related clinical outcomes Characterise the PK of OCA and its conjugates in a subset of subjects. Assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilisation, and quality of life measures in subjects treated with OCA. Assess the safety and tolerability in subjects treated with OCA		current placement on a liver transplant list, or a MELD score >12 or cirrhosis with complications (within the past 12 months), known or suspected hepatocellular carcinoma, prior transjugular intrahepatic portosystemic shunt procedure, hepatorenal syndrome, mean total bilirubin >5x ULN, or presence of other concomitant liver diseases including: • Hepatitis C virus infection • Active hepatitis B infection; however, subjects who had seroconverted (hepatitis B surface antigen and hepatitis B e antigen-negative) may be included in this study after consultation with the Medical Monitor • Primary sclerosing cholangitis • Alcoholic liver disease • Definite autoimmune liver disease or overlap hepatitis. • Non-alcoholic steatohepatitis • Gilbert's Syndrome		
747-301 Long term safety extension (LTSE) Phase 3, open-label	Primary Long-term safety Composite endpoint of the percentage of patients with ALP <1.67x ULN and total bilirubin ≤ULN and ALP decrease of ≥15% from Baseline.	193 enrolled into the LTSE and received open-label OCA	Key Inclusion Criteria Patients with definite or probable PBC diagnosis with an ALP ≥1.67x ULN and/or total bilirubin >ULN to <2x ULN	OCA 5-mg and OCA 10-mg tablets Patients receiving placebo started OCA 5 mg. Patients already on 5 mg continued the same dose. Patients receiving 10 mg at the end of the double-blind phase were titrated down to 5 mg.	Subjects who continued treatment with OCA: sustained % subjects achieving the primary composite biochemical endpoint. Same pattern observed for each biochemical parameters (ALP, BR, GGT, AST, ALT, and inflammatory markers) for subjects on continued treatment with OCA. Subjects switching from placebo to OCA: Similar effect reached. By LTSE month 60, nearly 50% of OCA-treated subjects saw a ≥ 40% improvement in ALP, while BR remained within normal values
747-401 Phase 3b/4, double-blind, randomized, placebo-controlled study	Primary Evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and OCA metabolite glucuronide compared with placebo and to evaluate the safety and tolerability of OCA treatment compared with placebo.	Planned: 50 subjects Randomised: 22	Key Inclusion Criteria 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	OCA 5-mg and OCA 10-mg tablets Placebo tablets	No clinically meaningful differences were noted between OCA and placebo for efficacy endpoints Patients with moderate or severe hepatic impairment are contraindicated per the revised EU SmPC; therefore,

	Secondary Evaluate the effect of OCA treatment compared to placebo on: • The MELD score and its components • CP score and its components • Liver biochemistry including total and direct bilirubin, ALP, and aminotransferases (ALT, AST, and GGT), international normalised ratio (INR), creatinine, albumin, platelets. Biomarkers of bile acid synthesis and homeostasis including fibroblast growth factor 19 (FGF-19), 7α-hydroxy-4-cholesten-3-one (C4), and plasma bile acids.				the data from this study are of limited value to prescribers for Ocaliva in PBC.

2.2. Data on efficacy

Ocaliva 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. Preliminary evidence of benefit supporting the CMA was a higher decrease from baseline in ALP levels observed in OCA compared to placebo group, in a subset of PBC patients with an early stage compensated liver condition with normal/near normal bilirubin values, as shown in the 3-month dose finding studies 747-201/202 and the pivotal phase 3 study 747-301, a 12-month, international, double-blind, placebo-controlled study. Same trends over time were observed for GGT, ALT, and AST in OCA group compared to placebo. Of note, an increase in bilirubin values was found in the study 747-202.

The effectiveness of OCA treatment to reduce clinically relevant disease symptoms (i.e. reducing disease burden for patient) was unknown at the time of the initial CMA.

The new and main relevant source of clinical efficacy data (biochemical and clinical outcomes) assessed in this procedure are those from study 747-302 imposed as a SOB of the CMA, and new efficacy data from the long-term safety extension of study 747-301 (747-301-LTSE). Additional evidence for liver biochemistry and clinical outcomes efficacy was available from real-world data (study 747-405) and from three other supportive RWE studies.

The term "compensated" will be used throughout this document to refer to both patients without cirrhosis and those with compensated cirrhosis. The compensated population in study 747-302 reflects the more advanced end of the spectrum of the SmPC indicated population. The focus of the discussion and comparison across datasets will be for the compensated population within study 747-302, compared to all other available data from trials and RWE.

2.2.1. Study 747-302

Study 747-302 was an SOB aimed to confirm the efficacy and safety (mainly long-term hepatic and cardiovascular safety), in clinically relevant outcomes/endpoints, associated with OCA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment.

It was a Phase 3b/4 double-blind, randomised, placebo-controlled, multicentre study which evaluated the effect of OCA on clinical outcomes in subjects with PBC. Study 747-302 was designed to enrol a patient population enriched for subjects with more advanced PBC compared to study 747-301. Subject eligibility required a diagnosis of PBC with bilirubin levels >ULN and ≤5x ULN and/or ALP levels >3x ULN. Randomisation was stratified by UDCA treatment (yes/no) and baseline bilirubin categories (>ULN/≤ULN). A minimum of 30% of subjects were required to have elevated bilirubin (>ULN) at Screening.

The primary objective of this study was to assess the effect of OCA compared 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 any of the following adjudicated events, derived as a composite event endpoint of death, liver transplant, model of end stage liver disease (MELD) ≥15, uncontrolled ascites, or hospitalisation for new onset or recurrence of variceal bleed, hepatic encephalopathy, or spontaneous bacterial peritonitis.

The study was event driven and was to continue until approximately 127 adjudicated primary endpoint events were accrued in unique subjects, or until the Sponsor (e.g. based on a recommendation from the independent data monitoring committee IDMC) terminated the study. Subjects were expected to be followed for a minimum of approximately 6 years.

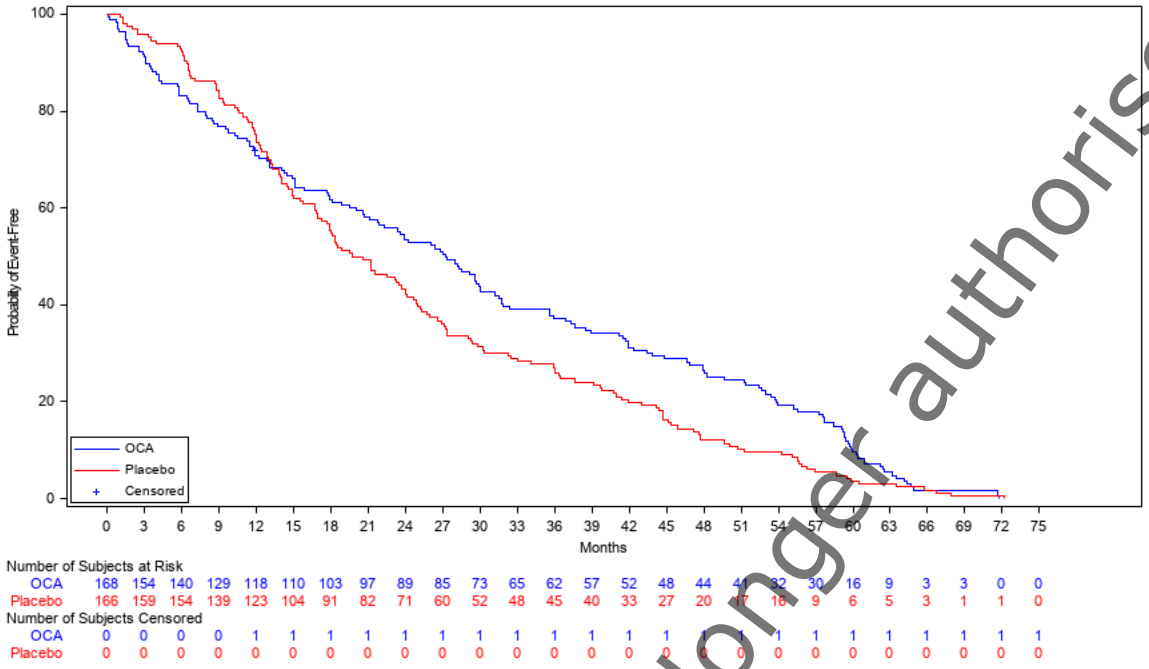
Baseline disease characteristics

Overall, the median age at time of diagnosis was 46.2 years. The median duration of PBC at time of informed consent was 7.0 years. In general, PBC disease history was balanced between placebo and OCA groups, except for stage of most recent liver biopsy. The majority (88%) of subjects were on UDCA at baseline. A total of 9% of subjects previously received UDCA but were not on UDCA at baseline and 3% had never received UDCA. The median duration of previous or current UDCA use at the time of informed consent was approximately 7 years.

Conduct of the study

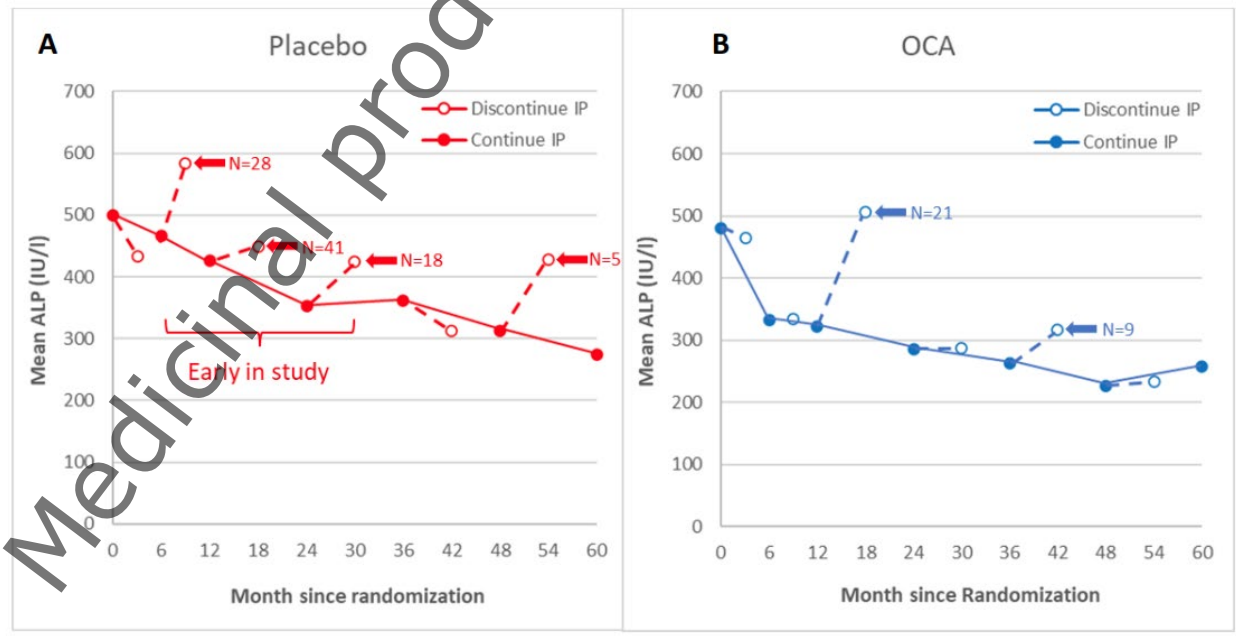
Patients randomised to placebo were more likely to discontinue investigational product, however similar proportion of placebo subjects (95 of 166, 57.2%) discontinued investigational product in the first 2 years compared to OCA-treated subjects (77 of 168, 45.8%). Twice as many subjects in the placebo group initiated commercial Ocaliva (26 of 166, 15.7%) compared to OCA-treated subjects (13 of 168, 7.7%), whilst in OCA twice as many subjects started bezafibrate (14% vs 7%). Changes in treatment regimen and study discontinuation in the placebo cohort were observed more frequently and earlier than in the OCA group (see Figure 1 below).

Figure 1: Investigational Product Discontinuation by Treatment Group (ITT Population)



The CHMP noted that the MAH claimed that placebo patients had on average a higher ALP level at time of discontinuation of investigational product compared to placebo patients who continued investigational product. The figure below shows the ALP levels at discontinuation for both placebo and OCA patients:

Figure 2: 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).

The estimands for the ITT analyses do not account for patients switching treatment due to functional unblinding and informative censoring. Several components of the expanded primary endpoint were not collected or were under-reported in biannual telephone follow-up period (i.e. patients who discontinued investigational product but who consented to be followed in the study for accrual of outcome and safety events). Data collected during the biannual telephone follow up period are subject to both recall and measurement bias. Patients randomised to placebo spent more patient-years in biannual telephone follow-up than those randomised to OCA.

In 2020, the IDMC, based on protocol-specified interim analysis of the primary endpoint, recommended to stop enrolment and to prematurely terminate the study as it considered it unlikely to provide evidence of efficacy for the enrolled PBC population as an aggregate or in any subpopulation due to feasibility concerns based on enrolment and retention challenges. However, results were obtained from a not negligible part of the expected sample size since the study randomised nearly 80% of the planned participants and approximately 67% of the protocol-specified number of clinical events had been observed (last visit Dec 2021).

Clinical Outcomes

Study 747-302 failed to demonstrate a statistically significant difference between the OCA-treated group and placebo group on the primary endpoint HR 1.01 (95% CI: 0.68, 1.51) (Table 2). The Hazard Ratios lowered to 0.82 (95% CI: 0.53, 1.27) but still did not reach statical significance when inverse probability of censoring weighting (IPCW) of the primary endpoint was carried out in an attempt to address the use of commercial OCA in the control arm.

