FIBROSIS REGRESSION OBSERVED IN TREATMENT WITH FGF19 VARIANTS IN A DIET INDUCED MOUSE MODEL OF NASH IS PREDOMINANTLY MEDIATED BY FGFR4 ACTIVITY AND INDEPENDENT OF WEIGHT LOSS OR DECREASES IN HEPATIC STEATOSIS

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BACKGROUND

- Fibrosis growth factor 19 (FGF19) is an endocrine hormone produced in the liver in an FGF19/Klotho receptor (FGFR)-dependent manner.7
- Similarly, M52 is also an engineered analog of FGF19 which retains bile acid regulation via FGFR4-Klotho binding, reduces insulin-resistance and body weight-reduction metabolic activities as FGF19-GFP, but lacks the potential tumorigenic activity of FGFR3.

STUDY METHODS and DESIGN

- C57BL6/J mice (Jackson Laboratories, #000664, 9-week old) were placed on a high-fat, high-fructose, high-cholesterol diet (HFFCD, 40% fat, 22% fructose, 9% cholesterol) for 20 weeks to establish extensive liver fibrosis and NASH phenotype.

RESULTS

- DEL30 does not effect liver weight or body weight.
- Chow Recovery and M52 normalize liver weight

- M52 Normalizes ALT and AST and Reduces Markers of Liver Inflammation

- NGM1 is a common chronic liver disease associated with obesity, diabetes, and metabolic syndrome and has limited treatment options17

NASH and HFFCD Model

- There is also an increased risk of HCC in NASH patients, independent of the mechanism of action responsible for the improvements in histology observed with NGM128 patients

- Additional anti-fibrotic and anti-inflammatory activities of M52 support other mechanisms (such as FGFR1c activity) further contribute to the improvements in NASH-related liver disease and fibrosis

- These data have important implications for understanding the multiple mechanisms of action responsible for the improvements in histology observed with NGM128 patients

CONCLUSIONS

- Treatment of M52 and DEL30 results in fibrosis regression in diet induced model of NASH (HFFCD model)
- FGF4 signaling is a primary driver of FGF19-mediated fibrotic activity that is independent of weight loss or decrease in hepatic steatosis
- Additional anti-fibrotic and anti-inflammatory activities of M52 support other mechanisms (such as FGFR1c activity) further contribute to the improvements in NASH-related liver disease and fibrosis

DISCLOSURES

- This study is funded by NGM Biopharmaceuticals, Inc.
- Maria Deato, Brian Ko, Emily Snyder, Bernard Allan, and Hui Tian are employees and stockholders of NGM Biopharmaceuticals, Inc.

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