Efruxifermin (EFX), a long-acting FGF21 analog as a therapy for NASH

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Lipotoxicity in hepatocytes drives NASH pathology and progression.
Removing lipotoxic fat in hepatocytes via weight loss resolves steatohepatitis within a year, but fibrosis regression takes ≥5 years

**Weight Loss Through Lifestyle Modification Significantly Reduces Features of Nonalcoholic Steatohepatitis**

Eduardo Vilar-Gomez,1,2 Yadina Martinez-Perez,3 Luis Calzadilla-Bertot,1 Ana Torres-Gonzalez,1 Bienvenido Gra-Oramas,3 Licet Gonzalez-Fabian,3 Scott L. Friedman,4 Moises Diago,2 and Manuel Romero-Gomez2

**Bariatric Surgery Provides Long-term Resolution of Nonalcoholic Steatohepatitis and Regression of Fibrosis**

Guillaume Lassailly,1,2 Robert Caiazzo,3,4 Line-Carolle Ntandja-Wandji,1 Viviane Gnenmi,5 Gregory Baud,6,7 Helene Verkindt,6 Massih Ningarhari,1,2,4 Alexandre Louvet,1,2 Emmanuelle Leteurtre,5 Violeta Raverdy,5,4 Sébastien Dharancy,1,2 François Pattou,7,8 and Philippe Mathurin1,2

**Evolution of Fibrosis**

- 55% of patients who lost ≥10% of body weight did not achieve fibrosis improvement at 52 weeks.
Pharmacology-driven reduction in lipotoxic fat in hepatocytes and improvement in glycemic control stabilizes but does not significantly improve fibrosis.

A Placebo-Controlled Trial of Subcutaneous Semaglutide in Nonalcoholic Steatohepatitis


**A Resolution of NASH with No Worsening of Liver Fibrosis**

- Semaglutide, 0.1 mg (N=57): 49/57 (86%)
- Semaglutide, 0.2 mg (N=59): 32/59 (54%)
- Semaglutide, 0.4 mg (N=56): 43/56 (77%)
- Placebo (N=58): 33/58 (57%)

**B Improvement in Liver Fibrosis Stage with No Worsening of NASH**

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Body weight — %
- −4.84
- −8.91
- −12.51
- −0.61

Glycated hemoglobin level among patients with type 2 diabetes — percentage points
- −0.63
- −1.07
- −1.15
- −0.01

**semaglutide did not improve liver fibrosis in patients with NASH cirrhosis after 48 weeks**
Ph2a BALANCED study evaluated efruxifermin (EFX), an Fc-FGF21 analog, in two cohorts: “Main Study” (F1-F3, moderate-to-advanced fibrosis) and “Cohort C” (F4, compensated cirrhosis).

Main Study

- **Screening**

- **Biopsy-Confirmed NASH**

- **Randomisation**

- **Screening**

- **Placebo (n=20)**

- **28mg EFX (n=20)**

- **50mg EFX (n=20)**

- **70mg EFX (n=20)**

- **16 WEEKS**

- **Safety Follow-Up**

- **Responder Paired Biopsies**

- **Post-Treatment**

- **Liver Biopsy**

- **MRI-PDFF**

Subjects achieving ≥30% relative reduction of hepatic fat at week 12 eligible for post-treatment biopsy; biopsy scoring based on NASH CRN

Cohort C

- **Screening**

- **Biopsy-Confirmed NASH**

- **Randomisation**

- **Screening**

- **Placebo (n=10)**

- **50 mg EFX (n=20)**

- **16 WEEKS**

- **FibroScan**

- **Liver Biopsy**

- **Fibrosis Biomarkers (ELF, Pro-C3)**

- **Post-Treatment**

EFX reduced lipotoxic liver fat substantially, such that LFC was normalized (≤5%) in almost half of treated patients within 12 weeks.

