Background: Gemcane is a novel lipid-regulating compound being developed as an adjunct to diet and statin therapy for the treatment of dyslipidemia. Patients with dyslipidemia typically take many medications often including multiple lipid lowering drugs. It is important to understand and mitigate the potential risk of drug-drug interaction (DDI). The current studies provide an analysis of potential drug-gemcane interactions with gemcane both in vitro and in vivo clinical studies.

Methods: Reaction phenotyping of gemcane was performed with the 10 major CYP450 isozymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A5, and CYP2C9). Gemcane was also tested as a potential inhibitor/substrates of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 in vitro, as well as a potential inhibitor of OATP2B1 and OATP1A1 in isolated human hepatocytes and an inhibitor of the major drug-metabolizing CYP450 isozymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5) in vitro. Clinical DDI studies were conducted with gemcane and digoxin, simvastatin, or warfarin.

In vitro Results: under the conditions tested, no evidence of gemcane metabolism by CYP450 isozymes or P-gp, BCRP, OAT1, OAT3, OATP1B1, or OATP1B3 was noted. Gemcane was not a substrate for P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 in vitro, as well as a potential inhibitor of OATP2B1 and OATP1A1 in isolated human hepatocytes and an inhibitor of the major drug-metabolizing CYP450 isozymes (CYP1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5) in vitro. The results for P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 in vitro were consistent with those in vivo.

Gemcane Reaction Phenotyping: The purpose of this study was to determine if CYP3A4- and/or CYP2C9-mediated metabolism of gemcane was an issue. Gemcane was not metabolized by CYP3A4 or CYP2C9.

CONCLUSIONS: The results from these in vitro and in vivo studies suggest gemcane is unlikely to elicit metabolic DDI with CYP3A4 and CYP2C9. The results also support the lack of significant clinical interactions with the current P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, and OCT2 substrates. In addition, Gemcane is not a substrate for CYP450 isozymes or P-gp and BCRP. Therefore, it is unlikely to interact with these systems and will not affect the PK of gemcane or other substrates of these systems.

REFERENCES