

Phase 2 studies of two novel treatments for primary biliary cholangitis report encouraging results

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Preliminary results from two ongoing Phase 2 studies of novel agents under investigation for the treatment of primary biliary cholangitis (PBC) have suggested promising efficacy, safety and tolerability profiles in patients not responding to current standard of care, potentially paving the way for longer-term studies. In the first study presented this week at The International Liver Congress 2018 in Paris, France, the non-bile acid farnesoid X receptor (FXR) agonist, tropifexor, demonstrated dose-dependent activity on markers of cholestasis and hepatocellular damage over 4 weeks, with no apparent increase in itching. The second study evaluated 12-26 weeks of treatment with the selective peroxisome proliferator-activated receptor-delta (PPAR- δ), seladelpar, at doses of 2, 5, and 10 mg/day, and reported potent and sustained anti-cholestatic and anti-inflammatory activity without an increase in pruritus.

Primary biliary cholangitis is a progressive cholestatic liver disease characterized by an immune-mediated destruction of intrahepatic bile ducts. Ursodeoxycholic acid (UDCA) has been the mainstay of treatment for PBC for more than 20 years, however, up to 40% of patients receiving UDCA have persistent elevations of alkaline phosphatase (ALP) or bilirubin, and a further 3-5% of patients are unable to tolerate treatment. The bile acid FXR agonist obeticholic acid (OCA) is approved as an add-on therapy in patients with PBC, or for those intolerant of UDCA;¹ however, approximately 50% of patients in the Phase 3 study of added OCA did not meet the trial's pre-specified

dichotomous biochemical efficacy endpoint.

Tropifexor is a novel, selective, non-bile [acid](#) FXR agonist that reduced cholestasis and hepatocellular damage in rodent models.¹³ The ongoing Phase 2 study reported this week enrolled PBC patients with an inadequate response to UDCA (ALP $\geq 1.67 \times$ ULN or bilirubin $>$ ULN), who were randomized to receive tropifexor 30 μ g, 60 μ g, or 90 μ g once daily or a matching placebo for 4 weeks. The primary endpoint was change from baseline in gamma-glutamyltransferase (GGT).

Dose-dependent decreases in GGT, ALP, bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed and, by Day 28, a 72% reduction in GGT and a 41% reduction in ALT were reported in the highest tropifexor dosing group (90 μ g/day; p

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