Intercept Announces New Long-Term Data Demonstrating Potential of Obeticholic Acid to Improve Transplant-Free Survival in Patients with PBC

November 15, 2021

Analysis compares findings from the long-term safety extension of the Phase 3 POISE trial to PBC natural history data from the Global PBC and UK-PBC databases

Results will be featured in a late-breaking podium presentation at The Liver Meeting®

NEW YORK, Nov. 15, 2021 (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 results from a new analysis examining obeticholic acid's (OCA) potential to improve transplant-free survival in patients with PBC. The data will be featured in a late-breaking podium presentation at The Liver Meeting®, the Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), which is being held virtually from Friday, November 12 to Monday, November 15, 2021. The analysis was also selected as a "Best of The Liver Meeting" abstract in the Cholestatic and Autoimmune Liver Diseases category.

"This collaborative study used an innovative approach to contribute new understandings about how treatment of patients with PBC with OCA may impact clinical outcomes: we compared patients with PBC who were treated with OCA in the open-label long-term safety extension of the Phase 3 POISE trial, with external controls from two large representative academic-led patient registries. When compared to real-world patient outcome data, the results provide insights into OCA's potential to improve transplant-free survival in patients with PBC treated in a trial setting," said Professor Gideon Hirschfield, FRCP, Ph.D., Lily and Terry Horner Chair in Autoimmune Liver Disease at the University of Toronto. "Data describing the effect of OCA on mortality and need for liver transplant in patients with PBC is eagerly awaited, but such data is inevitably challenging to generate. Notably, when doing this comparison, we found consistent results across the two databases. We hope this analysis can soon be extended to include more patients treated with OCA, and approaches such as this can help the field overcome obstacles to generating meaningful clinical outcome data."

The POISE long-term safety extension (LTSE) study included 209 patients dosed with OCA with a maximum follow-up time of 6.3 years. Propensity score-matched external controls were patients from the Global PBC (n=1,391) and UK-PBC (n=2,138) real-world databases who were diagnosed with PBC and who met POISE clinical trial entry criteria. Patients from the external control databases were untreated or treated with ursodeoxycholic acid (UDCA) with at least one year of follow-up but were not treated with OCA or other therapies. The primary endpoint was time to liver transplantation or death.

In this analysis, 209 patients treated with OCA in the POISE LTSE study had significantly greater transplant-free survival than patients in the external control groups. In the OCA arm, three events were observed versus 146 and 276 events in the Global PBC and UK-PBC external control cohorts, respectively. In a weighted analysis, the hazard ratio favoring OCA was 0.20 (0.06-0.64, p=0.001) in Global PBC and 0.28 (0.09-0.90, p=0.033) in UK-PBC. Thus, patients treated with OCA had a 72% to 80% lower risk of death or liver transplant than the control groups at any time during follow-up. Consistent findings were observed in multiple sensitivity analyses, as well as when testing for the influence of recruitment bias and potential confounding factors such as baseline bilirubin, ALP, AST or ALT, age, PBC duration, UDCA use, diagnosis year and sex.

"The methodology used in this study takes advantage of decades of research to understand the natural history of PBC, and we are thankful to all of the patients and researchers who have contributed data to the Global PBC and UK-PBC study groups," said M. Michelle Berrey, M.D., M.P.H., President of Research & Development and Chief Medical Officer of Intercept. "With a rare, progressive disease like PBC, there are well-known difficulties in conducting long-term, placebo-controlled trials after the approval of a therapeutic agent, so studies like this provide another way to address questions about the impact of OCA on clinical endpoints. The results add to an already substantial body of evidence supporting our belief in OCA's potential to provide benefit for appropriate patients with PBC. We are committed to generating additional long-term data to build on these findings."

About Primary Biliary Cholangitis
Primary biliary cholangitis (PBC) is a chronic, progressive liver disorder that affects mostly women, impacting approximately one in 1,000 women over the age of 40. If left untreated, survival of patients with PBC is significantly worse than the general population.

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). Founded in 2002 in New York, Intercept has operations in the United States, Europe and Canada. 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 incurrent 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, including, but not limited to, statements regarding the progress, timing and results of our clinical trials, including our clinical trials for the treatment of nonalcoholic steatohepatitis (“NASH”), the safety and efficacy of our approved product, Ocaliva (obeticholic acid or “OCA”) for primary biliary cholangitis (“PBC”), and our product candidates, including OCA for liver fibrosis due to NASH, the timing and acceptance of our regulatory filings and the potential approval of OCA for liver fibrosis due to NASH, the review of our New Drug Application for OCA for the treatment of liver fibrosis due to NASH by the U.S. Food and Drug Administration (FDA), our intent to work with the FDA to address the issues raised in the complete response letter (CRL), the potential commercial success of OCA, as well as our strategy, future operations, future financial position, future revenue, projected costs, financial guidance, prospects, plans and objectives.