Table 2: Study 747-302: Time to First Occurrence of Primary Outcome Event (Overall Population, ITT Analyses)

	Protocol V6 Primary Endpoint[a]		**Expanded Primary Endpoint[b]**	
	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; MELD=Model for End Stage Liver Disease; OCA=obeticholic acid.

[a] Protocol V6 Primary Endpoint: Time to first death (all-cause), liver transplant, MELD score ≥15, or hospitalisation (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); SBP (confirmed by diagnostic paracentesis); or uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)

[b] Expanded Primary Endpoint: Includes all components of protocol V6 primary endpoint as well as portal hypertension prespecified syndromes; progression to decompensated liver disease (for patients without decompensation at baseline); or progression to clinical evidence of portal hypertension without decompensation (for patients without decompensation or clinical evidence of portal hypertension at baseline).

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 (n=69; 21%) patients treated with OCA is shown (59.4% OCA vs 54.1% in placebo, HR 1.22 (95% CI: 0.65, 2.28)), though not statistically significant.

Results were nearly identical in both treatment arms in the subgroup of compensated (n=265; 79%) PBC patients (21.3% vs 21.7% OCA and placebo, respectively, HR 0.98 (95% CI: 0.58, 1.64)).

Biochemical Measurements Over Time

In terms of liver biochemistry parameters through month 60 in the ITT population, OCA treatment was associated with mean (SE) reductions from baseline in ALP, GGT, ALT, and AST over time with stabilisation of total bilirubin and direct bilirubin consistent with previous PBC studies (Table 3). However, for the placebo arm, the biochemical changes over time showed a reduction in ALP and Total Bilirubin, which is atypical for the placebo arm in all other placebo-controlled clinical trials, where ALP levels have been shown to remain elevated over a 12- to 24-month follow-up.

Subjects randomised to placebo were more likely to discontinue blinded study drug early in the study, and generally with a higher serum ALP than subjects who remained on blinded placebo, while some Ocaliva patients also had higher serum ALP levels at time of discontinuation compared to patients continuing on Ocaliva (Fig.2). 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 UDCA treatment or were treated in the past with it. Subjects randomised to placebo initiated commercially available PBC therapies earlier than patients randomised to OCA. Overall, ALP reductions in the OCA group were significantly greater compared to placebo up to month 24. 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).

Table 3: Study 747-302: Analysis of Change from Baseline in Selected Liver Biochemistry Results Assessed by MMRM at Month 3, Month 12, and Month 24 (ITT Population)

Parameter	Month 3		Month 12		Month 24	
	Placebo	**OCA**	**Placebo**	**OCA**	**Placebo**	**OCA**
ALP (U/L)	**n=164**	**n=164**	**n=138**	**n=126**	**n=102**	**n=98**
LS Mean Change (SE)	-29.7 (9.56)	-136.0 (9.52)	-68.8 (11.72)	-144.8 (12.05)	-113.1 (14.60)	-156.4 (14.93)
95% CI	-48.5, -10.9	-154.7, -117.3	-91.8, -45.7	-168.5, -121.1	-141.9, -84.4	-185.8, -126.9
LS Mean Difference (SE)	-106.3 (13.49)		-76.1 (16.81)		-43.2 (20.89)	
95% CI	-132.8, -79.7		-109.1, -43.0		-84.4, -2.1	
p-value	<0.001		<0.001		0.039	
GGT (U/L)	**n=164**	**n=164**	**n=138**	**n=126**	**n=102**	**n=98**
LS Mean Change (SE)	-37.5 (12.18)	-155.1 (12.17)	-63.4 (17.71)	-152.2 (18.24)	-127.7 (22.04)	-175.6 (22.49)
95% CI	-61.4, -13.5	-179.1, -131.2	-98.3, -28.5	-188.1, -116.3	-171.2, -84.3	-219.9, -131.3
LS Mean Difference (SE)	-117.7 (17.21)		-88.8 (25.42)		-47.8 (31.49)	

Parameter	Month 3		Month 12		Month 24	
	Placebo	OCA	Placebo	OCA	Placebo	OCA
95% CI	-151.5, -83.8		-138.8, -38.8		-109.9, 14.2	
p-value	<0.001		<0.001		0.130	
Total Bilirubin (mg/dL)	**n=164**	**n=164**	**n=138**	**n=126**	**n=101**	**n=97**
LS Mean Change (SE)	0.03 (0.052)	0.02 (0.051)	0.29 (0.111)	0.26 (0.113)	0.63 (0.138)	0.30 (0.141)
95% CI	-0.08, 0.13	-0.08, 0.12	0.07, 0.50	0.03, 0.48	0.36, 0.90	0.02, 0.58
LS Mean Difference (SE)	-0.01 (0.073)		-0.03 (0.158)		-0.33 (0.197)	
95% CI	-0.15, 0.14		-0.34, 0.28		-0.72, 0.06	
p-value	0.922		0.854		0.096	
Direct Bilirubin (mg/dL)	**n=163**	**n=162**	**n=138**	**n=121**	**n=97**	**n=96**
LS Mean Change (SE)	0.02 (0.037)	0.03 (0.037)	0.22 (0.071)	0.13 (0.073)	0.48 (0.106)	0.19 (0.107)
95% CI	-0.05, 0.09	-0.05, 0.10	0.08, 0.36	-0.01, 0.28	0.27, 0.69	-0.03, 0.40
LS Mean Difference (SE)	0.01 (0.052)		-0.08 (0.102)		-0.29 (0.150)	
95% CI	-0.10, 0.11		-0.28, 0.12		-0.59, 0.00	
p-value	0.918		0.409		0.053	
ALT (U/L)	**n=164**	**n=164**	**n=138**	**n=126**	**n=100**	**n=97**
LS Mean Change (SE)	-7.1 (4.05)	-14.4 (4.05)	-12.8 (3.37)	-20.5 (3.49)	-19.4 (2.87)	-28.5 (2.92)
95% CI	-15.1, 0.8	-22.3, -6.4	-19.4, -6.1	-27.4, -13.6	-25.1, -13.7	-34.2, -22.7
LS Mean Difference (SE)	-7.2 (5.73)		-7.7 (4.85)		-9.1 (4.10)	
95% CI	-18.5, 4.0		-17.3, 1.8		-17.2, -1.0	
p-value	0.208		0.111		0.028	
AST (U/L)	**n=164**	**n=164**	**n=138**	**n=124**	**n=102**	**n=97**
LS Mean Change (SE)	-3.5 (3.53)	-6.8 (3.53)	-5.4 (2.27)	-11.8 (2.36)	-6.0 (2.72)	-14.8 (2.78)
95% CI	-10.5, 3.4	-13.7, 0.2	-9.9, -0.9	-16.5, -7.2	-11.4, -0.7	-20.3, -9.3
LS Mean Difference (SE)	-3.3 (4.99)		-6.5 (3.28)		-8.8 (3.89)	
95% CI	-13.1, 6.5		-12.9, 0.0		-16.4, -1.1	
p-value	0.513		0.050		0.026	

ALP=alkaline phosphatase; ALT=alanine transaminase; AST=aspartate aminotransferase; CI=confidence interval; GGT=gamma-glutamyl transferase, IWRS=interactive web response system; ITT=intent to treat; LS=least squares; MMRM=mixed-effect model repeated measures; OCA=obeticholic acid; SE=standard error

Note: Statistics are from a restricted maximum likelihood based MMRM including treatment group, time, treatment group by time interaction, and randomisation stratification factors as entered in the IWRS as fixed effects and parameter baseline values as a covariate, where time included all post baseline visits. An unstructured covariance structure is used.

Consistent with the reduction in ALP following OCA treatment in PBC, at month 3, the LS Mean Change (SE) in ALP (U/L) was -136.0 (9.52) in the OCA arm (compared to -29.7 (9.56) in the placebo arm) showing a reduction in ALP from month 3 onward in the OCA arm. The difference in biochemical markers of effect narrowed over time and by month 24 the LS Mean Change (SE) in ALP (U/L) was -156.4 (14.93) in the OCA arm versus -113.1 (214.60) in placebo.

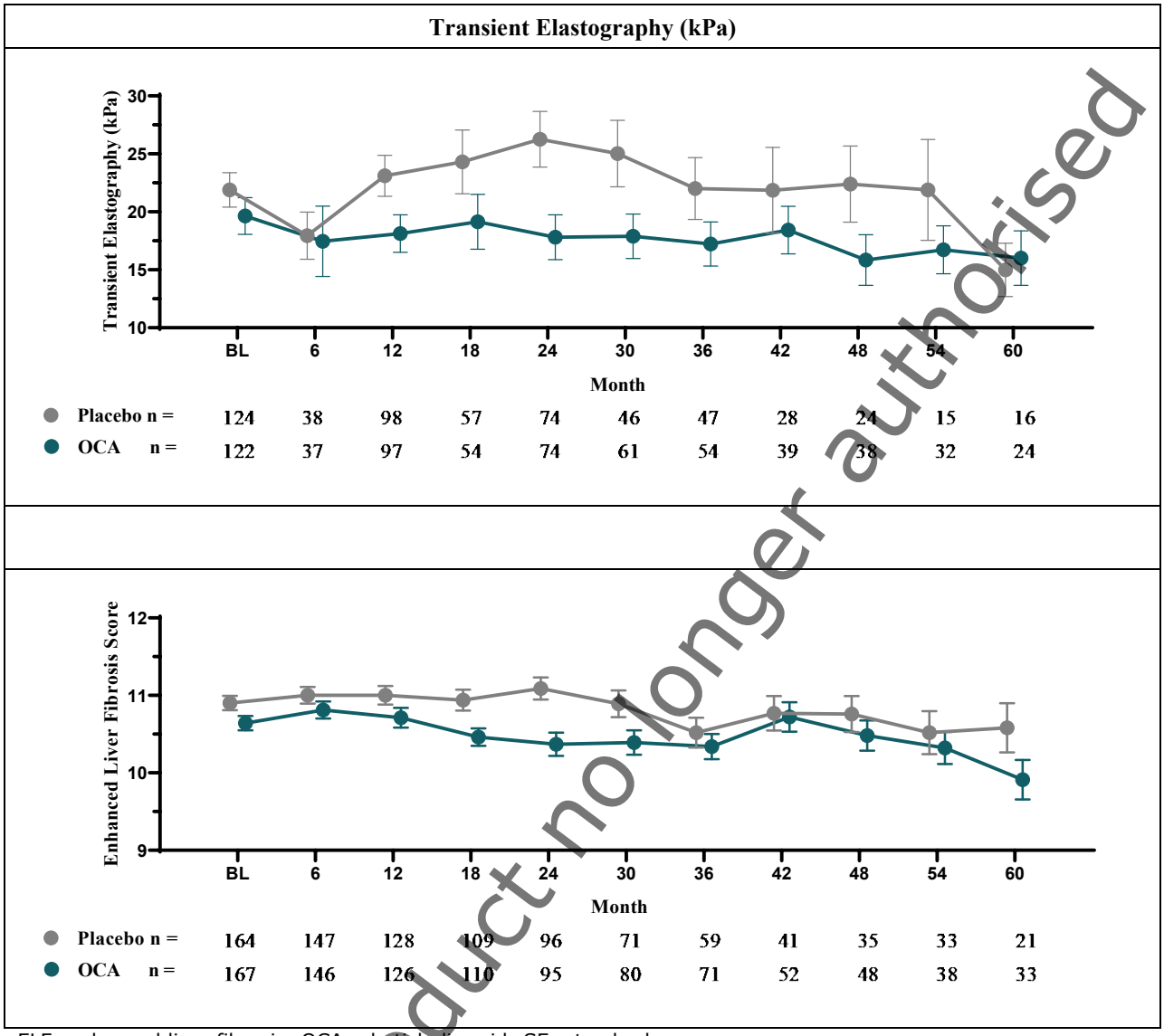
Non-invasive Measurements of Liver Stiffness and Liver Fibrosis

Mean (SE) liver stiffness (as measured by TE) and liver fibrosis (as measured by ELF) parameters over time through month 60 (carried out 6-monthly at study visits as a standard parameter) in the study are presented in Figure 3. Reduction or stabilisation of liver stiffness has been associated with improved survival in PBC (Corpechot 2022).

Mean (SD) baseline liver stiffness values were 21.9 (16.6) kPa for placebo and 19.7 (17.5) kPa for OCA, consistent with advanced fibrosis. 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.

Mean (SD) baseline ELF values were 10.9 (1.2) for placebo and 10.6 (1.2) for OCA, consistent with advanced fibrosis. 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.

Figure 3: Study 747-302: Mean (SE) Transient Elastography (TE) and ELF Over Time



ELF=enhanced liver fibrosis; OCA=obeticholic acid; SE=standard error

Liver stiffness in the placebo arm increased from month 6 to month 24. In the OCA arm there was no increase in liver stiffness and a gradual reduction up to month 60. Similar to findings with ALP, there was a difference between arms earlier in the trial for TE and ELF before 24 months, but as the trial progressed, this difference narrowed.

2.2.2. Study 747-301 LTSE

This study covered patients randomised to placebo in study 747-301 who crossed over to OCA treatment and all patients were followed for 5 additional years (747-301 LTSE). For subjects previously randomised to OCA and who continued treatment with OCA in the LTSE, the percentage of subjects achieving the primary composite biochemical 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 stayed 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 ≥ 40% improvement in ALP, while BR tended to remain within normal values.

Long-term data in a subset of 106 subjects shows no statistically significant difference in progression of hepatic stiffness as measured by TE or FibroScan between placebo and Ocaliva.

