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Biosketch

Yvonne Dragan is the Director of Global Discovery Toxicology at Takeda. Yvonne received her PhD in Pharmacology and Toxicology at the Medical College of VA and performed postdoctoral work in chemical carcinogenesis at the University of WI-Madison. She held appointments in WI in Oncology and later at OSU in the School of Public Health. Yvonne spent 5 years with NCTR/FDA leading preclinical hepatotoxicity efforts and establishing a Systems Toxicology group. She joined AstraZeneca to Lead the US-Investigative Group and its US- Discovery Toxicology efforts. She then joined DuPont as a business unit liaison to the bio-based businesses and initiated a Predictive Sciences group. Yvonne recently joined Takeda where she is responsible for developing and implementing the global discovery toxicology strategy to decrease safety-related attrition throughout the pipeline.

Abstract: TAK-875 (fasiglifam) –Preclinical and Clinical Safety Considerations. John Marcinak, Neila Smith, Juliana Oliveira, Nizar Smaoui, Mitchell Friedman, Francis Wolenski, Takashi Ohira, Yvonne Dragan, Takeda Pharmaceuticals

The potent GRP40 inhibitor, Fasiglifam (TAK-875), was being developed for the treatment of type 2 diabetes, but was terminated in phase 3 for consideration of safety due to liver signals. Nonclinical toxicology was not indicative of liver toxicity in the rat. In the dog, liver effects were observed at high doses with deposition of TAK-875 and its glucuronide in the biliary tract. Hepatobiliary transporters (Bsep, Mrps, and Ntcp) were inhibited at micromolar concentrations by TAK-875. In investigative single and multiple dose studies in mice, rats, and dogs (at >50X estimated human exposure), TAK-875 increased total bile acids. The increase in total bile acids included both conjugated and unconjugated bile acids as determined by liquid chromatography mass spectroscopy. In the rat, microscopic evidence of liver injury was not observed. In dog, plasma bile acid elevation preceded clinical chemistry evidence of liver injury. The clinical chemistry changes in the dog were coincident with the presence of portal/peri-portal granulomatous inflammation with intra-lesion crystal inclusions demonstrated to be TAK-875 and its glucuronide. While transporter inhibition may provide a susceptibility factor for TAK-875 in the dogs, the increase in bile acids or an alteration in bile composition may have impacted the low solubility limit of TAK-875 and its glucuronide. Clinical Phase 1 studies did not show a liver signal as defined by ALT>3XULN. Similarly, the incidence of ALT>3XULN in two Phase 2 studies (one in Japan and one in North/Latin America) at the TAK-875 25mg and 50mg doses was not above that in placebo. In a multi-center placebo-controlled Phase 3 trial for 24 weeks in Japan with TAK-875, the incidence of ALT increases greater than 3XULN was higher in the TAK-875 50 mg (5.5%, n=4) and 25 mg (4.8%, n=3) than in the placebo (1.5%, n=1). An ALT>10XULN and total bilirubin.3XULN was observed in one patient (2) with gallstones and adenomyomatosis. In the global phase 3 Cardiovascular Outcomes Trial, the incidence of ALT increases >3XULN, >5XULN, and >10XULN was 2.1, 1.3, and 0.3% respectively in the TAK-875 50mg group (n=1604) compared with 0.5, 0.1, and 0.1% in the placebo group (n=1603) at the time of the trial termination. One patient in the TAK-875 50 mg group had an ALT>3XULN and total bilirubin of 1.6XULN with no alternative etiology. An evaluation of the global phase 3 clinical data by three independent groups including the Data Monitoring Committee, the Liver Safety Evaluation Committee, the Executive Steering Committee as well as the Sponsor led to a termination of this program due to increased liver signals. The aggregated data that form the basis of the decision to terminate the program are being analyzed for a future publication, as is a pharmacogenomics study performed to provide a molecular understanding of those at risk for hepatotoxicity.