administrated for 2 weeks. At the end of treatment, the degree of fibrosis was evaluated by hydroxyproline (HP) contents and sirius red staining. Liver tissue samples were submitted to qPCR to determine the expression of relevant markers for inflammation and fibrosis, and blood levels of fibrosis surrogate markers were measured by ELISA.

**Results:** In AMLN/TAA mice, HM15211 treatment significantly reduced HP content (~53.1% vs. Veh.). In addition, the expression of markers for hepatic inflammation (~92.8, ~34.7 and ~32.7% vs. Veh. for F4/80, MCP-1, and IL-6) and fibrosis (~53.9, ~41.4, and ~51.9% vs. Veh. for alpha-SMA, TIMP-1, and collagen1a1) was significantly reduced in HM15211 treated group. Similar reduction in blood levels of TIMP-1, PIINP and hyaluronic acid (HA) (~49.3, ~48.0, and ~49.1% vs. Veh., respectively) was also observed. In BDL model, HM15211 treatment showed greater reduction in HP content (~33.4 ~43.7% and ~21.9% vs. Veh for HM15211 and OCA), and fibrosis score (1.0, 1.75, and 1.7 for HM15211, OCA and vehicle) compared to obeticholic acid (OCA). Consistently, blood levels of TGF-beta, HA, and TIMP-1 were also significantly reduced by HM15211 treatment.

**Conclusion:** Based on the beneficial effects in AMLN/TAA and BDL mice, HM15211 may provide therapeutic effects for fibrosis as well as NASH. Human efficacy studies are ongoing to assess the clinical relevance of these findings.

**AS016**

**Combination therapy with a dual CCR2/CCR5 antagonist and a FGF21 analogue synergizes in ameliorating steatohepatitis and fibrosis**

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**Background and Aims:** With new drug targets emerging, combination therapies appear attractive to treat NASH and fibrosis. Dual chemokine receptor types 2 and 5 (CCR2/5) antagonists can improve fibrosis by reducing monocyte infiltration and altering macrophage subsets in the liver. FGF21 is a nonmitogenic hormone that is a key regulator of lipid and glucose metabolism. A PEGylated FGF21 analogue has been shown to improve steatosis, liver injury and fibrosis markers in NASH patients. We compared effects of combined therapy to single drug treatment in mouse models of acute and chronic liver injury.

**Method:** We measured serum CCL2 in 85 patients with biopsy-proven NALFD. We tested a CCR2/5 antagonist (BMS-687681, 45 mpk bid PO or 15 mpk bid in combination) and/or a PEG-FGF21 variant (PEG-FGF21v, BMS-986171, 0.6 mpk biw SC) in male C57BL/6j mice, subjected to either acute liver injury (single carbon tetrachloride injection, CCL2) or chronic steatohepatitis and fibrosis (choline-deficient, L-amino acid-defined high-fat diet (CDAHFD) for up to 12 weeks.

**Results:** In NALFD patients, CCL2 levels correlated with fibrosis severity. In acute liver injury, CCR2/5 antagonist treated mice had significantly lower numbers of circulating and hepatic Ly6C inflammatory monocytes and monocyte-derived macrophages (MoMfs). Upon PEG-FGF21v treatment, hepatic MoMF numbers remained unaffected, but ALT and hepatocellular necrosis were reduced. In chronic steatohepatitis, compound dosing was initiated after 6w of CDAHFD, and effects were assessed after either short- (2w) or long-term (6w) treatment. In both regimens, CCR2/5 antagonism reduced MoMF, inflammatory markers and hepatic fibrosis, whereas PEG-FGF21v reduced body weight, liver triglycerides, steatosis, and NASH activity. Combination treatment demonstrated additive benefits of both therapies regarding weight gain, hepatic fat, ALT levels and fibrosis, while combination showed even synergistic effects on NALFD activity score.

**Conclusion:** CCR2/5 antagonism blocks inflammatory monocytes infiltration, and treatment with an FG21 analogue has beneficial effects on metabolism and pathogenic drivers of NASH and fibrosis. Combined therapy ameliorates progressive steatohepatitis and fibrosis more effectively than single drug treatment, corroborating the therapeutic potential of combining these two approaches in patients with advanced NASH.

**AS017**

A polygenic risk score for progressive non-alcoholic fatty liver disease risk stratification

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**Background and Aims:** Noninvasive identification of patients with dysmetabolism at risk of nonalcoholic fatty liver disease (NAFLD), severe fibrosis and hepatocellular carcinoma (HCC) is a major unmet clinical need. Genetic predisposition plays a major role in determining progressive NAFLD. We previously developed a genetic risk score (GRS) estimating the inherited predisposition to accumulate liver fat based on common variants in PNPLA3, TM6SF2, MBOAT7 and GCKR. The aim of this study was to examine the accuracy of GRS to stratify the risk of NAFLD, severe fibrosis, and HCC in a multicenter cross sectional cohort.

**Method:** We considered 2021 individuals: 464 without liver disease, 1034 with histological NALFD without severe fibrosis, 275 with NALFD and severe fibrosis without HCC, and 248 with NAFLD-HCC. All were genotyped for the rs738406 (PNPLA3 1148M), rs58542926 (TM6SF2 1617 K), rs641738 C>T at MBOAT7 and rs1260326 (CCKR P446L). Genetic data were combined in the GRS, and association with disease risk was tested by multivariate logistic regression models, adjusted for age, sex, BMI, presence of diabetes (and fibrosis).

**Results:** In the overall cohort, GRS predicted NAFLD independently of confounders (p < 10^-11, OR for the upper quartile: 4.22, 95%CI 2.72-6.54), more robustly than the single variants. In patients with