Metabolic, biochemical, histological, and transcriptomic effects of a long-acting FGF-21 analogue in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH

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Background & Aim

Fibroblast growth factor 21 (FGF-21) plays a key role in hepatic lipid metabolism and holds great promise as a therapeutic target for non-alcoholic steatohepatitis (NASH). The long-acting FGF-21 analogue efusiliberin has in a recent phase 2 clinical trial demonstrated promising efficacy for both NASH resolution and improvement in fibrosis stage as compared to placebo controls. The present study aimed to evaluate the therapeutic efficacy of the long-acting FGF21 analogue PF-05231023 in the GAN (Gubra-Amylin NASH) diet-induced obese (DIO) mouse model of NASH with hepatic fibrosis.

Improvement in NAFLD Activity Score and Fibrosis Stage

**Study outline**

**Improve in metabolic and biochemical parameters**

![Image](image_url)

**Figure 1. FGF21 (PF-05231023) improves hepatomegaly, biochemical parameters in GAN DIO-NASH mice.** (A) Body weight change relative to baseline (day 0). (B) Terminal body weight. (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver triglycerides. (F) Terminal liver total cholesterol. ***p<0.001, **p<0.01, *p<0.05 compared to corresponding CHOW vehicle control group (Dunnett test one factor linear model).

**Figure 2. FGF21 (PF-05231023) improves liver histopathological scores in GAN DIO-NASH mice.** Histopathological scores were determined by Gubra histopathological Objective Scoring Technique (HOST) deep learning-based image analysis. (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C) Comparison of liver weight (g). (D) Steatosis score (HE). (E) Number of inflammatory foci (HE). (F) Number of hepatocytes with lipid droplets (HE). (G) Adgre1 (% area). (H) Col1a1 (% area). (I) Col3a1 (% area). (J) Col5a3 (% area). (K) Col6a3 (% area). (L) Lgals3 (% area). (M) Mmp24 (% area). (N) Timp1 (% area). (O) Timp2 (% area).

**Figure 3. FGF21 (PF-05231023) improves quantitative liver histological markers in GAN DIO-NASH mice.** Histomorphometric assessments were performed by Gubra deep learning-based image analysis on scoring-associated variables (panel A) and counterstained hist image analysis (panel B). (A) NAFLD Activity Score (NAS). (B) Fibrosis stage. (C) Steatosis score (HE). (D) Number of inflammatory foci (HE). (E) Number of hepatocytes with lipid droplets (HE). (F) Adgre1 (% area). (G) Col1a1 (% area). (H) Col3a1 (% area). (I) Col5a3 (% area). (J) Col6a3 (% area). (K) Lgals3 (% area). (L) Mmp24 (% area). (M) Timp1 (% area). (N) Timp2 (% area).

**Figure 4. FGF21 (PF-05231023) suppresses inflammation-associated genes in GAN DIO-NASH mice.** (A) Principal component analysis (PCA) of samples based on top 500 most variable gene expression levels. (B) Heat maps depicting shared and separate differentially expressed genes in treatment groups. (C) Regulation of hepatic extracellular matrix (ECM) candidate genes (high fold change compared to DIO vehicle group) by blue color gradients indicate significantly (p<0.05) down regulated gene expression. White boxes indicate genes not significantly regulated compared to DIO vehicle group.

CONCLUSION

+ FGF21 (PF-05231023) reduces hepatomegaly, plasma ALT, liver triglycerides and liver total cholesterol.
+ FGF21 (PF-05231023) promotes ≥2-point significant improvement in NAFLD Activity Score.
+ FGF21 (PF-05231023) promotes 1-point significant improvement in Fibrosis Stage.
+ FGF21 (PF-05231023) reduces quantitative histomorphological markers of steatosis, inflammation and stellate cell activation.
+ FGF21 (PF-05231023) suppresses inflammation-associated gene expression.

**These findings agree with clinical findings, further highlighting clinical translatability of the GAN DIO-NASH mouse model.**