Phase 2b SYMMETRY Readout
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High Risk of Mortality Associated with Cirrhosis Due to NASH

Survival Free of Liver Transplantation

Cumulative Survival (%)

Follow-up (years)

~50% 5-year mortality without liver transplant for F4 patients

Landscape for Cirrhosis Due to NASH: 
Placebo-Corrected Fibrosis Improvement With No Worsening of NASH

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo-Corrected Fibrosis Improvement With No Worsening (NASH)</th>
<th>By Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 (Semaglutide)</td>
<td>2.4mg (n=47) -20%</td>
<td>2.4mg (n=47) -18%</td>
</tr>
<tr>
<td>ASK-1 (Selonsertib)</td>
<td>6mg (n=351) 0% 18mg (n=354) 1%</td>
<td>6mg (n=351) 0% 18mg (n=354) 1%</td>
</tr>
<tr>
<td>Peg-FGF21 (Pegbelfermin)</td>
<td>20mg (n=37) 40mg (n=39) -7%</td>
<td>20mg (n=37) 40mg (n=39) -7%</td>
</tr>
<tr>
<td>FGF19 (Aldafermin)</td>
<td>1% 2% 6% (n=42) 8% (n=55)</td>
<td>1% 2% 6% (n=42) 8% (n=55)</td>
</tr>
<tr>
<td>FXR (Obeticholic acid)</td>
<td>1% 2% 10% (n=306)</td>
<td>1% 2% 10% (n=306)</td>
</tr>
<tr>
<td>LOXL-2 (Simtuzumab)</td>
<td>0% 5% 8% (n=75) 700mg (n=79)</td>
<td>0% 5% 8% (n=75) 700mg (n=79)</td>
</tr>
</tbody>
</table>

Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to NASH reporting either ≥1-stage fibrosis improvement and no worsening of NASH (semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders.

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted.
Landscape for Cirrhosis Due to NASH: Placebo-Corrected NASH Resolution

Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to NASH reporting either ≥ 1-stage fibrosis improvement and no worsening of NASH (semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥ 1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders.


Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. No head-to-head clinical trials have been conducted.
Key Inclusion Criteria1
- F4 NASH
- T2D or 2 of 4 components of metabolic syndrome

Phase 2b Primary Endpoint
- ≥1 Stage Fibrosis Improvement with no Worsening of NASH

Key Secondary Efficacy Endpoints
- NASH Resolution
- Fibrosis Markers
- Lipoproteins
- Glycemic Control
- Weight Change
- Liver Injury Markers

36 Weeks
- Placebo (N=61)
- EFX 28mg (N=57)
- EFX 50mg (N=63)

60-Week Long-Term Follow-Up
- Placebo
- EFX 28mg
- EFX 50mg

Screening Liver Biopsy
- Week 36 Liver Biopsy
- Week 96 Liver Biopsy

1 All patients had biopsy-proven compensated cirrhosis (fibrosis stage 4) due to definitive NASH or cryptogenic cirrhosis presumed secondary to NASH. Subjects with cryptogenic cirrhosis were limited to approximately 20% of the total study population.
**Week 36 Patient Disposition & Key Analysis Sets**

- **Randomized (N=182)**
  - Randomized Not Dosed
    - EFX (N=1)
  - Discontinued Prior to Week 36 (N=26)
    - Other (11)
      - EFX (N=9)
      - Placebo (N=2)
    - Due to AEs (15)
      - EFX (N=13)
      - Placebo (N=2)
  - Biopsies Not Collected
    - EFX (N=2)

- **Dosed (N=181)**
  - Dosed (N=181)
  - Full Analysis Set / Safety Set – All subjects who were randomized and received at least one dose of study drug

- **Completed Week 36 (N=155)**
  - Completed Week 36 (N=155)

- **Biopsies Collected (N=153)**
  - Biopsies Collected (N=153)
  - Placebo (N=57)
  - 28mg (N=46)
  - 50mg (N=50)

- **Primary Endpoint**
  - Liver Biopsy Analysis Set
    - All subjects who have Baseline & Week 36 liver biopsy results

- **Secondary Histological Endpoints**
  - Liver Biopsy Analysis Set (Definitive NASH\(^1\) Only)
    - Excludes all subjects with cryptogenic cirrhosis

