Phase 2b HARMONY Study Results
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Evaluating EFRUXIFERMIN (EFX), An Fc-FGF21 Fusion Protein

Statistically Significant Effects after 24 Weeks

Fibrosis Improvement
NASH Resolution
Fibrosis Improvement and NASH Resolution
HARMONY Trial Design: Pre-Cirrhotic (F2-F3) NASH

Key Inclusion Criteria
- F2-F3 NASH
- NAS ≥4
- Liver Fat (MRI-PDFF) ≥8%

Phase 2b Primary Endpoint
- ≥ 1-stage fibrosis improvement without worsening of NASH

24 Weeks

Placebo

EFX 28mg

EFX 50mg

Long-Term Safety Follow-Up

Placebo

EFX Continuation Dose TBD

Key Secondary Efficacy Endpoints
- NASH Resolution & No Worsening of Fibrosis
- Lipoproteins
- Glycemic Control
- Weight Change
- MRI-PDFF
- Liver Injury Markers

Regulatory Requirements for Phase 3 Trials
- FDA accepts one of two endpoints for Phase 3 registrational trials: (1) Fibrosis improvement ≥1 stage & no worsening of NASH or (2) NASH resolution and no worsening of fibrosis
- EMA requires both endpoints to be met for marketing approval

1 FDA Draft Guidance, Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment (2018)
2 EMA, Draft Reflection paper on regulatory requirements for the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH) (2018)
**Week 24 Patient Disposition & Analysis Sets**

- **Randomized (N=128)**
  - Randomized Not Dosed
    - EFX (N=2)
  - Discontinued Prior to Week 24 (N=11)
    - Due to AEs
      - EFX (N=5)
    - Administrative
      - EFX (N=5)
      - Placebo (N=1)
  - Biopsies Not Collected
    - EFX (N=1); Placebo (N=1)

- **Dosed (N=126)**
  - Biopsies Collected (N=113)
    - Placebo (N=41)
    - 28mg (N=38)
    - 50mg (N=34)

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**Key Analysis Sets**

- **Full Analysis Set** – All subjects who were randomized
- **Safety Set** – All subjects who received at least one dose of study drug
- **Biomarker Analysis Set** – All subjects who have baseline and on-study biomarker measurement at given timepoint
- **Liver Biopsy Analysis Set** – All subjects who have Baseline and Week 24 liver biopsy results

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## Baseline Demographics

<table>
<thead>
<tr>
<th>Parameter (Mean)</th>
<th>Placebo (N=43)</th>
<th>EFX 28mg (N=42)</th>
<th>EFX 50mg (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>55</td>
<td>57</td>
<td>52</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>63</td>
<td>69</td>
<td>53</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>108</td>
<td>104</td>
<td>103</td>
</tr>
<tr>
<td>Type 2 Diabetes (%)</td>
<td>65</td>
<td>76</td>
<td>70</td>
</tr>
<tr>
<td>Fibrosis Stage (% F3)¹</td>
<td>70</td>
<td>64</td>
<td>63</td>
</tr>
<tr>
<td>Enhanced Liver Fibrosis (ELF) Score</td>
<td>9.8</td>
<td>9.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Pro-C3² (μg/L)</td>
<td>16.5</td>
<td>15.3</td>
<td>18.4</td>
</tr>
<tr>
<td>Liver Stiffness by VCTE³ (FibroScan) (kPa)</td>
<td>15</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Hepatic Fat Fraction by MRI-PDFF⁴ (%)</td>
<td>17.1</td>
<td>18.5</td>
<td>17.5</td>
</tr>
<tr>
<td>NAFLD Activity Score (NAS)</td>
<td>5.4</td>
<td>5.1</td>
<td>5.6</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT) (U/L)</td>
<td>62</td>
<td>50</td>
<td>63</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST) (U/L)</td>
<td>57</td>
<td>42</td>
<td>52</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8</td>
<td>6.8</td>
<td>6.7</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>170</td>
<td>158</td>
<td>154</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dL)</td>
<td>94</td>
<td>96</td>
<td>111</td>
</tr>
</tbody>
</table>

¹ All patients either fibrosis stage 2 (F2) or stage 3 (F3); ² Procollagen 3 N-Terminal Propeptide; ³ Vibration-controlled transient elastography; ⁴ Magnetic Resonance Imaging Proton Density Fat Fraction
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
• No paired biopsy reads (i.e., pre- and on-treatment biopsies not read side-by-side)
Both EFX Doses Achieved Statistical Significance on Primary Endpoint (Fibrosis Improvement)

Fibrosis Improvement ≥1 Stage & No Worsening of NASH\(^1\) at Week 24

- Placebo: 20% (N=41)
- EFX 28mg: 39%* (N=38)
- EFX 50mg: 41%* (N=34)