The assessment of changes in histology was limited to 17 PBC subjects who provided as part of a protocol-defined substudy 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 (12%) subjects showed improvements in histologic fibrosis, 10/17 (59%) showed stabilisation and 5/17 (29%) showed worsening (Bowlus 2020).

2.2.3. Other Studies

Study 747-401

This study was an SOB aimed at confirming the efficacy and safety of Ocaliva in the form of 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. The study was prematurely terminated. At termination of the study, it only included 22 out of the planned 50 subjects.

As such the data are limited and no clear evidence of efficacy could be seen in a small number of subjects who are now a population contraindicated for OCA, but data are presented in this report for completeness.

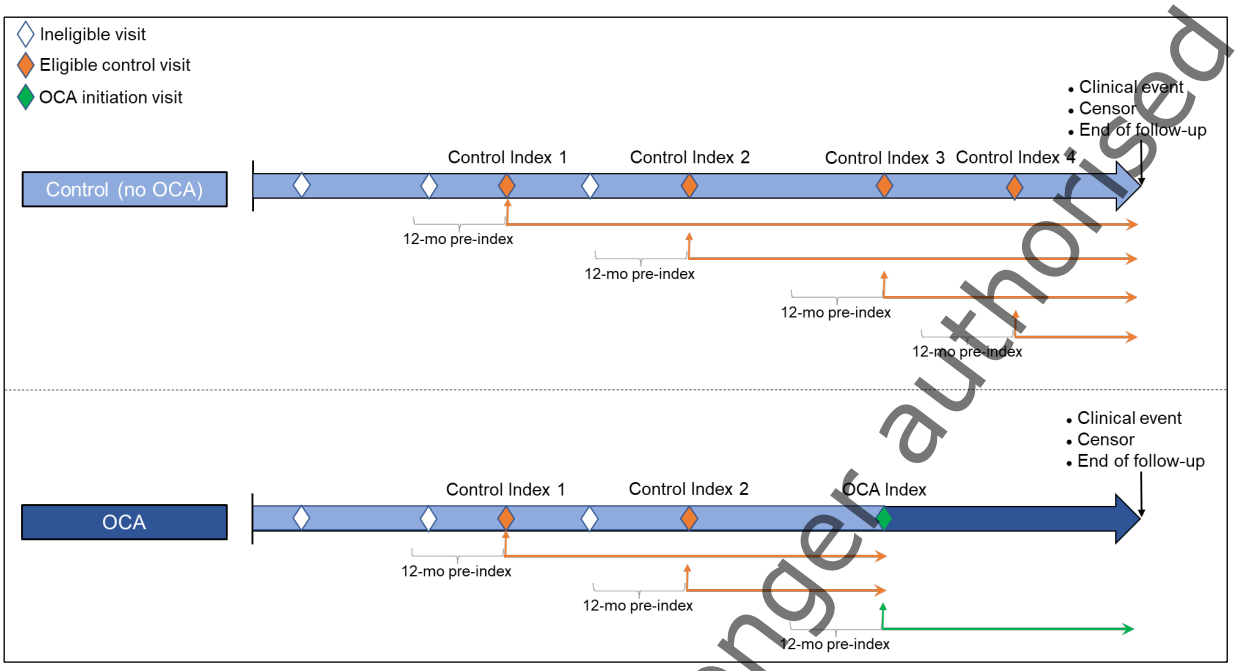
Real-World Efficacy Data

A total of four RWE studies (study 747-405, study 747-302 EC, an EC study using 747-301/301 LTSE-data (POISE), and RECAPITULATE), evaluating analyses of hepatic clinical outcomes were provided as supplementary evidence. The eligibility criteria in these real-world studies reflect patients with compensated PBC with or without cirrhosis (herein referred to as the compensated population) corresponding to the authorised indication of Ocaliva in the EU.

Study 747-405

Study 747-405 was a trial emulation study that, based on initial eligibility criteria for study 747-301, enrolled subjects from the Komodo Health claims database, containing >100,000 patients diagnosed with PBC. The treatment group included patients with PBC who initiated OCA, while the control group included patients who were OCA-eligible but not OCA-treated (Figure 4). 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 control patients.
The study was designed to replicate the results observed in the 747-301 open-label extension with an external controls outcomes study.

Figure 4 : Study 747-405: Study Design Schematic



Mo=month; OCA=obeticholic acid

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

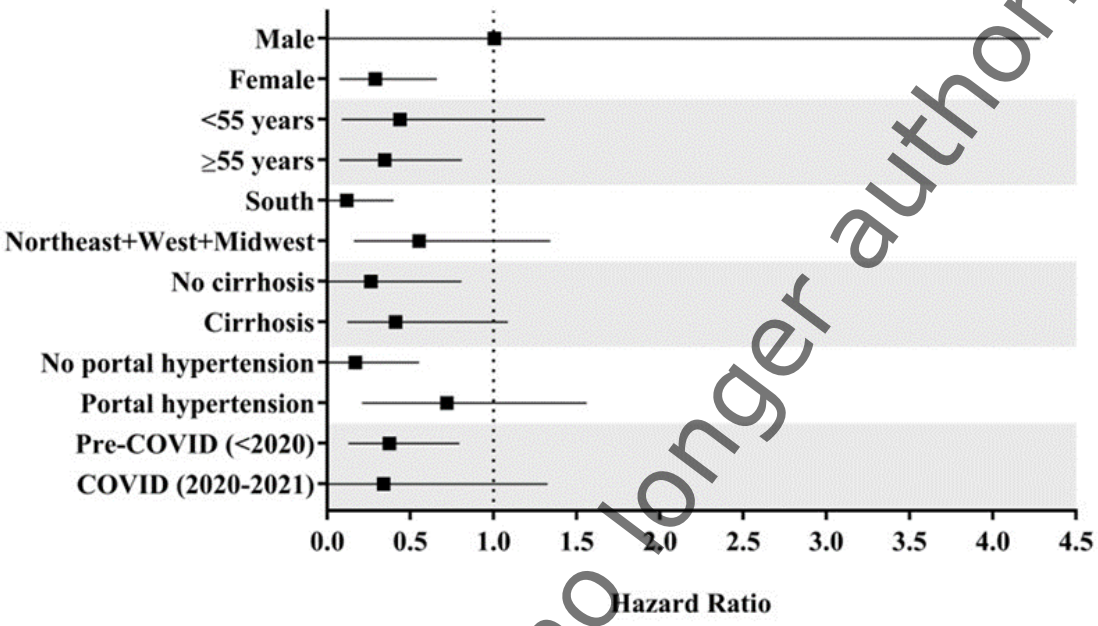
After applying study 747-301 eligibility criteria, 4535 patients contributed 12,399 control index dates, and 432 patients contributed an OCA index. After weighting, all standardised mean differences were within the pre-specified +0.10 threshold. Groups were considered balanced after weighting: >90% female; mean age, 56 years; UDCA use=73%; total bilirubin=0.7 mg/dL; and ALP=292 U/L to 294 U/L.

There were 8 events in the OCA arm and 32 in the weighted control arm (HR=0.37; 95% CI 0.14, 0.75; p<0.001). The following results were observed for each component of the composite endpoint in the OCA vs weighted control arm: 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).

Subgroup analyses by sex, age, region, baseline cirrhosis, baseline hypertension, and time period (pre/post-COVID) suggested a reduction in risk of clinical events in most of the subgroups. However, it should be noted that CIs include 1 for several of these subgroups (males, >55 years, portal hypertension, location (Northeast+ West+ Midwest) and Covid (2020-2021). (Figure 5).

Quantitative bias analyses did not influence the showed reduction in risk of clinical events even in the face of significant potential confounding. Statistical significance was eliminated only if a potential confounder was present in 50% of the population, the larger effect 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 5: Study 747-405: Subgroup Analysis of Time to Primary Endpoint for OCA-Treated vs Non-OCA-Treated Patients



Overall, after ensuring a balance in overall characteristics between the OCA-treated and non-OCA-treated groups (using propensity scores and standardised weights), a lower hazard ratio (HR) for the composite endpoint was found in the OCA arm compared to control (HR=0.37; 95%CI 0.14-0.75, p<0.001); the ITT analysis that did not censor control patients at initiation of commercial PBC treatments confirmed a lower HR for the composite endpoint in the OCA arm, although reduced in magnitude with a wide CI crossing 1 (HR=0.64; 95%CI 0.38-1.05).

Studies 747-302 EC, POISE and RECAPITULATE

Additional real-world evidence (RWE) data included:

- an external control (EC) study that compares the OCA-treated arm from study 747-302 versus a non-OCA-treated arm from Komodo Health US claims database (study 747-302 EC);
- an EC study that compares the OCA-treated arm from study 747-301 LTSE versus a non-OCA-treated arm from a Global and a UK PBC registry (Primary Biliary Cholangitis Obeticholic Acid International Study of Efficacy (POISE), Murillo Perez et al. 2022);
- an Italian independent real-world study (RECAPITULATE) conducted to evaluate OCA-treated patients from combined Italian PBC registries versus ECs from the Global PBC registry. (De Vincentis et al. 2022b, Vespasiani-Gentilucci et al. 2023).

These studies showed a reduction in risk of clinical events (death, liver transplant and hepatic decompensation) in patients with PBC treated with OCA (HR from 0.29 to 0.42).

Table 4: Key results (Death, Liver Transplant and Hepatic Decompensation events) from Real-world Studies in Patients Treated with OCA

Study & Data Source	Population	Endpoint	Events		HR (95% CI)
			OCA-treated	Controls	
Study 302	Decompensated OCA: **19.0%** External Controls: **22.0%** Clinical Evidence of PH: OCA: **48.9%** External Controls: **54.6%**	Death, LT, hepatic decomp	**28.6%**	**28.9%**	**1.01 (0.68, 1.51)**
Study 747-302 EC External Control: Komodo Health claims		Death and LT	**5.4%**	**12.7%**	**0.40 (0.18, 0.90)**
		Death, LT, hepatic decomp	**10.1%**	**21.5%**	**0.39 (0.22, 0.69)**
Study 747-301 (LTSE) with External Control External Control: GLOBAL PBC registry	Compensated PH with complications excluded	Death and LT	**2.4%**	**10.0%**	**0.29 (0.10, 0.83)**
		Death, LT, hepatic decomp	**7.7%**	**15.4%**	**0.42 (0.21, 0.85)**
Study 747-301 (LTSE) with External Control External Control: UK PBC registry	Compensated PH with complications excluded	Death and LT	**2.4%**	**13.2%**	**0.30 (0.12, 0.75)**
Study 747-405 Control: Komodo Health claims	Compensated PH with complications excluded	Death and LT	**0.5%**	**2.9%**	**0.30 (0.00, 0.96)**
		Death, LT, hepatic decomp	**2.0%**	**7.9%**	**0.37 (0.14, 0.75)**
RECAPITULATE External Control: GLOBAL PBC registry	Compensated PH with complications: OCA: :**>28%** Unknown Controls	Death and LT	Not Reported		**0.32 (0.15, 0.66)**
		Death, LT, hepatic decomp			**0.33 (0.20, 0.54)**

LTSE=long-term safety extension; RCT=randomised clinical trial; EC=external control; RWE=real world evidence; LT=liver transplant

Similar results were observed for 747-302 EC and 747-405 for the composite endpoint comprised of the endpoint death (all-cause), liver transplant, and hepatic decompensation (e.g. endpoint similar to the protocol V6 endpoint[1] of study 747-302):

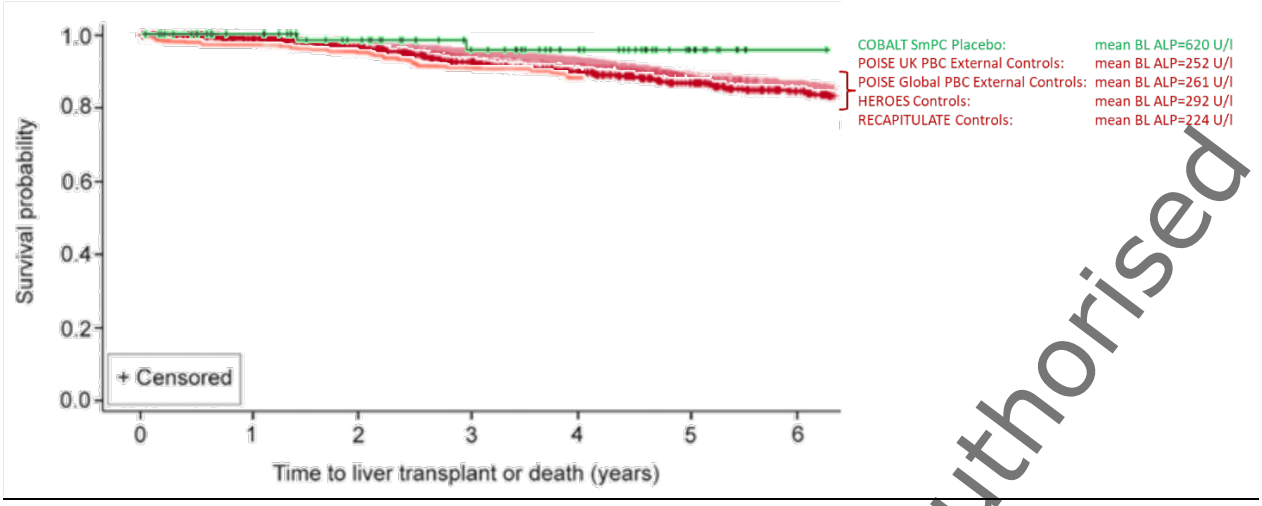
- In the 747-302 EC, the HR (95% CI) for the 302 EC composite endpoint was 0.24 (0.07, 0.90).
- In study 747-405, the HR (95% CI) for the composite endpoint was 0.17 (0.00, 0.53).

