THU455

Safety and Efficacy of the Farnesoid X Receptor Agonist Cilofexor in a Proof-of-Concept Study in Patients With Compensated Cirrhosis Due to Primary Sclerosing Cholangitis

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Introduction

- Primary sclerosing cholangitis (PSC) is a progressive liver disease without approved therapy
- Cilofexor (CILO) is a nonsteroidal farnesoid X receptor agonist being evaluated in the phase 3 PRIMIS trial of patients with PSC without cirrhosis
- A phase 2 placebo-controlled study of CILO demonstrated significant improvements in markers of cholestasis and liver injury[1]
- The safety and efficacy of CILO in patients with PSC and cirrhosis are unknown

Objectives

- To evaluate the safety and efficacy of escalating doses of CILO in patients with PSC and cirrhosis

Methods

Study Design

- Inclusion criteria: historical liver biopsy, abdominal imaging consistent with cirrhosis, FibroScan® (Echosens SA, Paris, France) ≥14.4 kPa, Enhanced Liver Fibrosis Test (ELF™; Siemens Healthcare GmbH, Erlangen, Germany) ≥11.3, or FibroTest (BioPredictive S.A.S, Paris) ≥0.75; platelet count ≥75,000/μL; and total bilirubin ≤2 mg/dL
- Exclusion criteria: decompensated liver disease, including ascites, hepatic encephalopathy, and variceal hemorrhage; Model for End-Stage Liver Disease (MELD) score >12 at screening; and Child-Pugh score >6 at screening
- Safety, liver biochemistry, and serum markers of fibrosis, cellular injury, and pharmacodynamic effects of CILO were evaluated

Results

Patient Characteristics*

	CILO: n=11
Age, y	48 (37, 56)
Men	6 (55)
White race	10 (91)
IBD	6 (55)
UDCA therapy	5 (46)
ALP, U/L	510 (269, 592)
GGT, U/L	344 (208, 455)
ALT, U/L	56 (37, 89)
Total bilirubin, mg/dL	1.1 (0.8, 1.5)
Fasting total bile acids, μM	26.1 (19.7, 52.9)†
Platelets, x10^3/μL	201 (113, 218)
ELF	10.4 (9.5, 12.6)
Transient elastography, kPa	18.0 (8.5, 67.6)
MELD	7 (6, 8)

*Data presented as median (interquartile range [IQR]) or n (%); †n=10 with bile acids above detection limit: 5 μM. ALP, alkaline phosphatase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; IBD, inflammatory bowel disease; UDCA, ursodeoxycholic acid.

Changes in Liver Biochemistries and Function at Week 12

Median Change at Week 12 (IQR)	CILO: n=11
ALP, U/L	-62 (-88, -11)
GGT, U/L	-147 (-288, -104)
ALT, U/L	-16 (-20, -2)
AST, U/L	-4 (-13, 7)
Total bilirubin, mg/dL	-0.1 (-0.4, 0.0)
Albumin, g/dL	-0.1 (-0.1, 0.2)
INR	0.0 (0.0, 0.1)

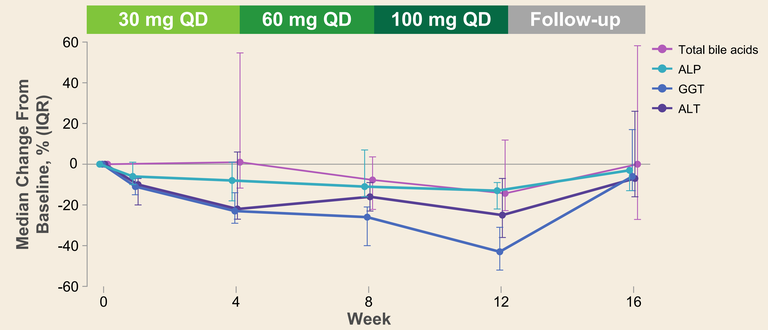
AST, aspartate aminotransferase; INR, international normalized ratio.

Changes in Noninvasive Markers of Fibrosis and Pharmacodynamic Activity at Week 12

Median Change at Week 12 (IQR)	CILO: n=11
Transient elastography, kPa	0.2 (-2.1, 2.6)
ELF	0.1 (-0.2, 0.6)
TIMP1, ng/mL	3.0 (-58.6, 22.1)
PIIINP, ng/mL	0.9 (0.0, 1.9)
Hyaluronic acid, ng/mL	4.5 (-23.7, 48.8)
Fasting FGF19, pg/mL	-13.4 (-30.5, 25.6)
Fasting C4, ng/mL	-2.60 (-6.32, -1.88)
Fasting total bile acids, μM	-4.3 (-5.6, 3.0)

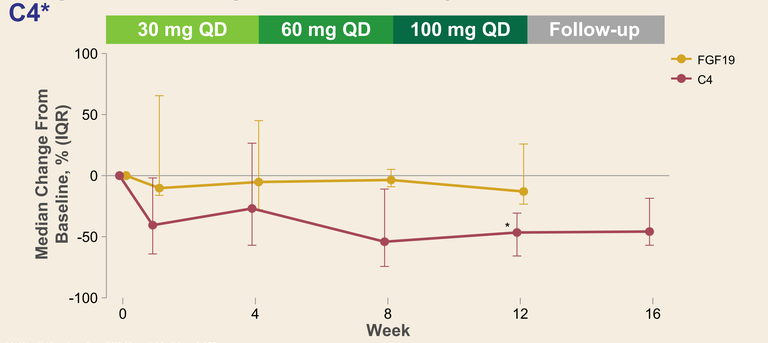
C4, complement component-4; FGF19, fibroblast growth factor-19; PIIINP, procollagen III N-terminal propeptide; TIMP1, tissue inhibitor of metalloproteinase-1.

Longitudinal Changes in Liver Biochemistry and Bile Acids*



*At Week 12 vs baseline: ALP, p=0.004; GGT, p=0.002; ALT, p=0.02; total bile acids, p=0.50.

Longitudinal Changes in Pharmacodynamic Markers FGF19 and C4*



*At Week 12 vs baseline: FGF19, p=1.00; C4, p=0.039.

Safety

- 1 patient prematurely discontinued treatment (patient decision)
  - No patients discontinued treatment due to pruritus
- No treatment-emergent serious adverse events or deaths occurred
- Grade ≥2 treatment-emergent adverse events occurred in 5 patients (45%)
- Pruritus was reported in 8 patients (73%), 7 of whom had Grade 1 or 2

Conclusion

- In this proof-of-concept study of patients with compensated cirrhosis due to PSC, escalating doses of CILO over 12 wk were well tolerated, and improved markers of cholestasis and liver injury

Reference: **1.** Trauner M, et al. Hepatology 2019;3:788-801. **Acknowledgments:** We thank the patients for their participation. This study was funded by Gilead Sciences, Inc. Editing and production assistance were provided by BioScience Communications, NY, New York, USA, funded by Gilead.