Combinations of an Acetyl Coenzyme-A Carboxylase Inhibitor, FXR Agonist, and GLP-1R Agonist Inhibit Fibrosis Progression in the Rat Choline-Deficient, L-Amino Acid–Defined, High-Fat Diet Model of Advanced Fibrosis

**Introduction**

- The combination of semaglutide (SEMA; glucagon-like peptide-1 receptor [GLP-1R] agonist) and cilofexor (CILO; farnesoid X receptor [FXR] agonist) and fibrostatin (FIR; acyl-coenzyme-A carboxylase inhibitor [ACCi]) is being investigated in patients with advanced fibrosis due to nonalcoholic steatohepatitis (NASH).
- SEMA is a GLP-1R agonist with many beneficial metabolic effects, such as improving glycemic control, increasing insulin sensitivity, and promoting weight loss; this reduces the influx of lipotoxic precursors, such as nonesterified fatty acids, from the periphery into the liver.
- In a 72-wk trial, 2 final trials in patients with NASH and fibrosis stages 1–3, SEMA promoted NASH resolution, with the highest response ratio observed in the SEMA 0.4 mg group (57% vs 20% in the placebo group).
- CILO is an intravenously active FXR agonist that reduces plasma fibroblast growth factor-19 levels, which reduces hepatic bile acid production, thereby improving hepatocyte health; FIR is a liver-targeted ACC-1/2 inhibitor that blocks de novo lipogenesis and increases fatty acid oxidation, thereby improving hepatic lipotoxicity.
- In a Phase 2 trial, in patients with advanced fibrosis (F3–4) due to NASH, treatment with CILO + FIR led to higher rates of fibrosis improvement (27%) vs placebo (11%) or other monotherapy (CICO: 12%, FIR: 12%) at Week 48.
- SEMA, CILO, and FIR target complementary mechanisms implicated in the pathogenesis of NASH, and the combination of these targets is hypothesized to provide greater histologic benefits, including fibrosis improvement and NASH resolution, rather than with a monotherapy approach.
- Furthermore, triple-combination SEMA + CILO + FIR therapy led to greater reductions in non-invasive assessments of liver steatosis and stiffness vs SEMA monotherapy over 24 wk in a Phase 2a study in patients with NASH.
- In the amylin liver NASH diet-induced mouse model, combinations of SEMA, CILO, and a FXR analog (GSK-843346 [ACC]) lowered liver fat, expression of fibrogenic markers, and nonalcoholic fatty liver disease activity score more than monotherapies; however, the mouse model developed mild–moderate fibrosis and may have limited utility in understanding the antifibrotic effects of the combinations.

**Objective**

To evaluate the effect of pairwise and triple combinations of SEMA, CILO, and ACCi on fibrosis progression in the rat choline-deficient, L-amino acid–defined, high-fat diet (CDHF) model of advanced fibrosis.

**Methods**

- **Introduction**: The combination of semaglutide (SEMA; glucagon-like peptide-1 receptor [GLP-1R] agonist) and cilofexor (CILO; farnesoid X receptor [FXR] agonist) and fibrostatin (FIR; acyl-coenzyme-A carboxylase inhibitor [ACCi]) is being investigated in patients with advanced fibrosis due to nonalcoholic steatohepatitis (NASH).
- **Objective**: To evaluate the effect of pairwise and triple combinations of SEMA, CILO, and ACCi on fibrosis progression in the rat choline-deficient, L-amino acid–defined, high-fat diet (CDHF) model of advanced fibrosis.
- **Methods**: The combination of semaglutide (SEMA; glucagon-like peptide-1 receptor [GLP-1R] agonist) and cilofexor (CILO; farnesoid X receptor [FXR] agonist) and fibrostatin (FIR; acyl-coenzyme-A carboxylase inhibitor [ACCi]) is being investigated in patients with advanced fibrosis due to nonalcoholic steatohepatitis (NASH).

**Results**

- **Target Engagement**:
  - Expected target engagement was observed across all groups (reduction in body weight with SEMA, reduction in hepatic Cyp1a1 expression with CILO, and increased Scap and Fasn expression with ACCi).

**Conclusions**

- **Combinations of SEMA, CILO, and ACCi almost completely halted fibrosis progression in the rat CDHF model, whereas monotherapies only had a partial effect on this parameter**.
- **Reductions in Ccl2+ area were similar to the trend observed in PSR area**.
- **Triple combination had greater effects on reducing eSMa+ area than the SEMA + CILO and CILO + ACC pairwise combimations**.

**Noninvasive Biomarkers of Fibrosis**

- **Combinations of SEMA, CILO, and ACCi almost completely halted fibrosis progression in the rat CDHF model, whereas monotherapies only had a partial effect on this parameter**.
- **Reductions in Ccl2+ area were similar to the trend observed in PSR area**.
- **Triple combination had greater effects on reducing eSMa+ area than the SEMA + CILO and CILO + ACC pairwise combimations**.

**Effects on Inflammation**

- **Similar to other endpoints, combinations had greater effects on immune-cell markers than monotherapies, with the triple combination resulting in numerically greater reductions than the pairwise combinations**.

**Antifibrotic Efficacy**

- **Representative PSR Images**
- **Representative CD68+ IHC Images**
- **Representative Galectin-3+ IHC Images**

**Summary**

- **Combinations of SEMA, CILO, and ACCi almost completely halted fibrosis progression in the rat CDHF model of NASH and fibrosis**.
- **The totality of data suggest that the triple (SEMA + CILO + ACCi) combination has a greater effect on reducing multiple endpoints than the pairwise combinations**.
- **These data support the ongoing clinical evaluation of the potential benefits of SEMA in combination with CILO and FIR in patients with advanced fibrosis due to NASH**.