Liver Transplants or Death (All-Cause)

The MAH considers that in comparison to the non-OCA-treated patients with PBC from real-world datasets, the liver transplant and death event rate in the placebo group of study 747-302 is epidemiologically and medically implausible considering that the patients enrolled had more advanced disease at baseline. The HR (95% CI) for liver transplant or death (all-cause) was 0.29 (0.08, 1.11) for study 747-302 EC, 0.31 (0.09, 1.04) for study 747-301/301 LTSE, and 0.22 (0.00, 0.91) for study 747-405, see also Figure 6 for data over time.

Figure 6: 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

[1] Protocol V6 Primary Endpoint: Time to first death (all-cause), liver transplant, MELD score ≥15, or hospitalisation (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); SBP (confirmed by diagnostic paracentesis); or uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month)



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.

Additional data from published literature

Conversely, one publication from a US veteran database (John et al. 2021) on retrospective data from 21 PBC patients all with cirrhosis (currently excluded from the authorised indication) concluded that OCA was associated with an increased risk of hepatic decompensation compared to a propensity matched no-OCA arm (n=84).

The time to decompensation in this study was not statistically different between the OCA and non-OCA arms (median 20.0 vs. 46.0 months respectively, p = 0.31). On multivariable analysis, after adjusting for potential confounders, the authors concluded that OCA use was associated with an increased risk of hepatic decompensation (adjusted hazard ratio [aHR], 3.9: 95% CI 1.33-11.57; P = 0.01).

Sedki et al. 2021 evaluated the waitlist survival of CP Class B or C patients with decompensated PBC patients (currently excluded from the authorised indication) before and after the approval of OCA. This study did not find that the availability of OCA was associated with increased mortality, and fewer deaths were observed (n=85) than predicted by the model (N=124) with a standardised mortality ration (SMR) of 0.68 (95% confidence interval: 0.55-0.85).

Additional analyses

The MAH also provided a comparison of biochemical efficacy from study 747-302 with 747-301 and RWE. Subjects recruited into study 747-301 were at an earlier stage of the disease when compared to study 747-302 and correspond more to the patient population currently included in the authorised indication of Ocaliva, while study 747-302, by design, recruited subjects with more advanced disease so as to enhance accrual of clinical events and deliver outcomes data expeditiously. The comparison analysis found that median baseline ALP and total bilirubin values were substantially higher in study 747-302 versus 747-301, and that the percent reduction from baseline required to achieve the target ALP (≤1.67x ULN) or total bilirubin (<ULN) thresholds from the primary response criteria of study 747-301 were significantly different between studies.

Statistically significant improvements in ALP and total bilirubin were observed in the OCA group compared to the placebo group in both studies 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.

Liver biochemistry data in restricted sub-population of the 747-301 study

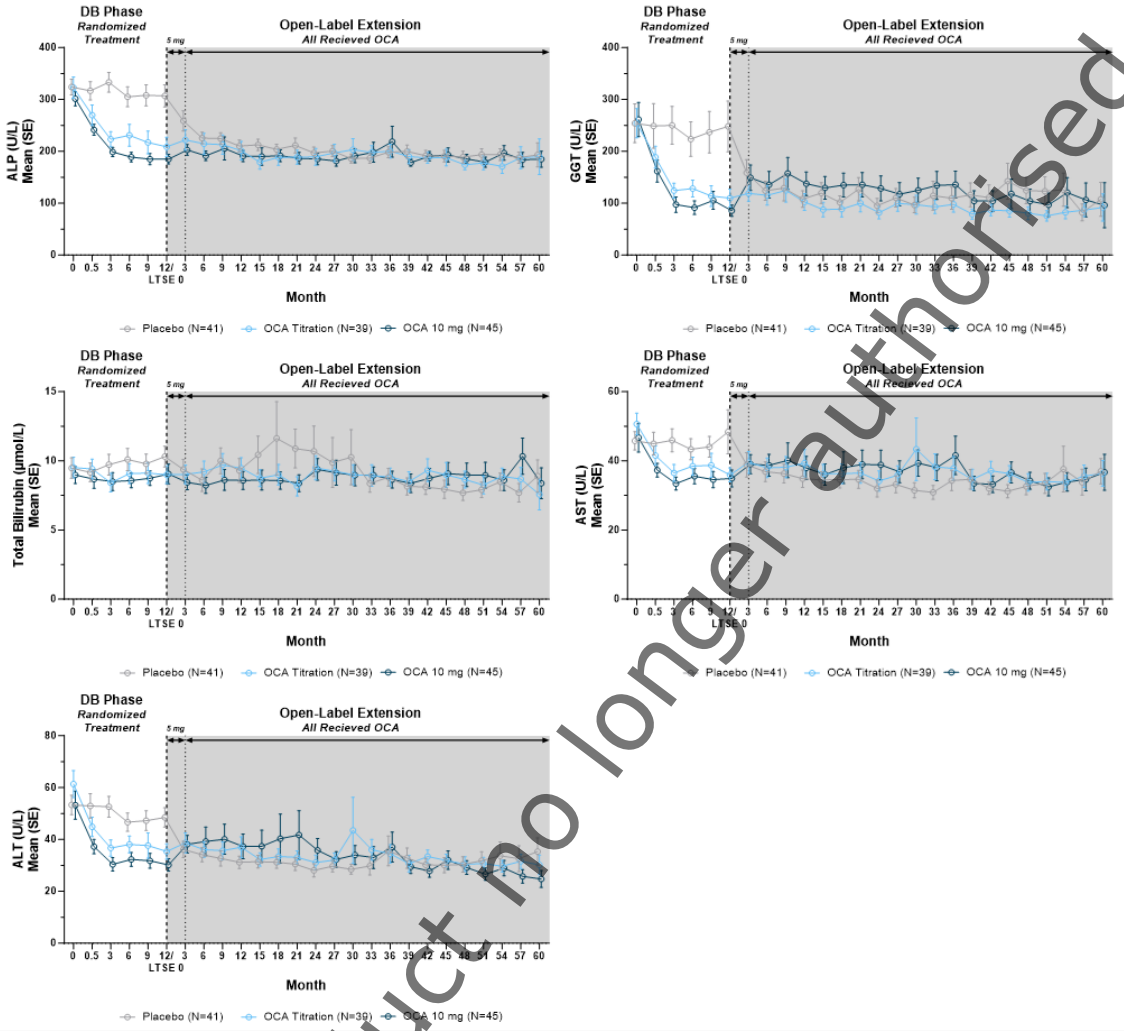
During the procedure, the MAH proposed to restrict the target population for Ocaliva to patients at an earlier disease stage. This was proposed to be implemented through the inclusion of a contraindication in patients with clinical evidence of portal hypertension (such as presence of gastroesophageal varices, splenomegaly, and persistent thrombocytopenia), and the introduction of a stopping rule for Ocaliva treatment to be interrupted if total bilirubin rises above 1.5mg/dL. Treating physicians would then be advised to further investigate the patient and permanently discontinue treatment if there is clinical evidence of portal hypertension detected.

An alternative stopping rule was also proposed to be added for Ocaliva to be permanently discontinued if, after 12 months treatment, there is failure to show either ≥ 40% reduction in ALP, OR ≤ 1.67x ULN ALP reduction.

Subset of patients at earlier disease stage

Liver biochemistry results over time from study 747-301 for both the 12-month double-blind, placebo-controlled period, as well as the long-term safety extension (LTSE) period up to 60 months were provided limited to the proposed restricted patient population at earlier disease stage (N=108), see Figure 7.

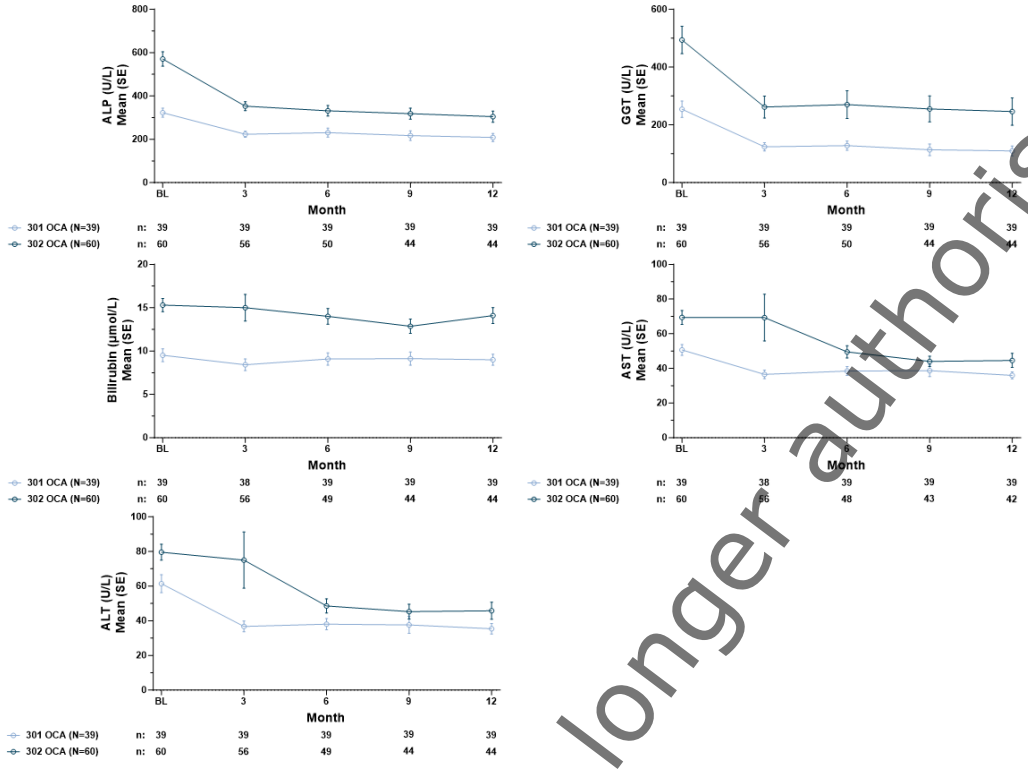
Figure 7: Continuous Variables of Liver Biochemistry in the Proposed Restricted Patient Population at Earlier Disease Stage (Study 747-301 LTSE) *



*Data are presented based on the randomised treatment arms of the double-blind period and based on a weighted average daily dose (WADD) of ≤10 mg in the LTSE Phase.

A new analysis of biochemical response of Ocaliva over the initial 12 months of the double-blind period of the confirmatory study 747-302 (i.e. prior to the timepoint beyond which treatment crossover occurred more frequently), limited to the restricted subgroup of patients were also presented (Fig. 8).

Figure 8: Biochemical Response During the Initial 12-Month Double-Blind Period in the Proposed Restricted Population: Study 747-302 versus Study 747-301*



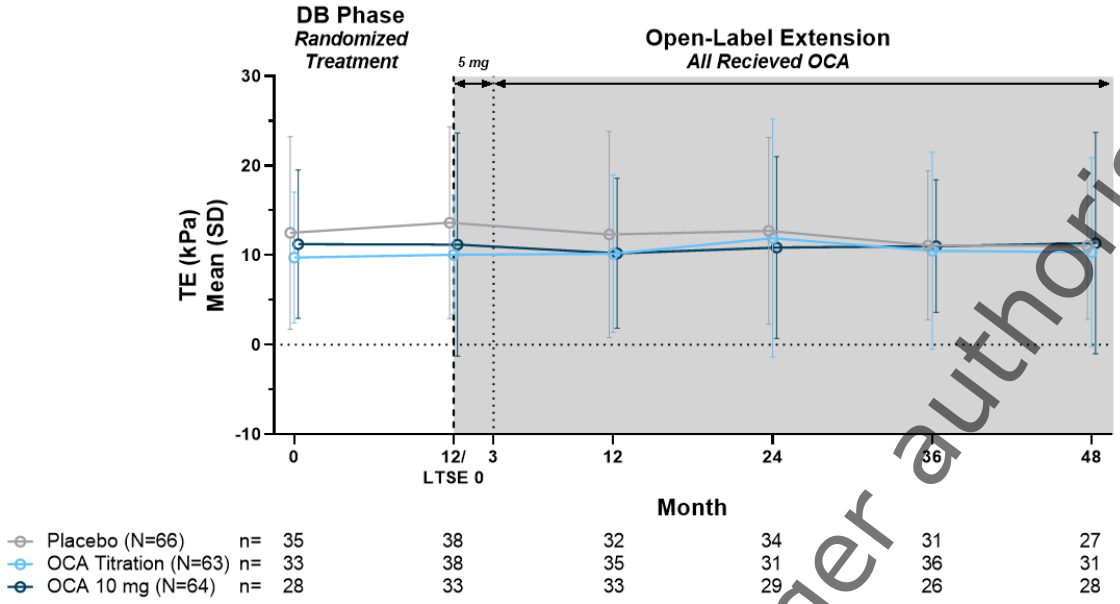
*Data for 747-301 LTSE are presented based on the randomised Titration arm of the double-blind period and based on a weighted average daily dose (WADD) of ≤10 mg in the LTSE Phase.

The response profile to Ocaliva has shown the same pattern in both studies despite enrolling PBC populations with different baseline ALP values. Similar trend is noted for other biochemical markers.