### Proportion of Patients Achieving Fat Reduction Thresholds

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N=20)</th>
<th>28mg (N=16)</th>
<th>50mg (N=17)</th>
<th>70mg (N=15)</th>
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<tbody>
<tr>
<td>Relative Reduction in Liver Fat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30%</td>
<td>10%</td>
<td>100%**</td>
<td>100%***</td>
<td>100%***</td>
</tr>
<tr>
<td>≥50%</td>
<td>5%</td>
<td>69%**</td>
<td>100%***</td>
<td>93%***</td>
</tr>
<tr>
<td>≥70%</td>
<td>5%</td>
<td>50%</td>
<td>53%**</td>
<td>80%***</td>
</tr>
<tr>
<td>Normalization of Liver Fat Content</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5%</td>
<td>5%</td>
<td>25%</td>
<td>53%**</td>
<td>67%**</td>
</tr>
</tbody>
</table>

* p<0.05, ** p<0.01, *** p<0.001, versus placebo (ANCOVA)

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**Endpoints**

- Placebo
- 28mg
- 50mg
- 70mg

**Absolute Reduction (%)**

- Placebo: 0%
- 28mg: -12.3***
- 50mg: -13.4***
- 70mg: -14.1***

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Fibrosis improved by ≥1 stage in half of pair-biopsied F1-F3 patients, and by 2 stages in half of F2-F3 patients, after just 16 weeks of EFX treatment.
In patients with compensated cirrhosis, EFX reduced fibrotic area and increased normal hepatocyte area, as scored by AI-based method (PathAI).
In patients with F1-F3 NASH, EFX consistently reduced Pro-C3 below the threshold associated with increased risk of ≥F2 fibrosis in NASH patients.
Synthesis of two major components of ECM in soft-tissue fibrosis, type-I and -III collagen, are correlated at baseline, particularly in patients with advanced fibrosis-to-cirrhosis.

**F1-F3 NASH (Main Study)**

- Spearman R = 0.500
- P < 0.0001

**F4 NASH (Cohort C)**

- Spearman R = 0.593
- P < 0.001

<table>
<thead>
<tr>
<th></th>
<th>Spearman R</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>F1</td>
<td>0.256</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>F2</td>
<td>0.612</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>F3</td>
<td>0.566</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>F4</td>
<td>0.644</td>
<td>&lt;0.001</td>
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</tbody>
</table>
Across all patients (F1-F4) in BALANCED, EFX appears to reduce synthesis of collagen-I and collagen-III synthesis in a concerted fashion.
C3M, a marker of collagen-III degradation, likely increases relative to soft-tissue collagen mass, leading to a shift in balance of collagen turnover from synthesis to degradation.
Antifibrotic activity of EFX in patients with NASH appears consistent with preclinical demonstration of FGF21’s antifibrotic activity

- ER stress\(^1\) and oxidative stress\(^2\) induce FGF21 *in vitro*, and diverse hepatic stressors (alcohol\(^3\), fructose\(^4\), acetaminophen\(^5\), protein restriction\(^6\)) induce FGF21 *in vivo*
- FGF21 up-regulates pathways associated with protecting against these stressors,\(^1-6\) as well as suppressing induction of pro-apoptotic pathways\(^1\)

- FGF21 improves fibrosis independent of metabolic etiology:
  - Suppresses human, rat HSC activation and collagen expression *in vitro*\(^7,8,9\)
  - Restores apoptosis and inhibits proliferation of activated rat HSC *in vitro*\(^9\)
  - Inhibits fibrogenesis in chemically-induced liver fibrosis\(^8,9,10\)
  - Protects the exocrine pancreas from cerulein-induced pancreatitis and fibrosis\(^11\)
  - Protects airway epithelia from bleomycin-induced pulmonary fibrosis\(^12\)
  - Protects the heart against oxidative damage, fibrosis, and cardiac dysfunction\(^13,14,15\)

Presence and resolution of underlying metabolic insult is not required for antifibrotic activity of FGF21

\(^13\)Zhang X et al. (2019) Heart Fail Rev 24:1005-17.
Acknowledgments

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