Intercept Announces Additional Positive Data in Fibrosis due to NASH from New Analysis of Phase 3 REGENERATE Study at AASLD The Liver Meeting® 2022

November 7, 2022

OCA 25 mg demonstrated double the response rate of placebo in reduction of liver fibrosis without worsening of NASH; consistent antifibrotic effect shown across multiple analyses

OCA 25 mg showed increased antifibrotic efficacy in patients with advanced fibrosis without cirrhosis

Robust safety assessment of 2,477 patients, including 1,000 on study drug for four years, supports chronic administration of OCA

REGENERATE data to be presented in late-breaking oral session on Monday, November 7

Company remains on track to resubmit new drug application for OCA in liver fibrosis due to NASH by end of 2022

MORRISTOWN, N.J., Nov. 07, 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 additional supportive data from its pivotal Phase 3 REGENERATE study of obeticholic acid (OCA) in patients with liver fibrosis due to nonalcoholic steatohepatitis (NASH). These analyses further demonstrate OCA's consistent and well-defined antifibrotic effect as well as its monitorable and manageable safety and tolerability profile in patients with liver fibrosis due to NASH. These data will be presented on Monday, November 7, 2022, at The Liver Meeting®, the annual meeting of the American Association for the Study of Liver Diseases (AASLD) in Washington, D.C.

"The antifibrotic effect of OCA has been demonstrated in multiple analyses of REGENERATE. This efficacy, together with extended exposure in the largest safety database in NASH, supports a positive benefit:risk for OCA in patients with fibrosis due to NASH," said Dr. Arun Sanyal, Chair, Division of Gastroenterology/Hepatology/Nutrition & Director, Stravitz-Sanyal Liver Institute, VCU Health, Department of Internal Medicine.

"The results of these new analyses – and specifically the consistent response rate for OCA 25 mg on multiple fibrosis endpoints vs. placebo – together with a detailed safety analysis, reaffirm our belief that OCA can be an important treatment for people living with fibrosis due to NASH," said M. Michelle Berrey, M.D., M.P.H., President of Research & Development and Chief Medical Officer of Intercept. "Importantly, in these new analyses, we found that this antifibrotic effect is even more pronounced in patients with advanced fibrosis without cirrhosis at baseline, which underscores the urgency in treating patients before they progress to liver cirrhosis. We look forward to resubmitting our new drug application for OCA in fibrosis due to NASH by the end of this year based on these positive data."

Interim Efficacy Analysis

As previously reported in July 2022, in a second interim analysis of the ITT population from REGENERATE (n=931), 22.4% of subjects randomized to once-daily oral OCA 25 mg met the primary endpoint of achieving at least one stage of fibrosis improvement with no worsening of NASH at Month 18 on liver biopsy compared with 9.6% of subjects on placebo ($p<0.0001$). There was not a statistically significant difference between OCA 10 mg and placebo; however, there was a clear dose-response across all arms. These results, which used a consensus panel approach to reading biopsies, were consistent with those from the original interim analysis in 2019, which used a single reader approach.

Additional Supportive Efficacy Analyses

Additional efficacy analyses conducted in the ITT population reinforced consistent antifibrotic effect, showing:

- Antifibrotic effect was more pronounced in individuals with advanced fibrosis without cirrhosis (F3) at baseline (n=520), with 25.4% of patients in the OCA 25 mg group demonstrating an improvement in fibrosis by at least 1 stage without worsening of NASH as compared to 9.5% in placebo ($p=0.0001$).
- In individuals with F2 fibrosis at baseline (n=411), 18.7% of patients in the OCA 25 mg group demonstrated an improvement in fibrosis by at least 1 stage without worsening of NASH as compared to 9.9% in placebo ($p<0.04$).

An additional analysis of the subset of patients in the ITT population who had evaluable biopsies at baseline and Month 18 (n=747) was conducted within each treatment arm to show improvement, worsening or no change in fibrosis stage. Within the OCA 25 mg group, there was a more than two-fold change in improvement relative to worsening, whereas more patients worsened than improved in the placebo arm.

Following the original analysis of the ITT population in 2019, an additional 676 patients became eligible for Month 18 biopsies prior to a protocol change in REGENERATE that eliminated this biopsy requirement. An analysis of the 676 patients combined with the ITT population (n=1,607) showed that 21.0% of patients in the OCA 25 mg group demonstrated an improvement in fibrosis by at least 1 stage without worsening of NASH compared to 12.3% in placebo.

Safety and Tolerability

Safety was evaluated in 2,477 subjects who took at least one dose of study drug (placebo, OCA 10 mg, or OCA 25 mg). As previously reported, patients in this second interim analysis of REGENERATE had significantly longer exposure to study drug compared to the original analysis in 2019 (median 42 months vs. 15 months), yielding more than 8,000 total patient-years and 3.4 times more exposure. Nearly 1,000 subjects had been on study drug for four years.

Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), and deaths were generally balanced across the OCA and placebo treatment groups. The most common TEAE was pruritus (24% in placebo, 33% in OCA 10 mg, 55% in OCA 25 mg) and pruritus was the most common cause for treatment discontinuation.