Cross study data on liver fibrosis

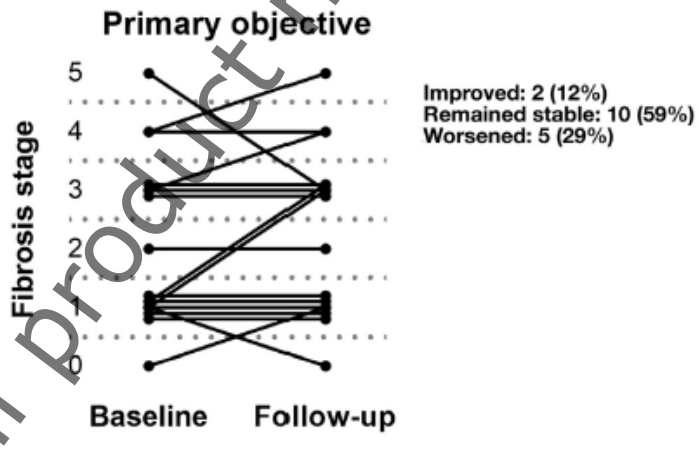
During the procedure, the MAH also submitted an analysis on Ocaliva's effect on fibrosis either by using non-invasive methods (Fig. 9) on the safety population from study 747-301 LTSE) or liver biopsy (Fig. 1 and 11). These are coming from: i) a subgroup of selected PBC patients extracted from the Italian RECAPITULATE cohort with availability of liver stiffness assessment by Fibroscan suggesting some correlation between biochemical response and liver stiffness at Fibroscan; ii) a small independent analysis from 9 Italian patients with paired liver biopsies (before and after 3 years of Ocaliva treatment) suggesting a potential beneficial effect on liver fibrosis.

Figure 9: Transient Elastography Over Time Using Observed Data Based on Double-Blind Baseline: Safety Population (N=193)



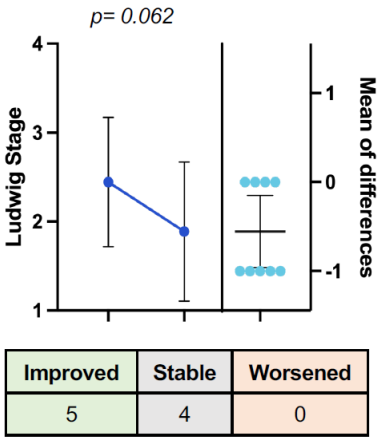
DB=double-blind; LTSE=long-term safety extension; OCA=obeticholic acid; SD=standard deviation; TE=transient elastography; UDCA=ursodeoxycholic acid
Data are presented as mean (SE). For all patients, double-blind baseline is the Day 0 value before double-blind treatment. Source: 747-301 LTSE CSR, Table 14.2.9

Figure 10: 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.

Figure 11: Treatment with OCALIVA for 3 Years Fibrosis as Assessed by Ludwig Stage



Improved	Stable	Worsened
5	4	0

For the Ludwig scale, fibrosis is on a scale of grade 1 to grade 4 with grade 4 being the most severe. Data on file. Safety in the Proposed SmPC population, Including Risk Minimisation Measures

2.2.4. Discussion on clinical efficacy

Efficacy was substantiated using surrogate endpoints ALP and bilirubin (which for UDCA are indicators for disease progression) at the time of the MAA. The adequacy of the primary composite endpoint, solely based on changes in biochemical parameters, was discussed during the CHMP PA (EMEA/H/SA/2016/1/2010/PA/III). It was considered acceptable, subject to the obligation of the Applicant to collect as much data as possible regarding harder clinical endpoints such as histology, cirrhotic related events, fibrosis markers and elastography. However, only limited non-invasive data (e.g. transient elastography, APRI score and ELF score) were provided in the initial application and OCA treatment benefit remained mainly based on the improvement of several biochemical parameters, such as ALP and bilirubin levels, whose predictive values of clinically relevant endpoints was, thus, not known in the specific context of Ocaliva treatment.

The effectiveness of OCA treatment to reduce clinically relevant disease symptoms (i.e. reducing disease burden for patient) was unknown at the time of the initial CMA. **Study 747-302** was therefore imposed (SOB) to address the uncertainties regarding the relationship between biochemical changes and liver clinical outcomes and long-term effects of the treatment, whilst **study 747-401** was imposed (SOB) as a double-blind, randomised, placebo-controlled study to address current uncertainties regarding efficacy, safety and PK in patients with a more advanced disease state.

Study 747-401 was prematurely terminated upon the EU SmPC update in 2021, following a contraindication for the use of OCA in patients with advanced liver disease. The study only included 22 out of the planned 50 subjects. Results of this study showed a significant toxicity, and the possible contribution of OCA treatment cannot be ruled out.

LTSE 747-301: Patients randomised to placebo in study 747-301 crossed over to OCA treatment and all patients were followed for 5 additional years (747-301 LTSE). Overall, although the results in liver biochemical parameters 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%), these support the maintenance of the biochemical 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 conclusion cannot be drawn.

Study 747-302 was a double-blind, randomised, placebo-controlled, multicentre study and it was an SOB 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 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 generate the necessary data to 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 randomised 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."

Study results show 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]) (this population subset is no longer part of the authorised indication), 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% for OCA and placebo, respectively, HR 0.98 [95% CI: 0.58, 1.64]). Thus, the study failed to demonstrate any efficacy of OCA treatment in terms of relevant clinical outcomes and across the severity spectrum of PBC patients.

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 claimed that this left the study underpowered to detect the proposed treatment effect. However, in view of the results detailed above, 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: as at least a consistent trend in the main clinical endpoints (even if not statistically significant) would have been expected in case of a real clinical benefit, but no trend was observed.

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, initiation of PBC treatment with a potential effect on ALP levels occurred in a small portion of subjects and was 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). However, 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).

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 <1.67x ULN and total bilirubin ≤ULN and ALP decrease from baseline of ≥15%. Indeed, the rate of responders (meeting said criteria) 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. It is 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. 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.

Consistent with previous findings, a negative effect on key PBC symptoms like pruritus was observed, being again the most frequently reported TEAE, which had a higher incidence in the OCA group (78.6%) than in the placebo group (51.2%), which was similar in the compensated subset of patients (79% vs 51% OCA and placebo, respectively).

During the procedure, the MAH argued that evidence from study 747-302 should not be considered as pivotal due to issues with the conduct of the study and as in the view of the MAH the ALP levels in the placebo group do not reflect the known natural history of PBC (Combes, 1995) and are inconsistent with the data from placebo arms from randomised controlled trials and RWE studies. Additional data was therefore provided (including from real-world sources, external controls, and other post hoc analyses) to support the efficacy of Ocaliva.

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 four 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) and RECAPITULATE, for the latter limited data was only available in an abstract. External controls come from the Global PBC and United Kingdom (UK) PBC registries, as well as from the Komodo Health US Claims database.

In those studies, hazard rates favouring OCA were observed, although with wide confidence intervals.

However, 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 argued that given the difficulties found in the conduct of study 747-302, the placebo test group results should be considered invalid, which is 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, by treatment interruptions and cross-over, 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 divergent from the results of a randomised comparison. Moreover, in contrast to the clinical 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 divergence of the EC results from the trial results is considered to be due to the lack of a randomised comparison and CHMP highlighted that there is a very high risk of residual confounding in the baseline balance and during the follow-up. Therefore overall, the results submitted from the above-mentioned external control (EC) studies/analyses, based on RWD, are not considered robust evidence sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial.

As a result of the limitations highlighted for the RWE studies and taking into consideration all data submitted by the MAH, the risk-benefit assessment of OCA in the treatment of PBC can only rely on the results from the randomised controlled trials. The RWE, the external controls and other post hoc analyses can merely be considered as complementary and exploratory, in view of their much lower level of evidence compared to the trial results.

During the current procedure, the MAH also proposed restricting the population to patients at an earlier disease stage, through the exclusion of patients with "compensated cirrhosis with clinical evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)", and by adding a stopping rule, for patients with total bilirubin >1.5 mg/dL, in order to investigate for clinical evidence of portal hypertension and discontinue treatment permanently accordingly.

The results of new post hoc analyses in this restricted population were in line with what is already known: a reduction in ALP, GGT and other liver markers is observed with Ocaliva, with long lasting biochemical effect. However, the clinical significance of ALP reduction is not established for this particular medicinal product, also in the restricted population.

Furthermore, the MAH provided additional data on elastography and histology in view of liver fibrosis. No statistically significant progression of hepatic stiffness was observed during the 747-301 LTSE as measured by TE, and the histology results provided some supportive evidence, but these are limited to selected subsets of subjects and thus, a firm conclusion cannot be drawn.

Overall, the biochemical results from post hoc analyses (reduction of ALP, AST, ALT, GGT and no increase in bilirubin) are pointing in the desirable direction; however, it remains that the clinical benefits of Ocaliva have not been demonstrated, including in this population at an earlier stage of the disease.

Of note, this latest restriction, added to past restrictions implemented in variation procedures, would exclude a large PBC population subset with a recognised unmet medical need from study 747-302 (i.e., exclusion of approximately 2/3 of patients with PBC covered by the study: new SmPC population: Ocaliva: n=60 Placebo: n=52, while the ITT population was Ocaliva: n=168, Placebo: n=166).

An additional restriction proposed by the MAH, adding a further stopping rule if after 12 months treatment there is failure to show either ≥ 40% reduction in ALP, or ≤ 1.67 x ULN ALP reduction, is based on ALP reductions at 12 months, as in study 301 Ocaliva biochemical response at 12 months was associated with reduction of liver stiffness and lower incidence of liver-related events. However, considering all available data, and in particular the failure of study 302, ALP has not been validated as a biomarker for efficacy on clinical outcome for Ocaliva. This view was shared by the AHEG convened

during the procedure which considered that in view of the missing validation of the biochemical markers for Ocaliva, in particular ALP, the relevance of OCA with regards to clinical outcomes in the current indication or a restricted subset of patients still needs to be proven. Therefore likewise, the clinical benefits of Ocaliva not having been demonstrated the proposed measures would also not be able to alleviate the CHMP's concerns on the clinical efficacy.

2.2.5. Conclusion on clinical efficacy

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). Further, the results submitted from the external control RWE studies are not sufficiently robust to overcome a failed RCT. The absence of improvement of hepatic stiffness in a subset of patients from study 747-302 further corroborates these findings, while liver histology data are only limited and not considered reassuring at this stage. In summary, OCA treatment has demonstrated to reduce ALP (and BR) levels, though this effect is of modest magnitude since few patients achieved ALP normal levels, and its clinical relevance remains to be demonstrated. The MAH´s proposal to limit use to an early stage PBC sub-population cannot be an acceptable strategy given that in the compensated population the results were nearly identical in both treatment arms (HR 0.98). The addition of stopping rules to these restricted populations were also not supported, since correlation of clinical outcomes with biomarkers has not been shown to date. Furthermore, the available evidence in early stage PBC subjects is limited to biochemical changes, without any demonstrated benefits in PBC symptoms (indeed, worsening, or new onset pruritus is expected in a substantial portion of PBC patients treated with OCA) or histology changes. Consequently, the clinical benefit of OCA treatment has not been demonstrated.

2.3. Data on Safety

At the time of the initial authorisation, main safety data were available for 306 subjects participating in double-blind (DB) studies, and 201 of these were exposed to doses ≤10 mg in the 12-month pivotal study 747-301. Main uncertainties at the time of the initial CMA were the lack of safety data in a more advanced PBC population and concerns on long-term (liver and cardiovascular (CV)) safety. The conduct of two clinical trials (747-302 and 747-401) was imposed on the MA in order to generate a comprehensive dataset.

2.3.1. Study 747-302

The safety population in this study included 334 subjects with PBC, who received at least 1 dose of investigational product (166 subjects received placebo and 168 subjects received OCA). The mean durations of exposure for the OCA and placebo groups in the Safety population (n=166 in placebo and n=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, while there was some overlap in populations, patients in study 747-302 reflected a more 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 SmPC revision that occurred while the study was ongoing (32 patients in the OCA group and 37 patients in the placebo group). The MAH has presented information for the overall population and for both the subset of compensated and decompensated patients at baseline. Patients with compensated disease (i.e. those covered by the current indication) in study 747-302 had higher baseline ALP, total bilirubin, Model for End-Stage Liver Disease (MELD) score, 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).

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 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. 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). Ocaliva is now contraindicated in those patients.

Overall, 62 (36.9%) subjects in the OCA group and 45 (27.1%) subjects in the placebo group had a treatment-emergent adverse event (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 ≤5.4% of subjects in any treatment group. Other AEs leading to treatment discontinuation more frequently in OCA vs placebo were: ascites, DILI, and thrombotic thrombocytopenic purpura (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, hypertransaminasaemia.

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), see table 5. 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.

Table 5. Overview of Treatment-Emergent Adverse Events by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Current SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)	
Number of subjects with: n (%)	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136
Any TEAE	158 (95.2)	162 (96.4)	36 (97.3)	32 (100.0)	122 (94.6)	130 (95.6)
Serious TEAE	53 (31.9)	53 (31.5)	13 (35.1)	20 (62.5)	40 (31.0)	33 (24.3)
TEAE Leading to Death	2 (1.2)	5 (3.0)	0	3 (9.4)	2 (1.6)	2 (1.5)
Severe TEAE	65 (39.2)	86 (51.2)	18 (48.6)	22 (68.8)	47 (36.4)	64 (47.1)
Treatment-Related TEAEs	111 (66.9)	133 (79.2)	31 (83.8)	26 (81.3)	80 (62.0)	107 (78.7)
TEAE Leading to IP Withdrawal	45 (27.1)	62 (36.9)	9 (24.3)	17 (53.1)	36 (27.9)	45 (33.1)
TEAE Leading to Dose Reduction	23 (13.9)	45 (26.8)	5 (13.5)	9 (28.1)	18 (14.0)	36 (26.5)
TEAE Leading to IP Interruption	43 (25.9)	48 (28.6)	7 (18.9)	14 (43.8)	36 (27.9)	34 (25.0)
TEAE Leading to Study Discontinuation	19 (11.4)	29 (17.3)	1 (2.7)	6 (18.8)	18 (14.0)	23 (16.9)

OCA=obeticholic acid; PBO=placebo; 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 compensated includes subjects who had not experienced decompensation at baseline. The decompensated includes subjects who had experienced decompensation at baseline.

