ABSTRACT FINAL ID: 198

TITLE: Anti-inflammatory and Antifibrotic Activity of NGM282, A Novel Variant of FGF19, in an Mdr2-Deficient Mouse Model of Primary Sclerosing Cholangitis

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

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ABSTRACT BODY:

Abstract Body: Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic inflammatory biliary disease characterized by periductal fibrosis and stricture formation. Recent data showed decreased expression and intraductular production of FGF19, which may worsen pre-existing inflammation and fibrosis. NGM282 is an engineered variant of FGF19 that inhibits Cyp7a1 but lacks the tumorigenic activity seen with FGF19. Mice deficient in phospholipid flippase multidrug resistant protein 2 (Mdr2-/-) are a preclinical model for PSC as they develop liver histopathology similar to human PSC. We studied FGF19 and NGM282 in Mdr2-/- mice to characterize the potential biologic activity in PSC. **Methods:** 12wk old Mdr2-/- mice with established hepatobiliary disease received 1 dose of adeno-associated virus carrying NGM282, FGF19 or control. Serum liver enzymes were analyzed at 4 and 24wks post-dose. Liver tissue was collected at 24wks and stained with Hematoxylin & Eosin and Sirius Red. **Results:** Significant decreases in alkaline phosphatase (ALP) were seen in male and female mice at 4wks with FGF19 (males=349±26 U/L to 107±16 U/L; females=565±49 U/L to 98±7 U/L; $p<0.001$) and NGM282 (male =343±18 U/L to 142±12 U/L; females=598±29 U/L to 130±7 U/L; $p<0.001$) treated mice. ALP was suppressed at 24wks with both FGF19 and NGM282 whereas increased in controls (males=331±21 U/L to 600±73 U/L; females=574±38 U/L to 1116 ±102 U/L). Marked reductions in serum ALT, AST, total bile acids liver weight were observed in both treatment arms. Histologic improvements in hepatic inflammation, bile duct hyperplasia and "onion skin" fibrosis were seen in both treatment arms vs controls (Figure 1). Hepatocellular karyomegaly, cytomegaly and lobular disorganization occurred primarily or only with controls. **Conclusions:** Ectopic expression of FGF19 or NGM282 significantly decreased hepatic injury, hepatic inflammation and biliary fibrosis in an mouse model of PSC, supportive of the biologic activity and therapeutic potential of NGM282 in human PSC.