Improved Transplant-Free Survival Observed with Obeticholic Acid in People with PBC Published in Gastroenterology

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Combined clinical trial and real-world data with six years of follow-up provides important evidence of efficacy

Analysis compares findings from the Phase 3 POISE trial and open-label extension to natural history data from the Global PBC and UK-PBC patient registries

MORRISTOWN, N.J., Sept. 20, 2022 (GLOBE NEWSWIRE) -- Intercept Pharmaceuticals, Inc. (Nasdaq: ICPT), a biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat progressive non-viral liver diseases, today announced a key publication in *Gastroenterology* showing that people receiving OCA for primary biliary cholangitis (PBC) in a clinical trial setting had greater transplant-free survival compared to patients with PBC selected from "real-world" patient registries who did not receive OCA.

Key findings include:

- Patients treated with OCA had an approximately 70 percent lower relative risk of death or liver transplant than the control patients at any time during follow-up.
- The primary outcome of time to first occurrence of liver failure or death was statistically significant, favoring OCA treatment in POISE compared to patients from "real-world" databases.
- There was a statistically significant and clinically meaningful reduction in death, liver transplant and hepatic decompensation in OCA-treated patients versus comparable untreated patients.

"This important study is the first to demonstrate that initiating treatment with OCA in appropriate patients with PBC appears to have a meaningful impact on clinical outcomes," said Professor Gideon Hirschfield, FRCP, Ph.D., Lily and Terry Horner Chair in Autoimmune Liver Disease at the University of Toronto. "I am proud of this innovative analysis, and further, the continued value we are deriving from large, academic-led, prospective databases like the Global PBC and UK-PBC study groups. Leveraging these registries helps advance our collective understanding of this disease to ultimately influence clinical decision-making and benefit people living with PBC."

"Given the known challenges associated with conducting blinded, placebo-controlled trials when the treatment has been approved and is available, this study provides evidence that a well-matched external comparator group can be a credible, alternate approach to evaluating clinical efficacy," said M. Michelle Berrey, M.D., M.P.H., President of Research & Development and Chief Medical Officer of Intercept. "We look forward to further leveraging real-world databases to continue generating insights on the clinical benefit of Ocaliva in PBC."

This study compared patients with PBC who received up to six years of OCA in the Phase 3 POISE study and its open-label extension (n=209) to external controls who were extracted from two large, academic-led patient registries. External controls met POISE entry criteria but were not treated with OCA. Treatment with ursodeoxycholic acid (UDCA) was permitted.

The primary endpoint of this study was time to first occurrence of liver transplant or death. Over the six-year follow-up, there were five deaths/liver transplants in 209 subjects in the POISE study, 135 in 1,381 patients in the Global PBC control, and 281 in 2,135 patients in the UK-PBC control. Preliminary results from this analysis were first presented at the 2021 Annual Meeting of the American Association for the Study of Liver Diseases (AASLD).

Data Sources for this Study:
The Global PBC registry included 6,484 patients with PBC from eight countries in Europe and North America during the study period who were not treated with OCA. Of these, 1,381 met the entry criteria for this study.

The UK-PBC registry included over 6,900 patients with PBC from the UK during the study period who were not treated with OCA. Of these, 2,135 met the entry criteria for this study.

The POISE trial studied the safety and efficacy of once-daily treatment with Ocaliva in PBC patients with an inadequate therapeutic response to, or who were unable to tolerate, ursodeoxycholic acid (UDCA). There were 217 patients randomized to one of three groups in the trial: placebo, OCA 10 mg, or OCA 5 mg for six months titrated to 10 mg based on clinical response. Seven subjects did not participate in the open-label extension and were not included in the current study. Patients completing the double-blind phase had the option to continue in an open-label extension (OLE) phase for a maximum of five additional years, during which all patients received treatment with OCA 5-10 mg once daily. Of the 198 patients who completed the double-blind phase, more than 95 percent continued in the long-term safety extension phase of the trial. Additional information regarding the POISE trial can be found on the NIH clinical study listing website: http://clinicaltrials.gov/ct2/show/NCT01473524.