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\(^1\) NAS ≥ 3 with a score of ≥ 1 for each of steatosis, inflammation and ballooning
## Baseline Demographics

<table>
<thead>
<tr>
<th>Parameter (Mean)</th>
<th>Placebo (N=61)</th>
<th>EFX 28mg (N=57)</th>
<th>EFX 50mg (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>61</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>62</td>
<td>68</td>
<td>70</td>
</tr>
<tr>
<td>Definitive NASH (%) / Cryptogenic Cirrhosis (%)</td>
<td>74 / 26</td>
<td>79 / 21</td>
<td>83 / 17</td>
</tr>
<tr>
<td>Enhanced Liver Fibrosis (ELF) Score</td>
<td>10.4</td>
<td>10.6</td>
<td>10.5</td>
</tr>
<tr>
<td>Pro-C3 (μg/L) (Generation 2 ELISA)</td>
<td>132</td>
<td>142</td>
<td>147</td>
</tr>
<tr>
<td>Liver Stiffness by VCTE (FibroScan) (kPa)</td>
<td>24.7</td>
<td>24.1</td>
<td>24.5</td>
</tr>
<tr>
<td>FAST Score</td>
<td>0.60</td>
<td>0.60</td>
<td>0.62</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT) (U/L)</td>
<td>40.3</td>
<td>40.1</td>
<td>38.4</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST) (U/L)</td>
<td>35.5</td>
<td>37.1</td>
<td>37.5</td>
</tr>
<tr>
<td>Type 2 Diabetes (%)</td>
<td>82</td>
<td>81</td>
<td>78</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8</td>
<td>6.8</td>
<td>6.6</td>
</tr>
<tr>
<td>Baseline Use of GLP-1 (%) / Sulfonylurea / (%) Insulin (%)</td>
<td>28 / 20 / 16</td>
<td>21 / 21 / 11</td>
<td>32 / 30 / 21</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>143</td>
<td>148</td>
<td>159</td>
</tr>
<tr>
<td>Statin Use (%)</td>
<td>52</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>102</td>
<td>99</td>
<td>95</td>
</tr>
</tbody>
</table>
Consensus Reading of Biopsies: Rigorous Approach to Histopathology Based on FDA Input to Minimize Variability

Key Features of EFX Biopsy Analysis Plan

- Biopsies independently scored by two pathologists, with a third pathologist available to adjudicate in absence of consensus
- Pathologists underwent protocol-specific training to align on NASH-CRN scoring interpretation
- Pathologists blinded to subject, treatment, and sequence
- Pathologists did not review Week 36 biopsy slides with the corresponding patient’s baseline biopsy slides as a comparison
- Previously interpreted baseline biopsy slides were randomly presented to pathologists throughout the study duration to minimize the potential for sequence bias

Consensus Biopsy Analysis Flow Chart
**Trend to Improvement for Primary Endpoint**

(≥1 Stage Improvement in Fibrosis and No Worsening of NASH)

**Fibrosis Improvement ≥1 Stage Without Worsening of NASH\(^1\) at Week 36\(^2\)**

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Baseline Fibrosis Stage</th>
<th>Week 36 Fibrosis Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject A</td>
<td>EFX 28mg</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Subject B</td>
<td>EFX 50mg</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F1</td>
</tr>
<tr>
<td>Subject C</td>
<td>EFX 28mg</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2</td>
</tr>
<tr>
<td>Subject D</td>
<td>EFX 50mg</td>
<td>F4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2</td>
</tr>
</tbody>
</table>

\(^1\) Per FDA guidance, this endpoint is defined as: "Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score) and no worsening of steatohepatitis (defined as no increase in NAS for ballooning, inflammation, or steatosis)."


