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TITLE: FGF15 and FGF19 Induce Disparate FGFR4-Mediated Hepatocarcinogenicity *In-Vitro* and In Two Murine Models: Implications for Drug-Associated Carcinogenicity Risk Assessments

ABSTRACT BODY: Sponsorship - This study was sponsored by:(If this abstract was not sponsored please indicate) (Oral or Poster Submission): NGM Biopharmaceuticals, Inc.

PRESENTER: Lei Ling

AUTHORS/INSTITUTIONS: L. Ling, M. Zhou, D. Lindhout, J. Luo, M. Chen, H. Yang, M. Humphrey, V. Phung, K. Mondal, H. Matern, M. Learned, S. Rossi, A.M. DePaoli, H. Tian, NGM Biopharmaceuticals, S. San Francisco, California, UNITED STATES|

ABSTRACT BODY:

Abstract Body: Background and Aims: FGF19 is a regulator of bile acid (BA) synthesis in humans. However, FGF19 produces hepatocellular carcinoma (HCC) in transgenic mice and is linked to increased risk of HCC post-resection recurrence in humans. FGF15 is the rodent ortholog of human FGF19 with 50% amino acid (AA) homology and used in rodents to assess the pharmacologic and caricongenic activity of FGF19. Both FGF15 and FGF19 are potent inhibitors of Cyp7a1-mediated BA synthesis in rodents but the carcinogenicity risk of FGF15 is not well characterized. The hepatocarcinogenicity of FGF15 and FGF19 was evaluated in leptin receptor-deficient (*db/db)* mice after 24 wks or diet-induced obese (DIO) mice after 52 weeks of treatment. *In vitro* receptor interaction and activation studies were performed.

Methods: FGF15, FGF19 or control was dosed by long-term transgene expression using 1 dose of adeno-associated virus (AAV)-mediated gene delivery. Liver tissue was examined for tumors and liver weight at 24wks post-dose (db/db) or 52wks post-dose (DIO). Gene expression of HCC-related and cell proliferation markers were measured in liver tissue. FGFR4-Klothoβ (FGFR4-KLB) receptor complex binding was assessed with SPR assays and transfected rat L6 cells were used to assess receptor activation.

Results: FGF19 induced liver tumors in both models post-treatment at concentrations as low as 1 ng/ml (Figures 1a, 1b). In contrast, FGF15 failed to induce liver tumors at supraphysiologic concentrations and maintained normal liver weight and liver-body weight ratios. Liver tissue expression of Ki-67 (Figure 1c), α-fetoprotein, glypican-3, cyclin-a2, Ccnb1 and Ccnb2 were induced with FGF19 but not FGF15. Reduced activation of FGFR4-KLB receptor complex was only seen with FGF15, as measured by decreased expression of STAT-3 target genes. These differences may be mediated by AA sequences unique to FGF15.

Conclusions: Significant differences in hepatocellular proliferation and tumorigenesis were observed with FGF15 vs FGF19. These data demonstrate the potential challenges of assessing the risks of increased FGF19 levels in humans using FGF15 in rodent carcinogenicity models.