When considering only the subset of compensated patients (according to current SmPC, i.e. 136/168 subjects in OCA vs 129/166 subjects in placebo treated arms of study 747-302), the incidence of patients who reported a 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 were observed in the overall safety population vs the subset of patients with compensated disease, which is not totally unexpected considering than 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 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 ≥10% of OCA-treated subjects were reported more frequently in the OCA group compared with placebo and these include 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.

In addition, a numerical imbalance was seen in the incidence of deaths across treatment groups. Seven subjects had a TEAE leading to death (five in OCA-treated subjects: acute respiratory failure, respiratory failure, subarachnoid haemorrhage, sepsis, and lower respiratory tract infection; and two in placebo-treated subjects: sarcopenia and hepatocellular carcinoma). Deaths occurred in both compensated (four 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 the subset of compensated PBC stage subjects 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, Dyslipidaemia, 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 (see table 6) 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 disfavouring 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.

Table 6. Summary of Treatment-Emergent AESIs by Overall and Baseline Disease Stage (Safety Population [N=334])

	Overall		Current SmPC			
			Decompensated (Contraindicated)		Compensated (Indicated)	
	PBO N=166	OCA N=168	PBO N=37	OCA N=32	PBO N=129	OCA N=136
Subjects with at least 1 TEAESI, n (%)	137 (82.5)	152 (90.5)	34 (91.9)	32 (100.0)	103 (79.8)	120 (88.2)
Hepatic, n (%)	97 (58.4)	80 (47.6)	24 (64.9)	22 (68.8)	73 (56.6)	58 (42.6)
Cholecystitis/Cholelithiasis, n (%)	9 (5.4)	9 (5.4)	1 (2.7)	2 (6.3)	8 (6.2)	7 (5.1)
Cardiovascular, n (%)	7 (4.2)	16 (9.5)	2 (5.4)	2 (5.4)	5 (3.9)	11 (8.1)
Dyslipidaemia, n (%)	9 (5.4)	6 (3.6)	3 (8.1)	1 (3.1)	6 (4.7)	5 (3.7)
Renal, n (%)	13 (7.8)	17 (10.1)	5 (13.5)	5 (15.6)	8 (6.2)	12 (8.8)
Pruritus, n (%)	86 (51.8)	133 (79.2)	19 (51.4)	24 (75.0)	67 (51.9)	109 (80.1)

AE=adverse event; AESI=adverse event of special interest; MedDRA=Medical Dictionary for Regulatory Activities; OCA=obeticholic acid; PBO=placebo; 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 excluded. AEs were coded using MedDRA Version 24.0.

The compensated included subjects who had not experienced decompensation at baseline. The decompensated included subjects who had experienced decompensation at baseline.

Cardiovascular events

A higher incidence of CV and dyslipidaemia events were observed in OCA treated subjects in the earlier stages PBC population included in study 747-301, what raised the need to collect long-term CV safety data in the confirmatory SOB study 747-302. 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 (TEAESIs) 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 overall safety population, 4 (2.4%) subjects in the OCA group reported a MACE vs no 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 MACE was low (two 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 (5.4% placebo vs 3.6% OCA for the overall, and 4.7% placebo vs 3.7% OCA in the compensated subset).

Cholecystitis/cholelithiasis

The incidence of cholecystitis/cholelithiasis TEAEs was 5.4% in both treated groups of the overall safety population, but a higher incidence of cholelithiasis TEAEs events was seen in the OCA treated group (4.2% vs 2.4%). For the compensated subset, a similar pattern was seen: 5.1% OCA-treated and 6.2% placebo-treated patients experienced a cholecystitis/cholelithiasis TEAEs, and again, the incidence of cholelithiasis was higher in OCA treated subjects (4.4% vs 3.1%). The incidence of serious events was 1.8%OCA vs 1.2% placebo in the overall safety population, and 1.5% OCA vs 0.8% placebo in the compensated subset. A potential association between treatment with OCA and these TEAEs appears at least a reasonable possibility in view of OCA's mechanism of action and available literature (Al-Dury et al, 2019).

Hepatic events

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. Furthermore, there was a slightly higher rate of GI severe TEAEs in the OCA group compared to placebo, both in the overall safety population (13.7% OCA vs 9.0% placebo) and in the compensated group (11.8% OCA vs 7.0% placebo), and the imbalance was due to abdominal pain upper, constipation, and portal hypertensive gastropathy. The overall incidence of serious hepatic TEAESI was quite similar in both treatment groups, both in the overall safety population (9.6% placebo vs 8.9% OCA) and in the subset of compensated PBC patients (7.0% placebo vs 6.6% OCA), which is not reassuring at all as a reduction would have been expected.

A total of 60 liver transplants and deaths events retrospectively adjudicated in a blinded manner by a Health and Safety Advisory Committee (HASAC) were reported (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 (n=26), and the remaining 34 occurred in patients with compensated disease (20 in OCA vs 14 in placebo). This remains a matter of concern, given that the aim of OCA treatment is just the opposite, to prevent these clinical outcomes. Although the vast majority of these events were considered unlikely related to treatment (from a safety perspective), this does not mitigate the concern, since overall, a lower proportion of transplants (and deaths) would have been expected as consequence of drug efficacy. 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.

Pruritus and fatigue

Pruritus was significantly higher in OCA (79.2%) vs placebo (51.8%) in the overall safety population. In patients with compensated disease, 80.1% patients in the OCA group and 51.9% patients in the placebo group reported pruritus. Most events were mild-moderate in intensity. The incidence of pruritus SAEs was low in the compensated group: 2 patients in the OCA group and none in the placebo group. Most 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 or use of medications (such as antihistamines or bile acid sequestrants) for control of symptoms. Management and dosage adjustment for intolerable pruritus are addressed in the SmPC.

Other relevant PBC symptoms like fatigue were more frequent in placebo or roughly similar across treatment groups (15.1% placebo vs 10.7% OCA for the overall safety population, vs 11.6% placebo vs 10.3% OCA in the compensated subset).

Renal events

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 at least 1 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 incidence of renal TEASIs remains rather consistent across OCA-treated subjects in the overall study population (10.1%), and in subjects with earlier stage compensated PBC (per current SmPC) (8.8%), but it is lower than in decompensated subjects currently contraindicated per SmPC (15.6%).

Overall, there is an imbalance observed in the safety population of study 747-302, and a contributory role of OCA cannot be excluded, as also acknowledged by the MAH.

Safety in special populations:

Only information on TEAESI has been provided, for the overall study population. 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 TEAESI 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.

No information on the overall incidence of TEAEs, serious & severe TEAEs, AE leading to discontinuation and leading to death have been provided, which preclude drawing firm conclusions.

Safety in subjects with renal impairment at baseline was also analysed. Most 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 summarised by stage 1 and stage 2/3 subgroups. 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, which was not unexpected, although it was noted that the risk of higher renal events in patients with CKD Stage 2 were not reflected in the SmPC Section 4.8 at the time, as well as the lack of data in subjects with more severe renal impairment, which would warrant including renal events under section 4.8 of the SmPC with a an appropriate frequency calculated based on clinical data.

2.3.2. Study 747-401

Results of this placebo-controlled study in advanced stage patients (now excluded from the indication) 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). 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, disfavouring 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 1placebo), 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 and 1 upper GI haemorrhage OCA treated groups), indicative of a severe toxicity profile of OCA treatment in these patients that has led, together with data from post marketing surveillance, to the inclusion of a contraindication and several precautionary measures to minimise the risk in the SmPC.

2.3.3. Other sources of safety evidence

A nested observational study (747-405, described above) carried out in subjects treated with OCA does not raise new safety concerns. Any comparison with non-OCA treated cohorts are deemed as exploratory, but no conclusions can be reached due to the high risk of bias.

A comprehensive literature search of available medical literature databases to gather all relevant safety data from full publications of predominantly cohort studies, excluding clinical trials, was also conducted. There were more than 40 real-world studies reported including >4,500 patients treated with OCA, 11 published articles are included in this section given that much of the RWE is reported without detailed safety information. The baseline characteristics of the patients treated with OCA in the reported studies were in keeping with SmPC indicated population and similar to the subjects treated in study 747-301.

Of note, the study by De Vincentis et al (2022a) on 100 patients with PBC and cirrhosis treated with OCA for up to 12 months showed that 9% of patients experienced a hepatic SAE. A total bilirubin ≥1.4 mg/dl was the most accurate biochemical predictor of hepatic SAEs, showing a specificity of 88%, Negative Predictive Value of 96% but with a limited Positive Predictive Value of 35%.

The reported safety profile of OCA was in keeping with safety data derived from study 747-301 LTSE. No safety signal was identified from published literature considering the overall safety and individual SOC categories presented from clinical trial data in the preceding sections. Overall, the most frequently reported AE was pruritus or exacerbation of pruritus with various incidence rates. Pruritus was one of the most frequent reasons for the drug discontinuation.

The post-marketing cumulative exposure (cut-off date 30/09/2023) was estimated to 40,349.02 patient-years (worldwide). Again, over half of these estimates derived from non-EEA countries, largely from USA (19,140.77 PY). In the EEA, patient exposure was lower, concentrated mainly in Spain (4016.26PY), Italy (3896.51 PY), UK (3385.79 PY), Germany (3349.02 PY) and France (1516.39 PY).

Data from the global safety database for OCA have been provided by the MAH, up until a data lock point of 30 September 2023. A total of 14,567 unique case reports were available in the global safety database, containing 42628 AEs. The post-marketing data available do not show new safety issues. The profile across the selected AESIs (e.g. hepatic, GI, thrombotic/CV, renal, cholelithiasis, pruritus) is in line with that observed in the clinical development studies, although limitations are observed regarding the ability to establish/rule out causality of OCA due to confounding factors or limited information.

Analysis of the safety information received cumulatively did not identify new risks or changes to recognised important or potential risks for Ocaliva.

2.3.4. Safety in restricted sub-population

During the procedure, the MAH presented analyses for the safety profile to support its proposal to restrict the target population for Ocaliva to patients at an earlier disease stage (see above for details). Treatment-emergent exposure-adjusted incidence rates (EAIRs) for all TEAEs, SAEs, deaths, and serious hepatobiliary, cardiac, and renal events of interest from the 747-301 LTSE of up to 6-year duration and study 747-302, were evaluated in the proposed restricted patient population and are presented below.

Table 7: Overview of Safety in Proposed restricted OCA-treated Patients (747-301 LTSE and 747-302): comparison of EAIRs per SOC

	Proposed restricted Population	
	747-301 LTSE	**747-302**
System Organ Class	**OCA[a] N=160 EAIR (PY)**	**OCA N=60 EAIR (PY)**
Any TEAEs	163.903 (94.57)	325.352 (17.52)
Serious TEAE	6.914 (578.51)	4.099 (170.79)
TEAEs Leading to Death	0.147 (679.07)	0
Pruritus Serious TEAEs	0	0.573 (174.48)
Hepatobiliary disorders Serious TEAEs	0.298 (671.40)	1.155 (173.10)
Cardiac disorders Serious TEAEs	0.443 (676.47)	0

System Organ Class	Proposed restricted Population	
	747-301 LTSE	747-302
	OCA[a] N=160 EAIR (PY)	OCA N=60 EAIR (PY)
Renal and Urinary Disorders Serious TEAEs	0.174 (679.18)	0

Pruritus (based on new analyses in the proposed restricted population)

None of the patients in study 747-301 LTSE reported a pruritus SAE; 1 patient reported an SAE of pruritus in study 747-302, which resolved with medication (rifampicin, phenobarbital and cholestyramine).

In study 747-301, discontinuation due to pruritus occurred at a rate of 10% in the double-blind phase and 11% in study 747-302. The risk of pruritus is considered already adequately managed in the PI.

Hepatic (based on new analyses in the proposed restricted population)

Three OCA-treated patients reported serious PTs in the hepatobiliary disorder SOC in study 747-301 LTSE (1 patient each: cholecystitis acute, cholelithiasis and hyperplastic cholecystopathy) and 2 patients in study 747-302 (1 patient each: cholelithiasis and drug-induced liver injury). The OCA-treated patient with drug-induced liver injury was diagnosed with choledocholithiasis on study Day 49 and was found to have an elevation in liver biochemistries on study day 80. The patient was also taking ibuprofen and simvastatin at the time of the event, drugs associated with risk of hepatotoxicity. The event was considered related to investigational product and resolved after discontinuation.

Adjudicated Hepatic Safety Events (based on new analysis in the proposed restricted population)

In study 747-302, all hepatic safety events were adjudicated by a blinded independent expert committee, the Hepatic Safety Adjudication Committee (HSAC).

Table 8: Study 747-302 – Adjudicated Hepatic Safety Events: Current versus Proposed restricted Population.