\(^1\) Improvement in liver fibrosis greater than or equal to one stage and no worsening of NASH (defined as no increase in NAS for ballooning, inflammation, or steatosis)

* \(p<0.05\), versus placebo (Cochran–Mantel–Haenszel test [CMH])

Source Data: Liver Biopsy Analysis Set
EFX Fibrosis Improvement in Context: Pre-Cirrhotic NASH (≥1 Stage Improvement in Fibrosis and No Worsening of NASH)

By Reported Effect Size (Treatment Minus Placebo)

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

Placebo Rate

EFX Effect Sizes

HARMONY Placebo Rate

1 Baseline and Week 24 biopsies available; 2 End-of-study biopsy available with no major protocol deviations; 3 Missing biopsies were imputed as non-responders; 4 Completed 36 weeks of treatment and had end-of-study biopsy; 5 End-of-study biopsy available.

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Both EFX Doses Achieved Statistical Significance on Key Secondary Endpoint (NASH Resolution)

1 NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning

\* p<0.01, \** p<0.001, versus placebo (CMH)

Source Data: Liver Biopsy Analysis Set
EFX NASH Resolution in Context: Pre-Cirrhotic NASH (NASH Resolution and No Worsening of Fibrosis)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Phase</th>
<th>F3 Resolution</th>
<th>Duration</th>
<th>Analysis</th>
<th>Readers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efruxifermin</td>
<td>Phase 2b (F2-F3)</td>
<td>66%</td>
<td>24 Wks / Completers¹</td>
<td>Consensus Readers</td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Phase 2b (F2-F3)</td>
<td>72 Wks / ITT²</td>
<td>Consensus Readers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanifibranor</td>
<td>Phase 2b (F1-F3)</td>
<td>% F3 Not Reported</td>
<td>24 Wks / Completers³</td>
<td>Single Reader</td>
<td></td>
</tr>
<tr>
<td>Resmetirom</td>
<td>Phase 2 (F1-F3)</td>
<td>54%</td>
<td>36 Wks / Completers⁴</td>
<td>Single Reader</td>
<td></td>
</tr>
<tr>
<td>Obeticholic Acid</td>
<td>Phase 3 (F2-F3)</td>
<td>72 Wks / ITT²</td>
<td>Consensus Readers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pegozafermin</td>
<td>Phase 1b/2a (F2-F3)</td>
<td>65%</td>
<td>20 Wks / Completers⁵</td>
<td>Single Reader</td>
<td></td>
</tr>
</tbody>
</table>

Note: These data are derived from different clinical trials at different points in time, with differences in trial design and patient populations. As a result, cross-trial comparisons cannot be made, and no head-to-head clinical trials have been conducted.

¹ Baseline and Week 24 biopsies available; ² Missing biopsies were imputed as non-responders; ³ End-of-study biopsy available with no major protocol deviations; ⁴ Completed 36 weeks of treatment and had end-of-study biopsy; ⁵ End-of-study biopsy available.

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Both EFX Doses Achieved Statistical Significance on Composite Endpoint (Fibrosis Improvement and NASH Resolution)

Source Data: Liver Biopsy Analysis Set

1 Improvement in liver fibrosis greater than or equal to one stage
2 NAS score of 0 or 1 for lobular inflammation and a score of 0 for ballooning
  ** p<0.01, *** p<0.001, versus placebo (CMH)
Magnitude of Reduction and Normalization of Liver Fat Comparable to Phase 2a BALANCED Study¹

Source Data: MRI-PDFF Analysis Set (All subjects who have Baseline and Week 24 liver fat measurements)

¹ The Phase 2a BALANCED study was a 12-week randomized clinical trial in patients with F1-F3 NASH
Rapid and Sustained Statistically Significant Improvements in Markers of Liver Injury

** ALT, LS Mean Percent Change from Baseline **

- Placebo
- EFX 28mg
- EFX 50mg

** AST, LS Mean Percent Change from Baseline **

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

¹ Mixed Model Repeated Measures

Source Data: Full Analysis Set
Statistically Significant Reductions in Non-Invasive Markers Reflect Histological Improvement in Fibrosis

**Pro-C3 (µg/L)**

Placebo: -5.1***
EFX 28mg: -5.2***
EFX 50mg: +0.1

*** p<0.001, versus placebo (MMRM)

**ELF Score**

Placebo: -0.7***
EFX 28mg: -0.6***
EFX 50mg: -0.1

*** p<0.001, versus placebo (MMRM)

**Liver Stiffness by FibroScan (kPa)**

Placebo: -2.6†
EFX 28mg: -4.3**
EFX 50mg: -4.3

** p<0.01, versus placebo (ANCOVA)
† p<0.01, versus baseline (ANCOVA)

Source Data: Biomarker Analysis Set (Pro-C3 and ELF); Full Analysis Set (Liver Stiffness) (non-missing values only, no imputation)
# Treatment-Emergent Adverse Events (TEAE)

