Efruxifermin is Associated With Improved Glucose Metabolism in Patients With NASH and Type 2 Diabetes

Juan Frias¹, Reshma Shringarpure², Erik Tillman², Chen Hu³, Erica Fong², Brittany de Temple², Timothy Rolph², Andrew Cheng², Kitty Yale² and Stephen A. Harrison⁴

¹ National research Institute, Los Angeles, CA ² Akero Therapeutics, South San Francisco, CA ³ MedPace, Inc, Cincinnati, OH, ⁴ Pinnacle Clinical Research, San Antonio, TX
Disclosures

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Speaker Bureau: Eli Lilly, Merck, Sanofi
Background and Aims

- One-third of patients with type 2 diabetes (T2D) are estimated to have NASH, therefore, the ability to further improve glycemic control in this patient population is a desirable attribute for future NASH therapies.

- Efruxifermin (EFX) is a long-acting Fc-FGF21 fusion protein being developed as a therapeutic for NASH.

- The BALANCED study\(^1\) was a randomized, double-blind, placebo-controlled study in patients with NASH and fibrosis stage 1-3, treated for 16 weeks with once weekly (QW) placebo or EFX 28, 50, or 70 mg.
  - QW dosing was supported by a Phase 1b study in T2D\(^2\) where markers of glucose metabolism improved with QW dosing, but not with Q 2-week dosing.

- Following 16 weeks of treatment, EFX demonstrated robust reductions in liver fat content (including normalization of liver fat in approximately half of all EFX-treated patients), as well as improvements in markers of liver injury, fibrosis, and lipid and glucose metabolism\(^1\).

The aim of this analysis was to evaluate the effects of EFX on markers of glucose metabolism in patients with NASH and in the subgroup with T2D (N=41).

### Demographics and baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Randomized Patients&lt;sup&gt;1&lt;/sup&gt; (N=80)</th>
<th>Patients with Type 2 Diabetes&lt;sup&gt;2&lt;/sup&gt; (N=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>52</td>
<td>54</td>
</tr>
<tr>
<td>% Female Sex</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>% Hispanic or Latino Ethnicity</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>% Type 2 Diabetes</td>
<td>51</td>
<td>100</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.34</td>
<td>6.96</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>103.5</td>
<td>104.7</td>
</tr>
<tr>
<td>BMI (kg/m&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>37.56</td>
<td>38.1</td>
</tr>
<tr>
<td>% F2 or F3</td>
<td>64</td>
<td>66</td>
</tr>
<tr>
<td>Alanine Aminotransferase (ALT) (U/L)</td>
<td>56</td>
<td>54</td>
</tr>
<tr>
<td>Aspartate Aminotransferase (AST) (U/L)</td>
<td>40</td>
<td>41</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>186</td>
<td>201</td>
</tr>
<tr>
<td><strong>Select Background Medications, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>38</td>
<td>71</td>
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<tr>
<td>Sulfonylureas</td>
<td>13</td>
<td>24</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
<td>9</td>
<td>15</td>
</tr>
<tr>
<td>Lipid-lowering medications (primarily statins)</td>
<td>37</td>
<td>54</td>
</tr>
</tbody>
</table>

<sup>1</sup> Full Analysis Set, F1-F3 (all subjects randomized into the BALANCED main study);  <sup>2</sup> FAS, T2D subgroup
Dose-dependent increases in adiponectin, a pharmacodynamic marker of FGFR1c activation, with efruxifermin

LS Mean Change in Adiponectin From Baseline to Week 16 (%)

All Patients (N=80)

Type 2 Diabetes Patients (N=41)

* p<0.05, ** p<0.01, *** p<0.001, versus placebo (ANCOVA)
Dose-dependent improvements in HbA1c with efruxifermin

LS Mean Change in HbA1c From Baseline to Week 16 (%)

All Patients (N=80)
Mean Baseline HbA1c=6.34%

Type 2 Diabetes Patients (N=41)
Mean Baseline HbA1c=6.96%

Source Data: Full Analysis Set; FAS Type 2 Diabetes Subgroup
Efruxifermin improved insulin sensitivity

LS Mean Change in C-Peptide From Baseline to Week 16 (%)

All Patients (N=80)

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean Change (Week 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>+21%</td>
</tr>
<tr>
<td>28mg</td>
<td>-24%</td>
</tr>
<tr>
<td>50mg</td>
<td>-22%</td>
</tr>
<tr>
<td>70mg</td>
<td>-29%</td>
</tr>
</tbody>
</table>

Type 2 Diabetes Patients (N=41)

<table>
<thead>
<tr>
<th>Group</th>
<th>LS Mean Change (Week 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5%</td>
</tr>
<tr>
<td>28mg</td>
<td>-27%</td>
</tr>
<tr>
<td>50mg</td>
<td>-28%</td>
</tr>
<tr>
<td>70mg</td>
<td>-29%</td>
</tr>
</tbody>
</table>

* * p<0.05, versus placebo (ANCOVA)

Source Data: Full Analysis Set; FAS Type 2 Diabetes Subgroup
Change in body weight following treatment with efruxifermin

LS Mean Change in Body Weight From Baseline to Week 16 (％)

- EFX enhanced insulin sensitivity without gain in body weight, and rather, demonstrated a trend for reduction in body weight

Source Data: Full Analysis Set; FAS Type 2 Diabetes Subgroup
Efruxifermin improved lipoprotein profile

**LS Mean Change From Baseline to Week 16 (mg/dL)**

- **Triglycerides**
  - Placebo (N=14)
  - 28mg EFX (N=7)
  - 50mg EFX (N=10)
  - 70mg EFX (N=10)

- **HDL Cholesterol**
  - Placebo (N=14)
  - 28mg EFX (N=7)
  - 50mg EFX (N=10)
  - 70mg EFX (N=10)

- **Non-HDL Cholesterol**
  - Placebo (N=14)
  - 28mg EFX (N=7)
  - 50mg EFX (N=10)
  - 70mg EFX (N=10)

- EFX restored a healthy lipid profile in NASH patients with T2D

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

SUMMARY

Half of the NASH patients with F1-F3 fibrosis randomized in BALANCED study had T2D
• >70% of T2D patients were on metformin and ~15% were on GLP-1 receptor agonists

Following 16 weeks of treatment, EFX resulted in:
• Reduction in HbA1c
• Improvement in insulin sensitivity
• Trend to reduce body weight
• Improved lipoprotein profile

Safety profile of the T2D subgroup was comparable to that of the overall study population\(^1\)
• The most frequent treatment emergent adverse events were mild to moderate GI events
• Two patients on EFX 70 mg experienced Grade 1 hypoglycemia
• One patient with T2D had an SAE of acute pancreatitis and was discontinued from the study

CONCLUSIONS: Once-weekly EFX (28 to 70 mg) improved markers of glucose control, insulin sensitivity, and lipoprotein profile in patients with NASH and type 2 diabetes following 16 weeks of treatment.

\(^1\)Harrison et al 2021. Nature Medicine, In Press