further transcriptomic patient evaluation and possible evolution depending on sAXL levels.

Conclusion: sAXL levels reveals as a potential NAFLD-NASH transition marker, indicative of the initiation of liver inflammation and fibrosis before histological detection. Early treatment with bemcentinib prevented experimental NASH appearance, pointing to AXL antagonism as possible strategy for future clinical trials.

SAT007

Efficacy and safety of an acetyl CoA carboxylase inhibitor are improved in combination with PPAR agonists in a dyslipidemic rat model

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Background and Aims: Firsocostat (FIR), a liver-directed acetyl-CoA carboxylase inhibitor (ACCi) is under investigation in NASH patients with F3/F4 fibrosis. FIR reduces hepatic steatosis and liver biochemistry in NASH patients but raises plasma triglycerides (TG) in some patients with high baseline TG. ACCi combination (combo) with fenofibrate (Feno, a peroxisomal proliferator-activated receptor (PPAR) α agonist (ag)) mitigates the plasma TG increase. Here we evaluated the safety (plasma TG reduction) and efficacy (liver TG reduction) of ACCi combo with PPAR ag with different selectivity profiles: Feno, Elafibranor (Ela, PPARα/δ ag), Seladelpar (Sela, PPARδ ag) and Lanifibranor (Lani, pan PPAR ag).

Method: Male rats were fed a fast food diet containing high fat, cholesterol and sugar for 28 days and were treated with Vehicle (Veh) or PPAR ag from Day 8–28, and ACCi from Day 15–28. ACCi alone (30 mg/kg) was compared to ACCi combo with Feno (1, 5, 15 mg/kg), Ela (1, 3, 10, 30 mg/kg), Sela (0.2, 1, 5, 15 mg/kg) and Lani (1, 3, 10, 30 mg/kg) (n = 10/dose group). Top doses of PPAR ag were determined from the literature. Plasma TG (absolute and normalized to baseline TG per animal), and hepatic TG and gene expression were assessed.

Results: PPAR ag differentially lowered plasma TG (37–54%, Feno; 43–70%, Ela; 11–52%, >1 mg/kg Sela; 12%, 30 mg/kg Lani; p < 0.05 vs Veh) while ACCi raised plasma TG by 43–129% (p = 0.02 vs Veh) after 1 week of monotherapy. While addition of ACCi slightly raised plasma TG in the combo groups, they were maintained at or below baseline in animals receiving Feno, Ela, >5 mg/kg Sela and 30 mg/kg Lani. Hepatic Apoc3 expression (PPARα target) was reduced dose-dependently with Feno (26–74%), Ela (50–97%) and Sela (<27%), and unchanged with Lani (vs Veh). ACCi lowered liver TG by 41–49% (p < 0.05 vs Veh). Further reductions were seen in combo arms with 15 mg/kg Feno (63% vs Veh, p < 0.001) and >10 mg/kg Ela (64–76% vs Veh, p < 0.001). Liver TG in the Lani and Sela combo arms did not improve or showed a trend to dose-dependently increase respectively, compared to ACCi alone.

Conclusion: At least one dose of all PPAR ag tested in combo with ACCi maintained plasma TG at or below baseline, mitigating the ACCi-induced rise in plasma TG. However, while Feno and Ela improved efficacy of ACCi to reduce liver TG, Lani and Sela did not alter or worsened steatosis. These studies support the use of PPARα ag to improve efficacy and safety of FIR in NASH patients.

SAT008

PBI-4050 restores liver and adipose tissue metabolic homeostasis, and decreases fibrosis in a high-fat-diet mouse model of non-alcoholic fatty liver disease

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Background and Aims: Non-Alcoholic Fatty Liver Diseases (NAFLD), characterized by fatty acid and glucose metabolism dysregulation, has become a major global health concern. PBI-4050 is a free fatty acid transport inhibitor that reduces hepatic TG accumulation and improves liver and adipose tissue metabolic homeostasis.

Method: Male C57BL/6 mice (n = 10/group) were fed a high-fat diet for 12 weeks before being randomized to receive vehicle (saline, 0.9%) or PBI-4050 (100 mg/kg) via gavage for 6 weeks. Over this period, body weight, food intake, and serum parameters were monitored. Liver and adipose tissue TG content and gene expression were measured.

Results: PBI-4050 significantly reduced liver TG (p < 0.05 vs vehicle) and improved adipose tissue TG content (p < 0.01 vs vehicle). Liver and adipose tissue gene expression for lipogenic and gluconeogenic pathways was also improved (p < 0.05 vs vehicle).