Four Patients Experienced Three- or Two-Stage Fibrosis Improvement Without Worsening of NASH at Week 36

Source Data: Liver Biopsy Analysis Set; Topline preliminary data
Statistically Significant Improvement on NASH Resolution for Both Doses

** p<0.01, versus placebo (Cochran–Mantel–Haenszel test [CMH])

1 Per FDA guidance, resolution of steatohepatitis is defined as “absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis”


2 Results for ITT Analysis: Placebo, 24%; 28mg, 51% (p<0.05, versus placebo [CMH]); EFX 50mg, 47% (p<0.05, versus placebo [CMH])

Source Data: Liver Biopsy Analysis Set (definitive NASH only); Topline preliminary data
Combined Histological Endpoint

Fibrosis Improvement ≥1 Stage AND NASH Resolution¹ at Week 36

Placebo  n=46  9%
EFX 28mg  n=38  21%
EFX 50mg  n=42  14%

¹ Per FDA guidance, this endpoint is defined as: “Both resolution of steatohepatitis and improvement in fibrosis…. Resolution of steatohepatitis is defined as absent fatty liver disease or isolated or simple steatosis without steatohepatitis and a NAS score of 0–1 for inflammation, 0 for ballooning, and any value for steatosis…. Improvement in liver fibrosis greater than or equal to one stage (NASH CRN fibrosis score)”
FDA Draft Guidance, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018), p.7-8
Landscape for Cirrhosis Due to NASH: Placebo-Corrected Fibrosis Improvement With No Worsening of NASH

Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to NASH reporting either ≥ 1-stage fibrosis improvement and no worsening of NASH (EFX, semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥ 1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders


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Landscape for Cirrhosis Due to NASH: Placebo-Corrected NASH Resolution

Includes results from publicly reported placebo-controlled studies in patients with compensated cirrhosis due to NASH reporting either ≥ 1-stage fibrosis improvement and no worsening of NASH (EFX, semaglutide, selonsertib, pegbelfermin, obeticholic acid) or only ≥ 1-stage fibrosis improvement (aldafermin, simtuzumab); numerical values represent percent responders.

**p<0.01, versus placebo (CMH)

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Evidence of Anti-Fibrotic Activity: Analysis of ELF Score and its Components

LS Mean Change From Baseline to Week 36

**ELF Score**
- Placebo: N=58
- EFX 28mg: N=47
- EFX 50mg: N=51

**ELF Component: P3NP (ug/L)**
- Placebo: N=58
- EFX 28mg: N=47
- EFX 50mg: N=51

**ELF Component: TIMP1 (ug/L)**
- Placebo: N=58
- EFX 28mg: N=47
- EFX 50mg: N=51

**ELF Component: Hyaluronic Acid (ug/L)**
- Placebo: N=58
- EFX 28mg: N=47
- EFX 50mg: N=51

**Evidence of Anti-Fibrotic Activity: Analysis of ELF Score and its Components**

Source Data: Full Analysis Set (non-missing values only, no imputation); Topline preliminary data

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Additional Non-Invasive Fibrosis Markers

### LS Mean Change From Baseline to Week 36

#### Pro-C3 (µg/L): Generation 2 ELISA
- Placebo: N=58, -16
- EFX 28mg: N=47, -59 ***
- EFX 50mg: N=50, -49 ***

*** p<0.001, versus placebo (MMRM¹)

#### Liver Stiffness (kPa)²
- Placebo: N=58, -4.3 **
- EFX 28mg: N=47, -3.6 *
- EFX 50mg: N=51, -3.8 **

* p<0.05, ** p<0.01, versus baseline (MMRM)

#### FAST Score
- Placebo: N=57, -0.1
- EFX 28mg: N=47, -0.2 **
- EFX 50mg: N=50, -0.3 ***

** p<0.01, *** p<0.001, versus placebo (MMRM¹)

¹ Mixed Model Repeated Measures; ² Measured by FibroScan

Source Data: Full Analysis Set (non-missing values only, no imputation); Topline preliminary data
Early and Sustained Statistically Significant Improvements in Markers of Liver Injury

**ALT**

LS Mean Change from Baseline (U/L)

Baseline: 38-40 U/L

-5 U/L

Placebo 28mg 50mg

-11 U/L

-13 U/L

Statistically significant improvements from baseline observed for platelet counts for both EFX groups

**AST**

LS Mean Change from Baseline (U/L)

Baseline: 35-38 U/L

-3 U/L

-10 U/L

-12 U/L

Mixed Model Repeated Measures

Source Data: Full Analysis Set; Topline preliminary data
## Safety & Tolerability Summary