About Primary Biliary Cholangitis
Primary biliary cholangitis (PBC) is a rare, progressive and chronic autoimmune disease that affects the bile ducts in the liver and is most prevalent (approximately 1 in 10,000) in women over the age of 40. PBC causes bile acids to build up in the liver, resulting in inflammation and scarring (fibrosis), which, if left untreated, can lead to cirrhosis, liver transplant, or death.

About Intercept
Intercept is a biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat progressive non-viral liver diseases, including primary biliary cholangitis (PBC) and nonalcoholic steatohepatitis (NASH). For more information, please

visit www.interceptpharma.com or connect with the company on Twitter and LinkedIn.

About Ocaliva® (obeticholic acid)

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of adult patients with primary biliary cholangitis (PBC).

- without cirrhosis or
- with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

IMPORTANT SAFETY INFORMATION

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS

- **Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in primary biliary cholangitis (PBC) patients with either compensated or decompensated cirrhosis.**
- **OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension.**
- **Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation; have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment.**

Contraindications

OCALIVA is contraindicated in patients with:

- decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event
- compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)
- complete biliary obstruction

Warnings and Precautions

Hepatic Decompensation and Failure in PBC Patients with Cirrhosis

Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in PBC patients with cirrhosis, either compensated or decompensated. Among post-marketing cases reporting it, median time to hepatic decompensation (e.g., new onset ascites) was 4 months for patients with compensated cirrhosis; median time to a new decompensation event (e.g., hepatic encephalopathy) was 2.5 months for patients with decompensated cirrhosis.

Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage for that patient population; however, cases of hepatic decompensation and failure have continued to be reported in patients with decompensated cirrhosis even when they received the recommended dosage.

Hepatotoxicity was observed in the OCALIVA clinical trials. A dose-response relationship was observed for the occurrence of hepatic adverse reactions including jaundice, worsening ascites, and primary biliary cholangitis flare with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCALIVA in two 3-month, placebo-controlled clinical trials in patients with primarily early stage PBC.

Routinely monitor patients for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments to determine whether drug discontinuation is needed. Closely monitor patients with compensated cirrhosis, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or with severe intercurrent illness for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia), or increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time to determine whether drug discontinuation is needed. Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy), have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia), experience clinically significant hepatic adverse reactions, or develop complete biliary obstruction. If severe intercurrent illness occurs, interrupt treatment with OCALIVA and monitor the patient's liver function. After resolution of the intercurrent illness, consider the potential risks and benefits of restarting OCALIVA treatment.

Severe Pruritus

Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in a 12-month double-blind randomized controlled clinical trial of 216 patients. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. Consider clinical evaluation of patients with new onset or worsening severe pruritus. Management strategies include the addition of bile acid binding resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing.

Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high-density lipoprotein-cholesterol (HDL-C). Dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

Adverse Reactions

The most common adverse reactions (≥5%) are: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema.

Drug Interactions

- Bile Acid Binding Resins
  Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

- Warfarin
  The International Normalized Ratio (INR) decreased following coadministration of warfarin and OCALIVA. Monitor INR and adjust the dose of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.

- CYP1A2 Substrates with Narrow Therapeutic Index
  Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline and tizanidine) is recommended when co-administered with OCALIVA.

- Inhibitors of Bile Salt Efflux Pump
  Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts including taurine conjugate of obeticholic acid in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitor serum transaminases and bilirubin.

Please click here for Full Prescribing Information, including Boxed WARNING.
To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals, Inc. at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Cautionary Note Regarding Forward-Looking Statements

This press release contains forward-looking statements (“FLS”), including regarding the results of our clinical trials, and the safety and efficacy of OCA. Important factors could cause actual results to differ materially from the FLS, including further developments regarding understanding of side effects, patient outcomes, or study methodology.

Contact

For more information about Intercept, please contact:

Investor inquiries: investors@interceptpharma.com

Media inquiries: media@interceptpharma.com

Source: Intercept Pharmaceuticals, Inc.