Independent groups of experts reviewed certain categories of safety events to provide a blinded adjudication as specifically requested by FDA. These included events pertaining to hepatic safety (excluding clinical outcomes), cardiovascular and renal. Analysis through four years of treatment showed:

- Most adjudicated hepatic safety events reflected biochemical changes common in patients with advanced fibrosis due to NASH and, for the OCA-treated arms, the effects of FXR agonism. There were a numerically higher number of adjudicated hepatic safety events in the OCA 25 mg arm (111 in placebo, 112 in OCA 10 mg, 140 in OCA 25 mg), the vast majority of which were mild. Across all treatment arms, the number of adjudicated hepatic safety events considered to be highly likely or probably related to IP were low (1 in placebo, 1 in OCA 10 mg, 7 in OCA 25 mg).
- The number of cases that met biochemical Hy's Law criteria were low and balanced across treatment arms (7 in placebo, 6 in OCA 10 mg, 6 in OCA 25 mg).
- The frequency of core major adverse cardiovascular events (MACE), 4-point MACE (defined as core MACE + unstable angina) and 5-point MACE (defined as core MACE + unstable angina and hospitalization for heart failure) was low and balanced among treatment groups.
    - Core MACE: 1.2% in placebo, 0.5% in OCA 10 mg, 1.3% in OCA 25 mg
    - 4-point MACE: 1.5% in placebo, 1.0% in OCA 10 mg, 1.6% in OCA 25 mg
    - 5-point MACE: 1.8% in placebo, 1.0% in OCA 10 mg, 1.6% in OCA 25 mg
- There was one adjudicated cardiovascular death in each of the three treatment arms.
- The number of renal events submitted for adjudication were balanced across treatment arms (33 in placebo, 34 in OCA 10 mg, 33 in OCA 25 mg). Additionally, the number of events adjudicated as acute kidney injury were low and balanced across treatments arms (3 in placebo, 0 in OCA 10 mg, 3 in OCA 25 mg).

Additional adverse events of special interest (AESIs) were also captured and monitored:

- Consistent with its known mechanism of action, higher rates of gallbladder-related adverse events, including gallstones, were seen in the OCA arms (4.0% in placebo, 5.2% in OCA 10 mg, 7.6% in OCA 25 mg). Serious gallbladder-related events, most commonly cholecystitis, were low in all treatment groups (0.7% in placebo, 1.0% in OCA 10 mg, 2.5% in OCA 25 mg).
- Rates of hyperglycemia or worsening diabetes were balanced across treatment arms (23.0% in placebo, 27.0% in OCA 10 mg, 24.3% in OCA 25 mg). A total of 5 cases of diabetic ketoacidosis (DKA) were reported across all arms (1 in placebo, 2 in OCA 10 mg, 2 in OCA 25 mg).
- The incidence of pancreatitis TEAEs was low and balanced across study arms (0.8% in placebo, 0.6% in OCA 10 mg, 1.0% in OCA 25 mg). In the placebo arm, there was one fatal case of pancreatitis.
- Rates of urinary tract stones were similar across all arms (3.9% in placebo, 3.8% in OCA 10 mg, 3.4% in OCA 25 mg).

Consistent with its mechanism of action as an FXR agonist, OCA treatment was associated with an increase in LDL at Month 1 which returned to near baseline values by Month 12. Patients who initiated a statin saw a more rapid reduction to near baseline values.

Changes in other blood chemistries including, GGT (gamma-glutamyl transferase), AST (aspartate aminotransferase), and ALT (alanine aminotransferase) also showed improvements, supporting the dose-response of OCA.

OCA has not been approved for the treatment of NASH by any regulatory authority in any geography and is considered an investigational treatment for this indication.

About the REGENERATE Study

REGENERATE (Randomized Global Phase 3 Study to Evaluate the Impact on NASH with Fibrosis of Obeticholic Acid Treatment) is an ongoing Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study assessing the safety and efficacy of obeticholic acid (OCA) on clinical outcomes in patients with liver fibrosis due to NASH. A pre-specified interim analysis was conducted in 931 subjects who had a liver biopsy at Month 18 to assess the effect of OCA on liver histology as compared to baseline biopsies. REGENERATE is fully enrolled with 2,480 randomized participants and is expected to continue while collecting data on the incidence of clinical outcomes for verification and description of clinical benefit. The end-of-study primary endpoint will compare the impact of treatment group (placebo, OCA 10 mg or OCA 25 mg daily) on all-cause mortality and liver-related clinical outcomes, as well as on long-term safety.

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 Liver Fibrosis due to NASH

Nonalcoholic steatohepatitis (NASH) is a serious progressive liver disease caused by excessive fat accumulation in the liver that induces chronic inflammation, resulting in progressive fibrosis (scarring) that can lead to cirrhosis, eventual liver failure, cancer and death. Advanced fibrosis is associated with a substantially higher risk of liver-related morbidity and mortality in patients with NASH. There are currently no medications approved for the treatment of NASH.

Forward-Looking Statements

This press release contains forward-looking statements (FLS), including regarding resubmission and timing of Intercept's new drug application for OCA for treatment of liver fibrosis due to NASH. Important factors could cause actual results to differ materially from the FLS. For example, our resubmission could be delayed or be unsuccessful because of efficacy, safety, or tolerability concerns, problems with our clinical studies and their data or methods, or our inability to address to the satisfaction of the FDA the issues raised in their complete response letter of June 2020 responding to our earlier submission.

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