<table>
<thead>
<tr>
<th>TEAE Overview</th>
<th>Placebo (N=61)</th>
<th>EFX 28mg (N=57)</th>
<th>EFX 50mg (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE Leading to Death</td>
<td>1 (2%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Treatment-Emergent Serious Adverse Event (SAE)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>6 (10%)</td>
<td>9 (16%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Drug-related TEAE Leading to Discontinuation</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Diarrhea (Grades 1-3)</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>2&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Pneumonia

<sup>b</sup> None of the SAEs were deemed by the investigator to be drug-related

<sup>c</sup> Retching/vomiting; palpitation/feeling jittery

<sup>d</sup> Soft feces/nausea; hypersensitivity (rash); injection site rash

Source Data: Safety Set; Topline preliminary data
Safety & Tolerability (continued)

### Most Frequent (≥15%) Drug-Related TEAEs

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=61)</th>
<th>EFX 28mg (N=57)</th>
<th>EFX 50mg (N=63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>9 (15%)</td>
<td>10 (18%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (12%)</td>
<td>11 (19%)</td>
<td>18 (29%)</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>3 (5%)</td>
<td>7 (12%)</td>
<td>17 (27%)</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>5 (8%)</td>
<td>8 (14%)</td>
<td>13 (21%)</td>
</tr>
</tbody>
</table>

### Vital Signs and Bone Mineral Density

No clinically meaningful changes were observed for heart rate or diastolic blood pressure. At Week 36, increases of 4-7mmHg in systolic blood pressure were observed in the EFX dose groups.

At Week 36, small reductions in bone mineral density were observed for the EFX dose groups in the lumbar spine region (≤1%) and the femoral neck region (2-3%).
Statistically Significant Improvements Observed in Insulin Sensitivity

**LS Mean Change From Baseline to Week 36**

**C-Peptide (%)**
- Placebo: N=59
- EFX 28mg: N=47
- EFX 50mg: N=48

**Insulin (mIU/L)**
- Placebo: N=59
- EFX 28mg: N=47
- EFX 50mg: N=48

**HbA1c (%)**
- Placebo: N=58
- EFX 28mg: N=47
- EFX 50mg: N=50

1 Relative percent change from baseline
* p<0.05, ** p<0.01, versus placebo (MMRM)

1 Absolute change from baseline, %
†† p<0.01, versus baseline (MMRM)

Source Data: Full Analysis Set; Topline preliminary data
Statistically Significant Improvements Observed in Lipoprotein Profile

**LS Mean Percent Change From Baseline to Week 36**

- **Triglycerides**
  - Placebo: 0%
  - EFX 28mg: -23***
  - EFX 50mg: -29***

- **Non-HDL Cholesterol**
  - Placebo: 0%
  - EFX 28mg: -3
  - EFX 50mg: -10†††

- **LDL Cholesterol**
  - Placebo: 0%
  - EFX 28mg: -1
  - EFX 50mg: -5

- **HDL Cholesterol**
  - Placebo: 0%
  - EFX 28mg: +1
  - EFX 50mg: +24***

*** p<0.001, versus placebo (MMRM)
** p<0.01, versus placebo (MMRM) ††† p<0.001, versus baseline (MMRM)

Source Data: Full Analysis Set; Topline preliminary data

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Statistically Significant Increases Observed in Adiponectin:
PD Marker for EFX’s Action on Adipose Tissue

Adiponectin, LS Mean Percent Change From Baseline to Week 36

*** p<0.001, versus placebo (MMRM)
Trend Toward Weight Loss for 50mg EFX Dose Group

Body Weight, LS Mean Percent Change From Baseline to Week 36

-0.8
-0.8
-1.4 †

Placebo
N=58

EFX 28mg
N=47

EFX 50mg
N=51

† p<0.05 versus baseline (MMRM)

Source Data: Full Analysis Set; Topline preliminary data
Looking Ahead

Three Planned Parallel Randomized, Placebo-Controlled Clinical Trials

- Biopsy confirmed F2-F3 NASH
- Primary endpoint: ≥ 1-stage fibrosis improvement AND resolution of NASH
- 28 and 50mg EFX

- Non-invasively diagnosed NASH/NAFLD
- Primary endpoint: safety & tolerability

Design to be finalized following discussion with FDA

Screening for SYNCHRONY Histology and SYNCHRONY Real-World has begun
First patient enrollments expected by December 2023