Dear all,

European Medicines Association (EMA) issued a statement on Obeticholic acid (Ocaliva) for the treatment of primary biliary cholangitis (PBC) on 28 06 2024.

The EMA human medicines committee (CHMP) have recommended that Obeticholic acid's market authorisation in the European Union (EU) be revoked. This recommendation was made following results of a post-market approval, phase IV randomised controlled clinical trial (the COBALT trial, 747-302). In this study, Obeticholic acid was specifically offered to patients with advanced liver disease / high-risk PBC, with the primary efficacy outcome being a reduction in liver event free survival (hepatic decompensation, hepatocellular carcinoma, need for transplantation and/or death).

These results should be viewed with caution. In the study, the patient population represented only 20% of overall PBC population eligible for second line therapy and occurred when Obeticholic acid was available as part of routine clinical care. Therefore, recruitment to the COBALT programme was challenging, moreover, high-risk liver disease opted for commercially available drug rather than take a chance at being on placebo for up to 7 years. Consequently, the COBALT trial was not able to recruit the required number of patients according to pre-specified power calculations and sample size and was terminated early.

The EMA CHMP recommended the following:

- The clinical benefits of Ocaliva (obeticholic acid), used to treat primary biliary cholangitis (PBC), have not been confirmed.
- The study (747-302) failed to show any differences between Ocaliva and placebo for the primary composite endpoint of death, liver transplant, or hepatic decompensation in the overall population of PBC patients who are either unresponsive or intolerant to ursodeoxycholic acid (HR 1.01 [95%CI: 0.68, 1.51], p-value: 0.954).
- The EMA has recommended that the marketing authorisation for Ocaliva be revoked in the European Union.
- If this is confirmed by the European Commission, Ocaliva will no longer be authorised in the EU.

The EMA CHMP did not consider any of the published real-world evidence evaluating Obeticholic acid over several years (at a population level), nor the clinical evidence and patient testimonials from countries where Obeticholic acid is used (such as the UK). Data from multiple sources show a significant improvement in liver biochemical markers and a reduction in clinical event rate in patients with earlier stage PBC.

At present, the final decision on the position of Obeticholic acid in the EU rests with the European Commission, and an appeals process has already begun from several

member states, PBC patient support groups, the European Association for Study of the Liver (EASL), and other international bodies.

With regards the UK specifically, EMA recommendations do not apply, as we are regulated by the Medicines and Healthcare products Regulatory Agency (MHRA). **At present, there are no changes to the recommendations on use of Obeticholic acid in PBC from the MHRA or the National Institute for Health and Care Excellence (NICE).** The EMA recommendation has NO direct impact on the use of Obeticholic acid in our routine clinical practice, do not apply to the UK and have no bearing on its use in clinical trials (e.g. the OPERA study or the OACS programme).

BASL, BSG and BHPG, DO NOT recommend that any patient empirically stop Obeticholic acid therapy at present, nor do we suggest that any patient eligible to receive Obeticholic acid *de novo* be stopped from doing so following the EMA recommendation.

We shall update the UK liver community if there are any changes to the recommendations on the use of Obeticholic acid.

Yours,

BASL, BSG, BHPG and the UK-PBC study group.