Conclusion: PBI-4050 improves metabolic homeostasis in a high-fat diet-induced NASH model by reducing liver and adipose tissue TG accumulation, and improving metabolic gene expression.
acid mimetic with GPR40 agonist and GPR84 antagonist activities. It was previously shown to possess pleiotropic activities and to reduce fibrosis in different rodent models. PBI-4050 has also completed open-label, non-placebo controlled, phase II clinical trials for the treatment of Idiopathic Pulmonary Fibrosis and Alström syndrome. In the present study, we used a high-fat diet (HFD) mouse model to evaluate the efficacy of this compound in preventing NAFLD progression, metabolic dysregulation, and the development of fibrosis in liver and white adipose tissue (WAT).

**Method:** C57BL/6 mice were fed with either a standard or a high-fat diet for 14 weeks. Mice fed with the HFD were then treated or not with PBI-4050 (200 mg/kg, oral once a day) for 6 weeks. Clinical manifestations of NAFLD, including hepatic steatosis, ballooning and inflammation, were monitored. Moreover, levels of fibrosis, a sign of NAFLD progression, were evaluated in liver and WAT. Glucose and fatty acid metabolism were also analyzed. 1H-NMR hepatic metabolic studies were used to quantify liver metabolites. Effect of PBI-4050 on mitochondrial respiration and glycolysis were measured in vitro in HepG2 hepatocytes using a Seahorse XF96 analyser.

**Results:** Histological analysis revealed that PBI-4050 treatment led to a significant reduction of hepatic steatosis, ballooning and total NAFLD score. PBI-4050 also led to a reduction in interstitial fibrosis which correlated with decreased gene levels of Col1a1, Col3a1, Ctgf, Timp1 and Mmp2. In WAT, PBI-4050 significantly reduced immune cell infiltration and collagen deposition as well as expression of pro-fibrotic and inflammatory genes. Serum adiponectin levels were also increased by PBI-4050. Metabolomic study from liver extracts revealed that PBI-4050 restored normal levels of amino acids and energy-related metabolites that were dysregulated by HFD. Interestingly, endogenous levels of glucose and ATP was decreased while NAD+ was increased by treatment with PBI-4050. mRNA expression of uncoupling proteins (Ucp3 in liver and Ucp1 in WAT) were also increased by PBI-4050 suggesting that PBI-4050 could affect mitochondria and increase energy expenditure. Moreover, mitochondrial oxygen consumption and acidification rate were reduced in HepG2 hepatocytes by PBI-4050 treatment in vitro, while in the presence of palmitate we observed an increase in fatty acid oxidation.

**Conclusion:** These results indicate that PBI-4050 offers the potential as a novel therapy for NAFLD, diabetes and associated metabolic syndrome.

**SAT010**

**Intermittent hypoxia featuring the obstructive sleep apnea syndrome contributes to hepatosteatosis by upregulating the intrahepatic expression of fatty acid translocase CD36 and lipogenic genes**

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**Background and Aims:** Non-alcoholic fatty liver disease (NAFLD) comprises varied grades of hepatic lipid accumulation, inflammation, ballooning and fibrosis; the most severe cases result in cirrhosis and liver failure. Recent evidence has linked obstructive sleep apnea syndrome (OSAS) to hepatic lipid accumulation. As OSAS is featured by periods of intermittent hypoxia (IH) during sleep, it has been suggested that IH alters hepatic lipid metabolism and could contribute to NAFLD development in OSAS patients, but little is known about the molecular mechanisms underlying increased hepatic lipid accumulation due to IH. The aim of the present study was to elucidate the molecular mechanisms by which excessive lipid accumulation occurs within the liver in conditions of IH.

**Method:** Histopathology and triglyceride content were assessed in livers from mice submitted to an IH protocol. Furthermore, expression of genes related to lipid synthesis (Fasn, Scd1), β-oxidation (Cpt1a, Ppara), and fatty acid uptake (Cd36) was tested by real-time PCR, Western-blot and immunohistochemistry. In addition, prevalence of NAFLD was evaluated in 90 patients with clinical and polygraphic features of OSAS and in 30 subjects with normal lung function tests by using a blood-based metabolomic assay (OWLiver test) capable to discriminate between simple steatosis, NASH and normal liver. None of patients and controls studied drank more than 20 g of alcohol per day.