	Current Indication			Proposed restricted population		
	Placebo N=129 n (EAIR)	OCA N=136 n (EAIR)	EAIR Difference (95% CI) per 100 PY	Placebo N=52 n (EAIR)	OCA N=60 n (EAIR)	EAIR Diffe-rence (95% CI) per 100 PY

	Current Indication			Proposed restricted population		
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥ mild severity)	4 (1.377)	10 (2.824)	1.448 (-0.763, 3.658)	1 (0.929)	4 (2.368)	1.439 (-1.510, 4.388)
Adjudicated Hepatic Safety Events (Possible/prob/highly likely causality and ≥ moderate severity)	3 (1.019)	5 (1.379)	0.360 (-1.311, 2.031)	1 (0.929)	2 (1.147)	0.218 (-2.199, 2.365)

Adjudicated Liver Transplants and Deaths

In study 747-302, hepatic events, including all-cause deaths and liver transplants were adjudicated by a blinded, independent Hepatic Outcomes Committee (HOC) and then retrospectively adjudicated for causality by an independent HSAC (table 9).

Table 9: Study 747-302 – Adjudicated Liver Transplant or Deaths Causality Assessment: Current indication versus restricted Population

	Current indication		Proposed restricted population	
	Placebo N=129	**OCA N=136**	**Placebo N=68**	**OCA N=81**
Liver Transplants or Deaths (All-cause), n (%)	**14**	**20**	**2**	**3**
Highly Likely Drug Related	0	0	0	0
Probable Drug Related	0	0	0	0
Possibly Related	0	3	0	1
Unlikely Related	14	17	2	2
Insufficient Information	0	0	0	0
Liver Transplants				
Possibly Related	0	3	0	1
Unlikely Related	7	10	1	1
Deaths (all cause)				
Possibly Related	0	0	0	0
Unlikely Related	7	7	1	1

Cardiac (based on new analysis in the proposed SmPC population)

Three patients reported serious PTs in the Cardiac disorders SOC in study 747-301 LTSE (atrial fibrillation, myocardial infarction, and cardiomyopathy). One of the 3 patients reported both atrial fibrillation and myocardial infarction. Of the 3, 1 patient had another event of atrial fibrillation that was considered possibly related by the Investigator. The remainder of the serious cardiac disorders in OCA-treated patients were considered unlikely or not related to investigational product.

Renal (based on new analysis in the proposed SmPC population)

Three OCA-treated patients reported serious events in the renal and urinary disorder SOC in study 747-301 LTSE (nephrolithiasis, renal atrophy, and renal failure acute). All serious renal and urinary PTs were considered unlikely or not related to OCA. No serious renal event was reported by any patient in the proposed SmPC population in study 747-302.

2.3.5. Discussion on clinical safety

As initially noted, study 747-302 found higher incidence rates of all types of TEAEs overall and compared to placebo treated patients. OCA treated patients showed similar rates compared to placebo of any TEAEs (96.4% OCA vs 95.2% placebo) and serious TEAEs (31.5% OCA vs 31.9% placebo), and higher incidence rates of severe TEAEs (51.2% OCA vs 39.2% placebo), TEAEs leading to death (3.0% OCA vs 1.2% placebo), TEAEs leading to treatment discontinuation (36.9% OCA vs 27.1% placebo)/ dose reductions (26.8% OCA vs 13.9% placebo)/ dose interruptions (28.6% OCA vs 25.9% placebo), and TEAEs leading to study discontinuation (17.3% OCA vs 11.4% placebo). This increased toxicity was seen both in the general safety population and the subset of patients with "compensated" liver disease, though, not unexpectedly, a slightly less toxic overall safety profile is noted in the less advanced PBC population: any TEAEs (95.6% OCA vs 94.6% placebo), serious TEAEs (24.3% OCA vs 31.0% placebo), severe TEAEs (47.1% OCA vs 36.4% placebo), TEAEs leading to death (1.5% OCA vs 1.6% placebo), TEAEs leading to treatment discontinuation (33.1% OCA vs 27.9% placebo)/ dose reductions (26.5% OCA vs 14.0% placebo)/ dose interruptions (25.0% OCA vs 27.9% placebo), and TEAEs leading to study discontinuation (16.9% OCA vs 14.0% placebo).

In particular, it is concerning the high rate of severe TEAEs observed in Ocaliva compared to placebo (both in the general safety population and in the subset of compensated patients) which are mainly driven by pruritus TEAEs, but also by higher rates of severe gastrointestinal disorders (oesophageal varices haemorrhage, abdominal pain, vomiting, melaena, and ascites), infections, hepatobiliary disorders (hepatic cirrhosis, hepatic failure), cerebrovascular accident.

Overall, the high rate of TEAE compared to placebo, including severe TEAEs and treatment discontinuations, dose interruptions, and dose reductions due to TEAE speak against the claimed tolerability for OCA.

In addition, the higher rates of some relevant AESIs observed in OCA treated patients like cardiovascular events (including adjudicated MACE), renal events (including AKI), including some relevant hepatic events like 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 when compared to placebo continue to be a matter of concern. 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 a matter of concern, since they occur in an early-stage target population.

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 a restricted subset of subjects at early stages of PBC. Considering that this pattern is seen independently of the populations studied in study 747-302, the possible contribution of OCA in the occurrence of renal TEASI events, including severe, serious, and fatal events, cannot be ruled out. This higher incidence of renal events in patients treated with OCA, regardless of the severity of the underlying liver disease, is worrisome.

An increased incidence in dose-related hepatic TEAESI was reported for OCA treated subjects at the time of CMA, which led to the SOB request to collect further long-term safety data to address this concern in study 747-302. The overall incidence of serious hepatic TEAESI was quite similar in both treatment groups, both in the overall safety population (9.6% placebo vs 8.9% OCA) and in the subset of compensated PBC patients (7.0% placebo vs 6.6% OCA), which is not reassuring, as a reduction would have been expected for a medicine that is intended to treat a liver disease.

The CHMP also noted that less than half of the liver transplants occurred in patients with decompensated liver disease (n=26), and the remaining 34 occurred in patients with compensated disease (n=20 in OCA vs 14 in placebo). This is considered a, again, matter of concern, given that the aim of OCA treatment is just the opposite: to prevent these clinical outcomes.

The number of events is sometimes too limited to firmly conclude on the actual contribution of OCA to the increased risk, but the consistency with previous findings and across the spectrum of PBC disease stages, and the robustness of the source evidence pointing into this direction is a matter of concern.

Furthermore, worsening, or new onset of pruritus is an identified safety risk associated to OCA treatment (79.2% in OCA vs 51.8% placebo in the overall safety population, vs 80.1% OCA-51.9% placebo in the compensated subset). Pruritus is a key symptom in PBC that is often difficult to control, has a negative effect on patient´s quality of life, and might lead to liver transplantation in refractory cases. Apart from the high incidence of the event, it is important to note that it led to frequent treatment interruptions and prompted the need for pharmacological intervention in a substantial portion of subjects. In addition, an increased incidence of fatigue was reported for OCA treated subjects in the pivotal study of the initial submission. By contrary, no notable differences were seen in the incidence of TEAEs fatigue between OCA and placebo in study 747-302. The actual effect on fatigue, either neutral or worsening, remains uncertain but a favourable effect can be ruled out based on the available evidence.

In view of safety findings from the RWE studies submitted, overall, the reported safety profile of OCA appears in keeping with previously submitted safety data and study 747-301 LTSE.The post-marketing data available did not show new safety issues to those previously mentioned.

In summary, even if an apparent less severe safety profile is seen in the authorised population of compensated 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 PBC condition. Moreover, the limitations of the extent of the overall safety database are noted, which makes it difficult to draw firm conclusions on some of the observed risks. However, the consistency with previous findings and across the spectrum of disease severity, and the clinical relevance of these events, cannot be ignored. In addition, the anticipated long-term exposure in clinical practice and difficulties to identify and exclude patients at risk of relevant events during the progression disease, add further concerns to these safety findings. The observed risks in the overall target PBC population (e.g. cardiovascular, hepatotoxicity), have been confirmed in the authorised compensated PBC population.

New *post-hoc* analyses from studies 747- 301 LTSE and 747-302 were provided to support the proposed restriction of the target population for Ocaliva to patients at an earlier disease stage, excluding patients with "compensated cirrhosis with clinical evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) and adding a stopping rule for patients with total bilirubin >1.5 mg/dL. However, the number of patients is limited, and safety data are thus difficult to interpret, hampering a sound conclusion. Of note, the pattern of safety concerns in the proposed restricted population seems to overlap with that reported in the current Ocaliva indication. Specifically serious hepatic, cardiac and renal events have been reported; in addition, a comparison of adjudicated hepatic events between the current and newly proposed population points to a very similar risk across the spectrum of severity independently from causality adjudication. Moreover, these additional results confirm the trend already seen across the whole safety dataset toward worse liver safety in Ocaliva than placebo. Therefore, the MAH's approach to further restricting Ocaliva's indication to patients in earlier stages (i.e. excluding subjects with clinical evidence of portal hypertension and adding a stopping rule based on total bilirubin) does not mitigate the known safety concerns associated to Ocaliva, nor improve the safety profile of Ocaliva.

2.3.6. Conclusion on clinical safety

The confirmatory study 747-302 found higher incidence rates of all types of TEAEs overall and as compared to placebo treated patients. The results of study 747-401 (prematurely interrupted) are noted, together with post-marketing safety data, as well as the ensuing contraindication and precautionary measures implemented.

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 concern.

The pattern of safety concerns in the proposed restricted population seems overlapping with that reported in the authorised indication of Ocaliva. Specifically serious hepatic, cardiac and renal events have been reported; in addition, a comparison of adjudicated hepatic events between the current and newly proposed population points to a very similar risk across the spectrum of severity independently from causality adjudication. Moreover, these additional results confirm the trend already seen across the whole safety dataset toward worse liver safety in Ocaliva than placebo.

Safety concerns known to be associated to Ocaliva in its authorised indication are not mitigated by the proposed restriction of indication targeting patients in early stages of PBC, who will undergo Ocaliva exposure for a very long period of time given the long natural history of the disease.

3. Expert consultation and other data

3.1. Ad hoc expert group meeting

The CHMP consulted an ad-hoc expert group composed of gastroenterologists and hepatologists, and also including patients' representatives, which provided advice on the following points:

Question 1

Keeping in mind the goals of PBC treatment (i.e., prevention of end-stage liver disease and amelioration of PBC-related symptoms) and considering all available data on biochemical markers and liver related events for Ocaliva:

a. what is the clinical relevance of the effect seen on the biochemical markers?

The experts recognised the value of surrogate biomarkers to predict clinical outcomes in PBC. To date biomarkers, and in particular ALP, are the main prognostic factors and are currently used in clinical practice to measure treatment response in PBC. However, data correlating treatment response based on ALP and clinical outcomes, are available only for UDCA. The clinical relevance (histological improvements or clinical outcomes) of those effects for Ocaliva is yet to be confirmed.

To determine the clinical effect of Ocaliva and its correlation with biomarkers further data on clinical outcomes would be needed. Data suggesting a correlation of ALP with Fibroscan/liver stiffness under Ocaliva treatment were considered useful by the experts as supportive information but not seen as confirmatory evidence, and the correlation of biomarkers with clinical outcomes in the case of Ocaliva remains to be demonstrated.

For the patient representatives, the immediate focus is on the reduction of the biomarkers and improvement of FibroScan results to monitor their disease progression. However, the clinical improvement or at least non-progression of the disease remains the most important aim for patients. One patient representative commented that the symptoms can flare up without biomarkers change.

b. do the experts consider that the treatment effect is clinically relevant for PBC patients in the current indication or a restricted subset of this patient population (e.g. PBC population without portal hypertension)?

The experts noted that the confirmatory trial 302 failed to confirm the efficacy of Ocaliva based on clinical outcome measures, in any subset of the included patient population. The patient cross-over to active treatment in the placebo arm was noted by the experts, as well as the use of commercial Ocaliva (15% in the placebo vs 7% in the Ocaliva group) and bezafibrate (7% in placebo vs 14% in Ocaliva) in both treatment groups. The interpretation difficulties in view of the untypical placebo response were acknowledged by the experts.

Some experts noted that more favourable results had been obtained from the RWE compared to the clinical study results and, also considering their clinical experience, that Ocaliva may have a place in PBC treatment, mainly in early stages. However, the experts considered that the RWE did not provide confirmatory clinical evidence of efficacy for Ocaliva in the current indication or in a restricted subset of the indication, and further efficacy data would be needed to define the population in which efficacy could be considered demonstrated.

Overall, the experts considered that also in view of the missing validation of the biochemical markers for Ocaliva, in particular ALP, the relevance of OCA with regards to clinical outcomes in the current indication, or a restricted subset of patients, still needs to be proven. One expert highlighted that for Ocaliva in study 302 the patients remained on ALP levels above the normal range on average, and only a few patients could reach normalisation.

The experts further noted that Ocaliva has also an immunosuppressive effect; however, its impact on therapy appeared to be not further explored by the MAH.

Overall, the experts highlighted the importance of defining the patient population that may benefit from treatment.

The patient representatives were concerned about the fact that it was possible that patients in clinical study 302 requested treatment from their physicians, while being in the study and suggested to use real world evidence wherever possible considering that for late stages a patient may be more acceptive of possible risks associated to treatment, whilst in early stages this may be constitute over-treatment. Another patient representative considered that restricting the prescription of Ocaliva to specialists would contribute to ensuring that only patients that may benefit most from treatment would receive it, preventing both overtreatment and treatment in patients at high risks of adverse reactions.

Question 2

Do the experts consider that the observed Ocaliva risk profile (i.e., CV events, liver transplant, DILI, renal events, death) and poor treatment tolerability (e.g., frequent treatment discontinuations,

worsening of pruritus) observed in PBC patients in the current indication or in a subset of this population (e.g. PBC population without portal hypertension), are acceptable?

