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EFFECTS OF ATRASENTAN ON MARKERS OF LIVER FUNCTION IN PATIENTS WITH TYPE 2 DIABETES AND CHRONIC KIDNEY DISEASE

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Objectives: The selective endothelin receptor A antagonist (ERA) atrasentan reduced the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease (CKD). Rare, but serious drug induced liver injury (DILI) has been previously reported with some ERAs, possibly due to chemical structure and modulation of hepatobiliary transporters, hepatic metabolism and/or hepatic clearance pathways. We assessed the effects of atrasentan on markers of liver function and liver-related adverse events, including DILI.

Methods: We performed a pre-specified analysis of the SONAR trial which randomized patients with eGFR 25-75 ml/min/1.73m^2 and urinary albumin-to-creatinine ratio (UACR) 300-5000 mg/g to atrasentan 0.75 mg or placebo (1:1). The effect of atrasentan compared to placebo on the mean change from baseline in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase, and Bilirubin was assessed. We summarized investigator reported treatment emergent liver-related adverse events (TEAE) by treatment group and searched for potential cases of Hy's law.

Results: We randomized 3668 participants to atrasentan (N=1834) or placebo (N=1834). Mean (SD) age was 64.5 (9) years, eGFR was 43.3 (14) mL/min/1.73m^2 and median UACR was 829 (25th to 75th Percentile 457-1556) mg/g. At baseline, 204 (5.6%) and 76 (2.1%) participants reported liver disease (excluding hepatitis) and hepatitis respectively. Median follow-up was 2.2 years. Atrasentan compared to placebo statistically significantly reduced ALT, AST and ALP (Table 1). Liver-related TEAE in the atrasentan and placebo group were not significantly different; 57 (3.1%) and 52 (2.8%) respectively, resulting in an exposure adjusted incidence rate of 1.6 and 1.4 per 100 person-year follow-up, respectively. Rare, severe, DILI was not observed with atrasentan treatment in SONAR.

Conclusions: In patients with type 2 diabetes and CKD, who are at high risk of liver disease, there was no evidence of liver function abnormalities or liver related adverse effects with atrasentan treatment.

Table 1. Liver function in patients with type 2 diabetes and CKD