These statements constitute forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “possible,” “continue” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Readers are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date of this release, and we undertake no obligation to update any forward-looking statement except as required by law. These forward-looking statements are based on estimates and assumptions by our management that, although believed to be reasonable, are inherently uncertain and subject to a number of risks. The following represent some, but not necessarily all, of the factors that could cause actual results to differ materially from historical results or those anticipated or predicted by our forward-looking statements: our ability to successfully commercialize Ocaliva for PBC; our ability to maintain our regulatory approval of Ocaliva for PBC in the United States, Europe, Canada, Israel, Australia and other jurisdictions in which we have or may receive marketing authorization; our ability to timely and cost-effectively file for and obtain regulatory approval of our product candidates on an accelerated basis or at all, including OCA for liver fibrosis due to NASH following the issuance of the CRL by the FDA; any advisory committee recommendation or dispute resolution determination that our product candidates, including OCA for liver fibrosis due to NASH, should not be approved or approved only under certain conditions; any future determination that the regulatory applications and subsequent information we submit for our product candidates, including OCA for liver fibrosis due to NASH, do not contain adequate clinical or other data or meet applicable regulatory requirements for approval; conditions that may be imposed by regulatory authorities on our marketing approvals for our products and product candidates, including OCA for liver fibrosis due to NASH, such as the need for clinical outcomes data (and not just results based on achievement of a surrogate endpoint), any risk mitigation programs such as a REMS, and any related restrictions, limitations and/or warnings contained in the label of any of our products or product candidates; any potential side effects associated with Ocaliva for PBC, OCA for liver fibrosis due to NASH or our other product candidates that could delay or prevent approval, require that an approved product be taken off the market, require the inclusion of safety warnings or precautions, or otherwise limit the sale of such product or product candidate, including in connection with our update to Ocaliva prescribing information in May 2021 contraindicating Ocaliva for patients with PBC and decompensated cirrhosis, a prior decompensation event, or compensated cirrhosis with evidence of portal hypertension; the initiation, timing, cost, conduct, progress and results of our research and development activities, preclinical studies and clinical trials, including any issues, delays or failures in identifying patients, enrolling patients, treating patients, retaining patients, meeting specific endpoints in the jurisdictions in which we intend to seek approval or completing and timely reporting the results of our NASH or PBC clinical trials; the outcomes of interactions with regulators (e.g., the FDA and the European Medicines Agency) regarding our clinical trials; our ability to establish and maintain relationships with, and the performance of, third-party manufacturers, contract research organizations and other vendors upon whom we are substantially dependent for, among other things, the manufacture and supply of our products, including Ocaliva for PBC and, if approved, OCA for liver fibrosis due to NASH, and our clinical trial activities; our ability to identify, develop and successfully commercialize our products and product candidates, including our ability to successfully launch OCA for liver fibrosis due to NASH, if approved; our ability to obtain and maintain intellectual property protection for our products and product candidates, including our ability to cost-effectively file, prosecute, defend and enforce any patent claims or other intellectual property rights; the size and growth of the markets for our products and product candidates and our ability to serve those markets; the degree of market acceptance of Ocaliva for PBC and,

if approved, OCA for liver fibrosis due to NASH or our other product candidates among physicians, patients and healthcare payors; the availability of adequate coverage and reimbursement from governmental and private healthcare payors for our products, including Ocaliva for PBC and, if approved, OCA for liver fibrosis due to NASH, and our ability to obtain adequate pricing for such products; our ability to establish and maintain effective sales, marketing and distribution capabilities, either directly or through collaborations with third parties; competition from existing drugs or new drugs that become available; our ability to attract and retain key personnel to manage our business effectively; our ability to prevent or defend against system failures or security or data breaches due to cyber-attacks, or cyber intrusions, including ransomware, phishing attacks and other malicious intrusions; our ability to comply with data protection laws; costs and outcomes relating to any disputes, governmental inquiries or investigations, regulatory proceedings, legal proceedings or litigation, including any securities, intellectual property, employment, product liability or other litigation; our collaborators' election to pursue research, development and commercialization activities; our ability to establish and maintain relationships with collaborators with development, regulatory and commercialization expertise; our need for and ability to generate or obtain additional financing; our estimates regarding future expenses, revenues and capital requirements and the accuracy thereof; our use of cash, cash equivalents and short-term investments; our ability to acquire, license and invest in businesses, technologies, product candidates and products; our ability to manage the growth of our operations, infrastructure, personnel, systems and controls; our ability to obtain and maintain adequate insurance coverage; continuing threats from COVID-19, including additional waves of infections, and their impacts including quarantines and other government actions, delays relating to our regulatory applications, disruptions relating to our ongoing clinical trials or involving our contract research organizations, study sites or other clinical partners, disruptions relating to our supply chain or involving our third-party manufacturers, distributors or other distribution partners, and facility closures or other restrictions, and impact of the foregoing on our results of operations and financial position; the impact of general U.S. and foreign economic, industry, market, regulatory or political conditions, including the impact of Brexit; and the other risks and uncertainties identified in our periodic filings filed with the U.S. Securities and Exchange Commission, including our Annual Report on Form 10-K for the year ended December 31, 2020.

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