Background and Aims: Portal venous pressure may begin to rise due to steatosis-induced changes in sinusoidal homeostasis in early stages of NASH and may contribute to progression of fibrosis and portal hypertension.1 FGF21 is an endogenous hormone regulating carbohydrate, lipid and energy metabolism. FGF21 analogs improve liver and metabolic abnormalities in NASH. In a phase 1b/2a POC study in subjects with NASH, BIO89-100, a glycoPEGylated FGF21 analog, led to significant reductions in hepatic fat fraction (HFF) and liver volume (LV) by MRI-PDFF, with concurrent metabolic benefits and a favorable safety and tolerability profile. This post-hoc analysis assessed the effect of BIO89-100 on spleen volume (SV).

Methods: The trial enrolled 81 subjects with liver fat ≥10% by MRI-PDFF and biopsy-confirmed NASH or phenotypic NASH. Subjects were treated for 12 weeks in 6 cohorts (3, 9, 18 or 27mg QW; 18 or 36mg Q2W) or placebo. Key endpoints were safety, tolerability, pharmacokinetics, change in HFF by MRI-PDFF and liver and metabolic markers, and have been previously reported. SV was assessed by MRI at baseline, Day 50 and Day 92 in 16 BIO89-100-treated (pooled; 8 on 27 mg QW, 8 on 36 mg Q2W) and 18 placebo subjects.

Results: Median baseline (BL) characteristics for BIO89-100 subjects (N=16) and placebo subjects (N=18) were: age 47.6 vs 56.5 years, BMI 36.6 vs 33.5 kg/m2, ALT 53 vs. 29 IU/L, VCTE 8 vs 7.1 kPa, liver fat by MRI-PDFF 19.3% vs 19.7%; 56.3% vs 38.9% of subjects were male, and 25% vs 61% had T2DM. Median SV at BL was within normal limits: 232.6 (range 137.6 – 504.4) cm3 vs 170.9 (range 107.6 – 366.9) cm3. At BL, there were correlations between SV and LV (r=0.58), HOMA-IR (r=0.39), Adipo-IR (r=0.43), BMI (r=0.38) and VCTE score (r=0.40), and negative correlations between SV and HDL cholesterol (r=-0.48), adiponectin (r=-0.35) and platelet count (PC; r=-0.37). On day 92, reduced SV was observed in BIO89-100-treated subjects [percent change LS mean -11.8 vs -0.8 (p=0.002)]. Percent reduction in SV correlated with % reduction in HFF by MRI-PDFF (r=0.55), % reduction in liver fat volume (r=0.55), reduction in HOMA-IR (r=0.55) and % change in CK-18 (r=0.74); and absolute reduction in SV correlated with absolute change in ALT (r=0.48) and negatively correlated with PC (r=-0.75).

Conclusion: These preliminary data suggest that in non-cirrhotic NASH, a subclinical increase in SV, within the normal range, is associated with a worsening metabolic profile, increased liver stiffness and decreased PC. Normalization of liver fat and LV may be associated with decreased intrahepatic resistance and improved portal flow (PF), thus decreasing SV, and possibly improving insulin sensitivity. The role of SV measurement as a
non-invasive tool for assessment of PF and the clinical significance of subclinical changes in SV

Presentation: Sunday, June 12, 2022 12:30 p.m. - 2:30 p.m., Monday, June 13, 2022 1:18 p.m. - 1:23 p.m.

specifically measures bioactive BNP (BNPMS) and ANP (ANPMS). Relationships between bioactive NPs measured by mass spectrometry (MS) with BMI, race, and glucose metabolism are not well-understood.

Methods: We measured bioactive BNP and ANP using a novel UPLC-MS/MS assay in 26 veterans without heart failure, diabetes, or significant cardiac/pulmonary/renal/hepatic disease. We also determined BNP using conventional immunoassay (BNPia), age, sex, race, BMI, fasting glucose, and HbA1c. We assessed relationships of NPs with continuous variables using Spearman’s correlation and multivariable linear regression, and with categorical variables using Wilcoxon rank-sum.

Results: Among 26 veterans (aged 25-55, 69% male), 8 were lean (BMI 23.1 +/- 1.4 kg/m²) and 18 were obese (BMI 34 +/- 2.9 kg/m²). ANPMS was negatively associated with BMI (rs = -0.59, p = 0.0015). Moreover, when analyzed by BMI category, ANPMS was lower in obese compared with lean individuals (mean 113.9 +/- 74.9 vs. mean 220 +/- 173.7 pg/mL, respectively, p = 0.020).

BNPMS was lower in blacks; all 5 black individuals had undetectably low BNPMS (<5 pg/mL), whereas whites had a higher mean BNPMS (19.3 pg/mL, p = 0.011). BNPMS was negatively associated with fasting glucose (p = 0.03) in