<table>
<thead>
<tr>
<th>TEAE Overview</th>
<th>Placebo (N=43)</th>
<th>EFX 28mg (N=40)</th>
<th>EFX 50mg (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE Leading to Death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Drug-Related Serious Adverse Event (SAE)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TEAE Leading to Discontinuation</td>
<td>0 (0%)</td>
<td>2 (5%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (7%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most Frequent (≥15%) Drug-Related TEAEs</th>
<th>Placebo</th>
<th>EFX 28mg</th>
<th>EFX 50mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>6 (14%)</td>
<td>14 (35%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (12%)</td>
<td>10 (25%)</td>
<td>14 (33%)</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>2 (5%)</td>
<td>7 (18%)</td>
<td>10 (23%)</td>
</tr>
<tr>
<td>Frequent Bowel Movements</td>
<td>1 (2%)</td>
<td>8 (20%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Injection Site Erythema</td>
<td>5 (12%)</td>
<td>6 (15%)</td>
<td>7 (16%)</td>
</tr>
<tr>
<td>Injection Site Bruising</td>
<td>1 (2%)</td>
<td>6 (15%)</td>
<td>3 (7%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> (1) Esophagitis  
<sup>b</sup> There were three additional non-drug-related SAEs: (1) Edema; (2) Covid-19; (3) Pancreatitis  
<sup>c</sup> (1) Increased appetite & weight gain; (2) diarrhea  
<sup>d</sup> (1) Esophagitis & vomiting; (2) Nausea; (3) Lymphadenopathy (not drug-related)

Source Data: Safety Set
Clinically Meaningful Improvements Observed in Glycemic Control and Insulin Sensitivity, Particularly in Patients with T2D

LS Mean Change From Baseline to Week 24²

**HbA1c(%)¹**

<table>
<thead>
<tr>
<th>T2D Subset</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>EFX 28mg</td>
<td>-0.5%*</td>
</tr>
<tr>
<td>EFX 50mg</td>
<td>-0.5%*</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>T2D Subset</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>EFX 28mg</td>
<td>-0.5%*</td>
</tr>
<tr>
<td>EFX 50mg</td>
<td>-0.4*</td>
</tr>
</tbody>
</table>

* p<0.05, versus placebo (MMRM); † p<0.05, versus baseline (MMRM)

**C-Peptide³**

<table>
<thead>
<tr>
<th>T2D Subset</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
</tr>
<tr>
<td>EFX 28mg</td>
<td>-17%**</td>
</tr>
<tr>
<td>EFX 50mg</td>
<td>-22%**</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>0.0</td>
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<tr>
<td>EFX 28mg</td>
<td>-17%**</td>
</tr>
<tr>
<td>EFX 50mg</td>
<td>-22%**</td>
</tr>
</tbody>
</table>

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

¹ Absolute change from baseline, %; ² Patients remained on diabetic medications; ³ Relative percent change from baseline

Source Data: Biomarker Analysis Set
Significant Improvements Observed in Lipoprotein Profile

LS Mean Change From Baseline to Week 24 (%)

**Triglycerides**
- Placebo: N=42
- EFX 28mg: N=35
- EFX 50mg: N=35

**LDL Cholesterol**
- Placebo: N=42
- EFX 28mg: N=35
- EFX 50mg: N=35

**Non-HDL Cholesterol**
- Placebo: N=42
- EFX 28mg: N=35
- EFX 50mg: N=35

**HDL Cholesterol**
- Placebo: N=42
- EFX 28mg: N=35
- EFX 50mg: N=35

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Source Data: Full Analysis Set, non-missing values only, no imputation

*** p<0.001, versus placebo (MMRM)
** p<0.01, versus placebo (MMRM)
* p<0.05, versus placebo (MMRM)
Weight Loss Observed for 50mg EFX Dose Group

Body Weight, LS Mean Change at Week 24 (kg)

- Placebo: N=42, -0.6
- EFX 28mg: N=37, -0.2
- EFX 50mg: N=36, -2.9††

†† p<0.01, versus baseline (MMRM)

Source Data: Full Analysis Set, non-missing values only, no imputation
EFX: A Potentially Foundational NASH Therapy

ADDRESSING ALL CORE ASPECTS OF NASH PATHOGENESIS IN A SINGLE TREATMENT

FIBROSIS IMPROVEMENT AND NASH RESOLUTION

AFTER 24 WEEKS

LIVER HEALTH IMPROVEMENT

HEALTHY METABOLISM RESTORATION

NASH RESOLUTION