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Sustained Improvement in the Markers of Cholestasis in an Open Label Long Term Safety Extension Study of Obeticholic Acid in Primary Biliary Cirrhosis Patients

Category: Human Cholestatic and Autoimmune Liver Diseases

Descriptor: IO1. PBC/PSC and Other Cholestatic Disease

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Obeticholic Acid (OCA) is a potent FXR agonist developed for treatment of primary biliary cirrhosis (PBC). 217 patients were enrolled in a randomized double-blind, placebo-controlled phase 3 PBC trial; 198 patients completed the trial and 193 (97%) patients enrolled in an open-label long term safety extension (LTSE). The LTSE aim is to assess the durability of OCA on the markers of cholestasis and safety. Study inclusion criteria: PBC diagnosis, ALP $\geq 1.67 \times$ ULN and/or total bilirubin $>ULN$ to $<2 \times$ ULN, stable UDCA dose or unable to tolerate UDCA. During the double blind (DB) phase, patients were randomized to: daily Placebo (PBO), 5 to 10mg OCA titration group (after 6 months based on response), or 10mg OCA. In the LTSE, all patients were initially treated with 5 mg OCA regardless of DB treatment with the option to increase OCA doses after 3 months. LTSE demographics: mean age 55 y; female: 92%; Caucasian 94%; mean UDCA dose 16 mg/kg. In the DB

period, all OCA groups had significant reductions in ALP, GGT, ALT and AST (Table 1). In OCA Titration and 10mg groups, this response was durable for 24 months. For PBO, bilirubin increased during the DB period, but decreased following the initiation of OCA. OCA Titration and 10mg groups sustained no increase in bilirubin in the DB or LTSE. Overall OCA was safe and well-tolerated; pruritus was the most common AE associated with OCA. Patients on OCA in the DB period showed a decrease in incidence of pruritus in the LTSE, from 53-67% to 15-21%. PBO subjects who initiated OCA in the LTSE saw an increase in pruritus consistent with initiation of OCA. Unrelated to OCA, 1 patient died as a result of sepsis secondary to endocarditis after a prosthetic aortic valve replacement. OCA treatment produced a durable improvement in hepatic biochemistry through 24 months of treatment. Pruritus was the most common AE, but its incidence appeared to lessen with longer treatment.



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