The experts noted that the results of the randomised controlled trial 302, despite methodological weaknesses, are picturing a concerning safety profile especially considering that some patients in the placebo arm crossed over to the treatment arm, which would be expected to lead to a more similar safety profile between the treatment groups. According to one of the experts, cardiac and renal events in the PBC population are generally rare and few events were seen in both treatment groups in study 302. Overall, there were lower proportions of serious adverse events in compensated vs decompensated patients. Pruritus (which is also a manifestation of the disease itself) is an obvious side-effect, leading to discontinuation, certainly to be considered in early stages, which also occurred more in the Ocaliva arm including when considering the proposed restricted subset. One patient representative argued that while pruritus is a concerning side effect, patients may be willing to accept this to a certain degree in case the treatment would be effective. Dyslipidaemia associated with Ocaliva was noted by one expert as one adverse event that is often overlooked but is also important.

The data from study 302 is in contrast to the additional data provided, including from RWE. In this context, the experts considered that the RWE was not providing sufficient assurance on an acceptable safety profile considering the known weaknesses of real-world data such as selection and reporting bias.

The experts considered that, if efficacy were confirmed for Ocaliva, it could be used provided liver toxicity does not occur. They also considered that they may be able to choose patients at an early stage of the disease, likely to better tolerate Ocaliva, but were concerned about absence of adequate data to define this patient population, considering that decompensated patients are already excluded from the indication. Indeed, in theory, limiting the use based on safety data to a very restricted subset might help alleviating the concerns, but the overall data in the restricted subsets presented (safety and efficacy) is insufficient to support such use.

From a patient perspective the importance of the safety was highlighted, together with the difficulty in this case of making a judgement on the safety for specific patients. The patient representatives noted that in the absence of Ocaliva many patients may no longer have a treatment alternative, and advocated for transitory measures if Ocaliva was taken off the market. In reference to this, some experts reported that it may be difficult to change treatment in patients currently being treated with Ocaliva and tolerating well the treatment.

The experts noted that acceptability of the safety profile is hindered by the previously mentioned issues around the efficacy.

Overall, the experts agreed that specialists may be able to select patients susceptible of tolerating treatment with Ocaliva but that the data available did not allow to define this patient population.

Finally, the experts pointed to a general problem of confirmatory data generation in PBC. Whilst ideally a RCT would be needed for this purpose, the feasibility of such trials should be carefully assessed in a setting where treatments are commercially available, such as in trial 302, and it was recommended to consider a role for prospective registries or synthetic control arms for future data comparison.

3.2. Stakeholders input

Written statements were also received from fourteen third parties, namely patients' associations, healthcare professionals and academia. The third parties shared their experiences, advocated for the continuous availability of Ocaliva as second line of treatment, and for the views of patients and HCP to

be taken into account in the present review. Results from a survey on quality of life in PBC patients were also provided. All data submitted was considered by the CHMP in reaching its conclusions.

4. Benefit-risk balance

Ocaliva was granted a CMA in the EU in December 2016 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. The initial approval was based on results from the phase 3, randomised, double blind, placebo-controlled, parallel-group study 747-301 (POISE), which showed superiority over placebo on the primary endpoints based upon surrogate (not validated) biochemical markers (percentage of patients reaching alkaline phosphatase and bilirubin levels below predefined cut-off values). Available data on UDCA treatments indicated a correlation between normalisation of ALP levels and progression-free survival. Therefore, at the time of the granting of the MA, the CHMP considered it reasonably likely that the results on biochemical parameters for Ocaliva would translate into benefit in terms of clinical outcome. This was to be confirmed post-authorisation with the results of a double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva (OCA) treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints: study 747-302 (COBALT). The conduct and submission of the results from study 747-302 were imposed as a specific obligation at the time of the granting of the conditional marketing authorisation (SOB 1) with the aim of confirming a favourable benefit-risk balance for the conditional marketing authorisation for Ocaliva.

Study 747-302, with 67% of the planned events (a non-negligible portion), 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. For decompensated patients (at present excluded from the authorised indication) a numerical imbalance in favour of placebo was observed (HR 1.22; [95% CI: 0.65, 2.28]), though not statistically significant. In the subgroup of compensated PBC patients, which falls within the currently authorised indication, results were nearly identical in both treatment arms (21.3% vs 21.7% OCA and placebo, respectively, HR 0.98 [95% CI: 0.58, 1.64]). Thus, the study failed to demonstrate any efficacy of OCA treatment in relevant clinical outcomes and across the severity spectrum of PBC patients.

The MAH claims that due to the premature termination of the study, namely due to "feasibility issues," the study was underpowered to detect the proposed treatment effect. However, in the opinion of CHMP it is highly unlikely that the observed lack of effect with nearly 70% of the planned number of events could have been reverted should the study not have been prematurely terminated as at least a consistent trend in the main clinical endpoints (even if not statistically significant) would have been expected in case of a real clinical benefit, but no trend was observed.

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 <1.67x ULN and total bilirubin ≤ULN and ALP decrease from baseline of ≥15%. It is noted that, the rate of responders (proportion of patients meeting the primary endpoint) was substantially lower compared to that previously reported and this was the case in both treatment arms, with a reduction of about 70% in each arm compared to the respective arm of the previous study (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. It may be considered that subjects with higher values at baseline are unlikely to 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 with Ocaliva and changes in indicators of fibrosis remains uncertain in the absence of correlation to clinical outcomes.

Additional data including from four real-world evidence studies and from the long-term safety extension (LTSE) of the pivotal phase 3 trial that supported the MAA (study 747-301) were considered. In those studies, hazard rates favouring OCA were observed, although with wide confidence intervals. However, the divergence of the real-world data from the results observed in the controlled trial is considered to be due to the lack of a randomised comparison with a very high risk of residual confounding in the baseline balance and during the follow-up. Therefore, overall, the results submitted from the above-mentioned external control (EC) studies/analyses, based on RWD, are not considered robust evidence sufficient to overcome the negative results of a double-blind, randomised, placebo-controlled trial. Therefore, these other studies and the RWE available is considered only as complementary and exploratory, but not sufficient to demonstrate the clinical efficacy of Ocaliva.

Summarising, OCA treatment has demonstrated to reduce ALP (and BR) levels, though this effect is of modest magnitude and its clinical relevance remains to be demonstrated, in particular considering that the confirmatory trial has failed to demonstrate the efficacy of OCA treatment in clinical outcomes. This conclusion is shared by the AHEG convened during the current procedure. The experts considered that the clinical relevance (in terms of histological improvement or clinical outcome) of the biochemical changes induced by Ocaliva remained to be demonstrated and, therefore, that additional data on clinical outcomes would be needed to determine the clinical effect of Ocaliva and its correlation with biochemical changes.

From a safety point of view, Study 747-302 similarly to the data assessed for the MAA and the known safety profile of Ocaliva, showed high incidence rates of all types of TEAEs comparably, in the OCA treatment and in the placebo arm. 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, remain a matter of concern. Additional analyses based on age (<65 and ≥65) indicated a worse tolerability and safety profile in the elderly population subset. Consistent with previous findings, a negative effect on pruritus, a key PBC symptom, was shown. It was the most frequently reported TEAE, with higher incidence in the OCA group (78.6%) than in the placebo group (51.2%). Similar figures were observed in the compensated subset of patients (79% Ocaliva vs 51% placebo).

Overall, the identified risks in the PBC population, for which Ocaliva is indicated, have been confirmed in the restricted otherwise asymptomatic or early stage PBC subset. The safety profile of Ocaliva, would only be considered acceptable in front of an unequivocally demonstrated disease modifying clinical benefit. Since the study failed, and data from real-world cohorts have shown an increased risk of hepatic adverse events in Ocaliva treated patients with cirrhosis, portal hypertension and raised bilirubin (De Vincentis, 2022b) the MAH proposed to limit the study results further to a subpopulation restricted to an early stage PBC (i.e. excluding patients with clinical evidence of portal hypertension and interrupting treatment if total bilirubin rises above 1.5mg/d) in which they claim the benefit-risk balance would be positive. In case this stopping rule would be met, treating physicians would have been advised through the SmPC to investigate for clinical evidence of portal hypertension, and permanently discontinue treatment when detected.

While also in this sub-population the known reduction of ALP and other biomarkers has been seen, the

post hoc efficacy analysis using the above restricted population could not confirm a statistically significant difference in terms of death, liver transplant or hepatic decompensation compared to the placebo group (HR=0.62, CI: 0.25, 1.55), which was also supported by the AHEG experts, who stated that the confirmatory trial 747-302 failed to confirm the efficacy of Ocaliva based on clinical outcome measures, in any subsets of the included patient population.

Also, comparative safety data in the restricted subsets of patients with PBC without cirrhosis or with compensated cirrhosis with no clinical evidence of portal hypertension or a prior decompensation event have been presented to support this proposal. While the number of AEs overall was low in these subsets due to the reduced sample size (n=68 OCA vs n=61 placebo), higher frequencies of the events were observed in OCA treated patients compared to placebo, similarly to what was observed in the population corresponding to the currently authorised indication. In addition, an increase of CV events (including MACE), liver DILI, renal, transplant death events, and poor treatment tolerability have been confirmed, both in the overall study population and in the restricted early-stage subset, reflecting earlier findings from the MAA. Further as this was a data-driven analysis that included a limited subset of early stage PBC subjects of study 747-302 the interpretation of the reported results is hampered.

An alternative stopping rule was also proposed by the MAH during the procedure to be added for Ocaliva to be permanently discontinued if, after 12 months treatment, there is failure to show reduction in ALP to predefined levels. This stopping rule was not accepted, since CHMP considered that based on the data available, ALP is not a validated biomarker for efficacy on clinical outcome for Ocaliva. Overall, based on the above, the restriction to this patient population, together with stopping rules based on bilirubin or ALP levels were not accepted by the CHMP to support a positive benefit-risk balance. Critically, as mentioned above, study 747-302 failed to demonstrate any efficacy of OCA treatment in relevant clinical outcomes and across the spectrum of PBC patients. Moreover, the proposed restricted indication was considered not acceptable for the following reasons: 1) no clear clinical benefit was shown in the subgroup of patients with an early stage of the disease; 2) safety risks were already evident in this subpopulation; 3) starting Ocaliva treatment in these patients would translate in exposing this "less affected" subgroup to the known safety profile of Ocaliva, for a longer time, but with uncertain effectiveness. Concerns regarding the safety of Ocaliva were also endorsed by the AHEG experts, who were concerned about absence of adequate data to define a patient population that would likely tolerate Ocaliva better. The experts also considered that the RWE did not provide sufficient assurance of an acceptable safety profile, considering the known weaknesses of real-world data such as selection and reporting bias.

In addition, given the long natural history of the disease requiring long-term treatment, the lack of adequate evidence to support Ocaliva clinical benefit and the not-negligible safety risks, exposing patients with earlier stage PBC is not acceptable.

In conclusion, in the context of the failed confirmatory study 747-302, the totality of data available from clinical trials and real-world data does not confirm the clinical benefit of Ocaliva in its authorised indication nor in the proposed target population restricted to the subgroup of patients without clinical evidence of portal hypertension or with lower bilirubin or limited reduction of ALP after 12 months of treatment. Consequently, taking into account the totality of available data including clinical trials and real-world data, as well as the views of patient representatives and the views expressed by a group of independent experts at an ad hoc meeting and written interventions received from third parties, the CHMP concluded that the efficacy of Ocaliva is not established and therefore that the benefit-risk balance of Ocaliva is negative.

While it is understood from the MAH that a study employing a target trial emulation framework to provide further data on the efficacy and safety of Ocaliva may be performed in the future, this has no bearing on the conclusion based on the data available at present.

In order to ensure continued supply of Ocaliva to patients who are currently on treatment and who appear, in the opinion of the treating physician, to be benefiting from obeticholic acid treatment, the MAH proposed that the marketing authorisation is maintained temporarily with amendments to the product information to reflect that treatment would be reserved for this group of patients. However, this is not an option in view of the clear conclusion that the benefit-risk balance is negative. The CHMP noted that where the marketing authorisation of a medicinal product has been revoked there are *lex specialis* provisions in the European Union legislation (Article 117(3) of Directive 2011/83/EC) regarding the possibility to allow continued supply after revocation of the marketing authorisation, should this be considered appropriate by the national competent authorities.

5. Summary of new activities and measures

5.1. Direct Healthcare Professional Communications and Communication plan

The Committee adopted the wording of a direct healthcare professional communication (DHPC) to inform HCPs of the conclusions of the review and upcoming unavailability Ocaliva. The Committee also agreed on a communication plan.

6. Grounds for Opinion

Whereas,

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Ocaliva.
- The CHMP reviewed the results of the study 747-302 (COBALT), a specific obligation (SOB#1) pursuant to Article 14-a of Regulation (EC) No 726/2004, conducted with the aim of confirming a favourable benefit-risk balance for the conditional marketing authorisation for Ocaliva.
- The CHMP also took into consideration all available data, including the responses submitted by the marketing authorisation holder (MAH) in writing and during an oral explanation, views of patient representatives, as well as the views expressed by a group of independent experts at an ad hoc meeting and written interventions received from third parties.
- The CHMP noted that in study 747-302 no clinical benefit was observed from treatment with Ocaliva, regardless of the stage of the disease.
- The CHMP considered that in the context of the failed confirmatory study 747-302, the totality of data available from clinical trials and real-world data do not confirm the clinical benefit of Ocaliva in its authorised indication nor in the proposed target population restricted to the subgroup of patients without clinical evidence of portal hypertension or with lower bilirubin or limited reduction of ALP after 12 months of treatment.
- The Committee, as a consequence, concluded that the efficacy of Ocaliva is not established and therefore that the benefit-risk balance of Ocaliva is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisation.

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