Annex

Scientific conclusions

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At the time of the marketing authorisation (MA) of Ocaliva (OCA), uncertainty remained as to the extent to which the observed changes in laboratory parameters (levels of alkaline phosphatase (ALP) and bilirubin (BR)) 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 that study 747-302 had failed to demonstrate the clinical benefit of Ocaliva across the spectrum of primary biliary cholangitis (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 in the frame of a variation to switch to a full MA at the time. The CHMP considered that these results showing a potential lack of efficacy and worsen safety profile raised serious concerns as to whether the benefit of Ocaliva still outweighed its risks in its authorised indication.

On 12 October 2023, pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the opinion of the Agency on whether the marketing authorisation of Ocaliva should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The conduct and submission of the results from study 747-302 were imposed as a specific obligation (SOB) 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 intention-to-treat (ITT) population: Hazard Ratio (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 marketing authorisation application (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 real -world data, 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 real-world evidence (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 bilirubin) 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 treatment-emergent adverse events (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 adverse events of special interest (AESI) like cardiovascular events (including adjudicated major adverse cardiac events (MACE)), renal events (including acute kidney injury (AKI)), drug -induced liver injury (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, 2022[1]) 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

[1] De Vincentis A, Terracciano F, D'Amato D, Invernizzi P, Morgando A, Vanni E. Real-world data on long term efficacy and safety of obeticholic acid for primary biliary cholangitis: first release from the Italian RECAPITULATE study (poster). American Association for the Study of Liver Diseases, The Liver Meeting Boston, US 2022.

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 was not providing 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 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. Consequently, taking into account the totality of the data available 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.

Whilst it is understood from the MAH that a study employing a target trial emulation framework aiming 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. This is however 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 the continuing supply after revocation of the marketing authorisation, should this be considered appropriate by the National Competent Authorities.

CHMP 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 randomised 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 the benefit-risk balance of Ocaliva is not favourable.

The CHMP is therefore of the opinion that the marketing authorisation(s) for Ocaliva should be revoked.