Intercept Announces New Clinical Trial and Real-World Outcomes Data for Ocaliva in PBC

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COBALT study in advanced PBC, previously terminated early due to feasibility challenges, did not demonstrate a statistically significant difference in clinical endpoints between Ocaliva® and placebo

HEROES-US real-world analysis demonstrated statistically significant improvement in event-free survival in patients receiving Ocaliva for PBC

Intercept plans to include these data in an evidence package that will be submitted to U.S. FDA in 2H 2022 to support post-marketing regulatory requirements

MORRISTOWN, N.J., June 03, 2022 (GLOBE NEWSWIRE) -- Intercept Pharmaceuticals, Inc. (Nasdaq: ICPT), a biopharmaceutical company focused on the development and commercialization of novel therapeutics to treat non-viral liver diseases, today announced results from two studies designed to evaluate clinical outcomes in patients with PBC on Ocaliva (obeticholic acid or OCA): COBALT, a Phase 3b/4 confirmatory clinical outcomes study, and HEROES-US, one of two HEROES real-world studies. Findings from these studies will be part of a broader evidence package being submitted to the U.S. Food and Drug Administration (FDA) in the second half of 2022.

Ocaliva was granted an accelerated approval in 2016 based on a reduction in alkaline phosphatase (ALP), a blood marker of liver injury. COBALT was designed to determine rates of clinical events in patients with advanced PBC and was initiated to support post-marketing requirements.

In 2021, Intercept announced COBALT would be terminated early as a result of conversations with regulatory authorities and guidance from the study's data monitoring committee (DMC). The DMC noted that the objectives of the trial were not feasible given the inherent challenges with enrolling and maintaining patients in a placebo-controlled study in a rare disease when the study drug is commercially available. Given this feedback, Intercept closed the trial and began to compile available data from COBALT. Intercept also initiated multiple real-world analyses, including the HEROES studies to provide greater insight into the impact of Ocaliva on clinical outcomes in patients with PBC.

COBALT Study Results
In COBALT, patients were randomized 1:1 to Ocaliva (n=168) or placebo (n=166). The primary endpoint, as agreed with the FDA, was time to first occurrence of any of the following clinical endpoints: all-cause death, liver transplant, or hospitalization for other serious liver-related events. The study did not demonstrate a statistically significant difference between Ocaliva and placebo on the primary endpoint: 71 subjects in the Ocaliva arm progressed to clinical events compared to 80 in the placebo arm (p=0.30; HR 0.84). The safety and tolerability of Ocaliva were consistent with its known profile; adverse events were in line with expectations for patients with advanced PBC based on the natural history of the disease.

At the time of the early termination, COBALT was less than 80% enrolled. More than 50% of patients discontinued the study prior to meeting the study endpoint. In addition, at least 14% of patients on placebo initiated commercially available Ocaliva during the study but remained in the placebo arm for reporting purposes. The majority of patients in COBALT had advanced PBC and more than half (55%) would have been contraindicated for treatment with Ocaliva based on the current U.S. Prescribing Information[1]. Given these factors, the data from COBALT could not provide a fulsome assessment of the impact of Ocaliva on clinical outcomes.

"We have long acknowledged the limitations of running a placebo-controlled study in a rare disease like PBC when the active arm is a commercially available therapy. These data from COBALT do not demonstrate a difference between the placebo and active arms but were not unexpected based on the feasibility challenges we encountered while running the study," said M. Michelle Berrey, M.D., MPH, President, Research & Development and Chief Medical Officer of Intercept. "With a full understanding of the limitations of placebo-controlled studies such as COBALT, we initiated our HEROES real-world studies to evaluate the effect of Ocaliva on clinical outcomes in medical practice. We remain committed to meeting our post-marketing requirements and are compiling data from COBALT, HEROES-US, and additional real-world datasets as part of a comprehensive evidence package that will be submitted to FDA later this year."

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[1] The Ocaliva U.S. Prescribing Information was updated in May 2021 to contraindicate PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis with evidence of portal hypertension.

