EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Authorisation of Ocaliva for PBC in the EU

EMA stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)

Session 1: Primary Biliary Cholangitis (PBC)

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Presenter Disclosure Information Elements

FINANCIAL DISCLOSURE:

Nothing to declare

UNLABELED/UNAPPROVED USES DISCLOSURE:

The views and opinions expressed in the following PowerPoint slides are those of the individual presenter and should not be attributed to the European Medicines Agency.

Ocaliva (Obeticholic acid)

October 13th 2016: The Committee for Medicinal Products for Human Use (CHMP) recommends:

- **A conditional MA** in the interest of public health because the medicine addresses an **unmet medical need** and the **benefit of immediate availability** outweighs the risk from less comprehensive data than normally required.
- That the MA holder shall complete **specific obligations** with a view to providing comprehensive data confirming that the benefit-risk balance is positive.
- That Ocaliva shall be **subject to additional monitoring** to allow quick identification of new safety information.

Ocaliva was developed for use against a rare, life-threatening or chronically debilitating condition

11th December 2016: The European commission issues marketing authorisation valid throughout the European Union

Ocaliva: At approval stage

Primary biliary cirrhosis (PBC):

A rare, serious, life-threatening liver disease

Approved drugs in the EU:

Ursodeoxycholic acid (UDCA), first line therapy for patients with PBC (EASL and AASLD Guidelines)

- **Improves biochemical indices** such as ALP and bilirubin and **delays histological progression** (Poupon 1997, Corpechot 2008).
- Strong evidence that treatment with UDCA **increases progression-free survival, with** significantly **greater benefit for patients who demonstrate** greater **response** as measured by decreases in **ALP, bilirubin and ALT.**

Unmet medical need in the EU for a second line treatment:

- **Up to 50% failed / suboptimal biochemical to response or are intolerant to UDCA**
- **Patients with inadequate response frequently progress** to hepatic fibrosis and eventual cirrhosis, hepatic decompensation, and death unless a patient receives a liver transplant (Kuiper 2010).

Main clinical study

Single pivotal study

Obeticholic acid (OCA) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

Primary Endpoint

Percentage of subjects (**OCA 10 mg vs. placebo**) at Month 12 with **ALP <1.67x ULN** and **ALP decrease of ≥15% from Baseline and total bilirubin ≤ULN**.

OCA 10 mg group: n=34, 47% vs. placebo n=7, 10% demonstrating superiority (p<0.0001)

Key secondary Endpoint

Percentage of subjects (**OCA titration vs. placebo**) achieving composite endpoint at Month 12.

OCA titration group (key secondary endpoint): n=32, 46% (p<0.0001)

Change from baseline to 6 and 12 months in ALP, conjugated bilirubin, GGT, ALT, and AST showed statistically significant differences over placebo

Approximately one third of patients in each OCA treatment group achieved an ALP reduction of >40%, compared with 1% in the placebo group

Main efficacy results

Effect	Short Description	Unit	OCA fixed 10mg	OCA titration	Placebo	Uncertainties / Strength of evidence
Favourable Effects						
ALP<1.67 ULN and ≥15% reduction in ALP and a total bilirubin ≤ULN at month 12	Primary composite Endpoint	%	47 %	N/A	10 %	-Only biochemical data is available (ALP levels) - ALP normalisation with UCDA relays to better prognosis; it is unknown if the same can be extrapolated to OCA results - Very few patients on either OCA group normalised ALP levels -Relevance of OCA Anti-inflammatory effects is unknown
Composite endpoint	key secondary endpoint	%	N/A	46 %	10 %	
Responder analyses (12months) ALP≥40%	secondary endpoint	%	30 %	34 %	1 %	

Uncertainties Efficacy

Few patients achieved normalization of ALP levels. To what extent changes in laboratory parameters correlate with clinical liver outcomes?

Demonstration of clinical relevance of the observed results **based on** data from **Global PBC Study group database and the UK-PBC Cohort suggesting an association** between ALP (and bilirubin) levels and clinical outcomes. Post-hoc analyses **applying post hoc study 747-301 inclusion criteria** and evaluating the primary endpoint.

Is the patient population enrolled in the pivotal trial sufficiently representative?

- **Lack of data in** patients **with a more advanced disease stage**: **Patients with total bilirubin ≥2x ULN**, severe portal hypertension **or hepatic failure were excluded** from both the main studies disease). The **majority of patients** entered with normal/near normal bilirubin values (<2 ULN) and **remained normal.**
- **Limited long-term data** (up do 30 weeks)

Main safety results

Most commonly reported adverse reactions

Pruritus (63%) (also most frequently reported TEAE); tendency to resolve with continued dosing

Fatigue (22%).

Adverse reactions leading to discontinuation

1% in the OCALIVA Titration group and 11% in the OCALIVA 10 mg group

Hepatic-related effects: Incidence of TEAEs low in general. **Clinical hepatic AEs at doses ≤10 mg** were considered likely related to disease progression by the Investigators or the Sponsor and occurred mainly in **patients with more advanced liver disease.** However a **dose related pattern was observed**. PK data and simulations demonstrated **increase in systemic exposure** of OCA in patients with liver impairment.

Therefore details regarding serious hepatic events and **detailed dosage recommendations** moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment were **included in the SmPC**

Uncertainties safety

Representation of **patients with more advanced disease** and/or various degree of liver impairment was **scarce**:

- **Further characterization of the safety profile in moderate and advanced disease** (ie, Child-Pugh Class B and C), **needed.**
- Reductions in HLD-c levels and increases in LDL-c where seen without a clear pattern for the changes. Lipid disorders are commonly seen in PBC patients but **Further characterization of the long-term safety** of OCA with respect to **changes in lipid levels and CVD** in patients with PBC

Risk management plan

Summary of safety concerns	
Important identified risk	Pruritus
Important potential risks	Liver injury Atherosclerotic cardiovascular events secondary to changes in lipids
Missing information	Use in patients with other concomitant liver diseases
	Use in patients with moderate to severe hepatic impairment (Child-Pugh Class B and Child-Pugh Class C)
	Use in patients with hepatocellular carcinoma
	Use post liver transplantation
	Use in elderly and very elderly patients (≥65 years)
	Use during pregnancy and breast-feeding
	Long-term safety

Balance of benefits and risks

In the context of:

- **A serious, severely debilitating disease**
- **Up to 50%** of patients either **not responding satisfactorily or** are **unable to tolerate** UDCA treatment

OCA treatment has **demonstrated relevant ALP reductions** in patients with insufficient response / intolerance to UDCA. It is **reasonably likely** that the results on biochemical parameters **translate into benefit in terms of clinical outcome** data, although this remains to be formally demonstrated

The studies conducted show a **clinically manageable safety profile**

This is **weighed against the risks related to the absence of fully comprehensive data** in particular:

- **Clinical evidence on** the **extent of efficacy and safety** also in the **long term** treatment and in more **advanced liver disease stages**

Conditional Marketing Authorisation

Fully comprehensive data on the product are not available however:

The product fulfils the requirements **for a conditional marketing authorisation**:

- The **benefit-risk balance is positive**
- The unmet medical need will be addressed (please refer to second line indication)
- The benefits to public health of the immediate availability outweigh the risks due to need for further data.
- It is considered sufficiently likely that **the applicant will** be able to **provide comprehensive data**

Remaining open issues (Specific Obligation)

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of OCALIVA, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with OCALIVA treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the **effect of OCA on clinical outcomes** in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of OCALIVA, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of OCALIVA in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the **lack of data in a population with more advances liver disease**	Final report: 2020

Thanks for your attention

Further information

[https://www.ema.europa.eu/en/medicines/human/EPAR/ocaliva]

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