HEROES-US Study Results
The HEROES-US retrospective real-world analysis leveraged Komodo Health, a U.S. claims database, to compare clinical outcomes in a pre-defined group of patients with PBC who were treated with Ocaliva (n=429) and a comparable group of PBC patients who were eligible, but who were not treated with Ocaliva (n=4,585). The study showed a statistically significant and clinically meaningful reduction in all-cause death, liver transplant, or hospitalization for hepatic decompensation among Ocaliva-treated patients compared to the control group. In the Ocaliva arm, 8 events were observed compared to 226 in the control group with a weighted hazard ratio of 0.38 (p= 0.027). Thus, individuals with PBC who received Ocaliva had a 62% reduction in risk of all-cause death, liver transplant or hospitalization for hepatic decompensation than the control groups at any time during follow up.

Dr. Kris V. Kowdley, Director of Liver Institute Northwest, and Professor at the Elson S. Floyd College of Medicine, Washington State University, stated: "These data from HEROES-US further augment the results from the POISE long-term safety extension compared with external controls that were presented at last year's AASLD Annual Meeting. In addition, the observed event-free survival adds to the weight of evidence regarding the impact of Ocaliva on clinical outcomes. We have a well-established understanding of the effect of Ocaliva on biochemical measures such as ALP and on various scores used to predict clinical outcomes, but the HEROES-US study provides additional information regarding the impact of Ocaliva on the ultimate goal of PBC treatment: slowing and preventing disease progression to liver transplant or death."

Intercept intends to share these results at an upcoming medical meeting.

COBALT Study Design
COBALT (NCT02308111) was a Phase 3b/4, double-blind, randomized, placebo-controlled, multicenter study that was designed to assess the effect of Ocaliva on clinical outcomes in people living with PBC with an inadequate therapeutic response to UDCA or who were unable to tolerate UDCA.

In this trial, eligible people with PBC who were enrolled while on UDCA treatment remained on therapy and were randomized into one of two treatment arms. Patients received placebo or Ocaliva 5 mg daily or 5 mg weekly, based on disease severity, and titrated over the course of the trial to a maximum of Ocaliva 10 mg daily, based on tolerability and biochemical response. Patients were evaluated every three months.

The original primary endpoint of the trial was time to first occurrence of any of the following adjudicated events: all-cause death, liver transplant, or hospitalization for other serious liver-related events. Prior to early termination of COBALT, FDA and Intercept agreed on a new primary composite endpoint consisting of a set of expanded, clinically relevant events, including additional decompensation events, as well as clinical events that occur earlier in the disease course and indicate progression toward decompensation.

HEROES Study Design
HEROES is a set of two retrospective studies (NCT05292872, NCT05293938) which leverage real-world datasets to assess the impact of Ocaliva on important clinical outcomes in people living with PBC.

The first of these, HEROES-US, leveraged the Komodo Health claims database, linked via Datavant tokenization to Quest and LabCorp laboratory data and the Social Security Death Index, to compare clinical outcomes (defined as all-cause death, liver transplant, or hospitalization for hepatic decompensation) of PBC patients who were treated with Ocaliva with PBC patients who were eligible, but not treated with Ocaliva.

In the analysis, patients were required to have one inpatient PBC claim, or two outpatient claims separated by more than one day; a history of UDCA use; an elevated ALP and/or total bilirubin; and meet comorbidity exclusion criteria.

Propensity scores and standardized morbidity ratios were used to weight cohorts to ensure comparable baseline clinical and demographic characteristics, comorbidities, disease and treatment history.

This trial was designed and executed following FDA's draft guidance on use of real-world evidence to support regulatory decision-making for drug and biological products.

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, 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 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 acid to build up in the liver, resulting in inflammation and scarring (fibrosis), which, if left untreated, can lead to cirrhosis, a liver transplant, or death.

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, 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 latest Annual Report on Form 10-K and/or Quarterly Report on Form 10-Q.

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