Aldafermin (NGM282) Produces Greater Anti-Fibrotic Response in Patients with Nonalcoholic Steatohepatitis and Advanced Fibrosis

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Disclosure

[Guy Neff]
I disclose the following financial relationship(s) with a commercial interest:

• **Advisory Board/Consultant**: Auxillium Pharmaceuticals
• **Grant/Research Support**: Ecosens
• **Stock/Shares**: NA
Aldafermin, FGF19 analogue, Impacts the Key Mechanisms of NASH Pathogenesis

**Aldafermin (FGF19 Analogue)\(^1\)**

- FGFR4/KLB
- FGFR1c/KLB

- Insulin Sensitization
- Reduce Toxic Fatty Acids
- Reduce De Novo Lipogenesis
- Reduce Bile Acid Production

**Metabolic Dysregulation**
- Insulin Resistance, Toxic Fatty Acids

**Bile Acid Dysregulation**
- Elevated Bile Acids Exacerbate Injury

**Resulting Impact on Disease Progression in the Liver**
- Liver Fat STEATOSIS
- Immune Response INFLAMMATION
- Hepatic BALLOONING
- FIBROSIS


Aldafermin was previously known as NGM282 or M70
### Aldafermin Phase 2 NASH Program Overview

<table>
<thead>
<tr>
<th>Status</th>
<th>Completed&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Completed&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Completed&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>12 Weeks</td>
<td>24 Weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldafermin Dose (# Patients)</td>
<td>Placebo (27)</td>
<td>3 mg (27)</td>
<td>6 mg (28)</td>
<td>0.3 mg (23)</td>
</tr>
</tbody>
</table>

#### KEY ENDPOINTS/ Assessment Measures

- **NON-INVASIVE MEASURES**
  - STEATOSIS: % Liver Fat Content (LFC) (MRI-PDFF)
  - INFLAMMATION: ALT/AST (Biomarkers)
  - BALLOONING

- **HISTOLOGY (Biopsy)**
  - FIBROSIS: ELF/PRO-C3 (Biomarkers)
  - BILE ACIDS: C4<sup>4</sup> (Biomarker)

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1 Harrison et al., Lancet 2018;391:1174-1185; 2 Rinella et al., J Hepatol 2019;70:735-744; 3 Harrison et al., Hepatology. 2020;71:1198-1212; 4 C4: 7α-hydroxyl-4-cholesten-3-one
Cohort 4: A 24-Week Phase 2 Study of Aldafermin in Patients with Biopsy-Proven NASH

- **Key inclusion criteria include:**
  - Biopsy-confirmed NASH with NAS ≥ 4 (1 point in each component); stage 2 or 3 liver fibrosis (F2 or F3 by NASH CRN criteria)
  - Absolute liver fat content (LFC) ≥ 8% by MRI-PDFF
  - ALT > 19 IU/L in females, ALT > 30 IU/L in males

- **Primary endpoint:** change from baseline in absolute LFC (as measured by MRI-PDFF) at W24
- **Secondary and exploratory endpoints** include liver histology, ALT, AST and biomarkers of fibrosis at W24
- Rosuvastatin (ROS 20 mg) started at W2 if low-density lipoprotein cholesterol (LDL-C) rise of 10 mg/dL observed

<table>
<thead>
<tr>
<th>Safety population</th>
<th>N=78</th>
<th>Aldafermin : placebo (2:1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy population</td>
<td>N=77</td>
<td>At least one dose and valid post-dose efficacy value</td>
</tr>
<tr>
<td>Liver histology population</td>
<td>N=72</td>
<td>Valid, non-missing biopsy at baseline and W24</td>
</tr>
</tbody>
</table>
Cohort 4 final analysis presented this morning by Dr. Stephen Harrison

Abstract Number: 0072
Abstract Title: FINAL ANALYSIS OF A 24-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY OF ALDAFERMIN (NGM282) IN PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS
Presentation Type: Oral presentation, Parallel Session
Presenting Author: Dr. Stephen Harrison
Session Title: Parallel 9: NAFLD and NASH: Therapeutics
Session Date and Time: Sunday, November 15, 2020, 10:30 AM

→ Current presentation focuses on subpopulations of patients with NASH CRN fibrosis Stage 2 (F2) vs Stage 3 (F3) at baseline
## Patient Baseline Demographics and Characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Placebo (N=25)</th>
<th>Aldafermin 1 mg (N=53)&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.1 (9.7)</td>
<td>53.0 (12.1)</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>9 / 16</td>
<td>27 / 26</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>102.5 (29.7)</td>
<td>99.8 (20.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.8 (9.0)</td>
<td>35.8 (6.3)</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>114.3 (17.0)</td>
<td>111.9 (15.4)</td>
</tr>
<tr>
<td>Type 2 Diabetes, n (%)</td>
<td>16 (64%)</td>
<td>32 (60%)</td>
</tr>
<tr>
<td>NAFLD Activity Score (NAS)</td>
<td>5.4 (1.0)</td>
<td>5.7 (1.1)</td>
</tr>
<tr>
<td>Fibrosis stage (F2 / F3)</td>
<td>15 / 10</td>
<td>29 / 24</td>
</tr>
<tr>
<td>Liver Fat Content (% by MRI-PDFF)</td>
<td>18.5 (6.8)</td>
<td>18.0 (5.9)</td>
</tr>
<tr>
<td>Alanine aminotransferase, ALT (IU/L)</td>
<td>55.1 (29.6)</td>
<td>73.3 (39.6)</td>
</tr>
<tr>
<td>Aspartate aminotransferase, AST (IU/L)</td>
<td>44.3 (23.7)</td>
<td>54.5 (27.4)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>34.5 (16.7)</td>
<td>31.7 (12.5)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>95.0 (31.6)</td>
<td>95.1 (31.0)</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>167.7 (119.2)</td>
<td>194.2 (164.3)</td>
</tr>
<tr>
<td>Pro-C3 (ng/mL)</td>
<td>17.1 (7.0)</td>
<td>17.5 (8.4)</td>
</tr>
</tbody>
</table>

<sup>1</sup> One patient did not have any post-baseline measurements and was excluded from efficacy analysis as pre-specified in the statistical analysis plan; Liver histology population (aldafermin n=50; placebo n=22)
## Patient Characteristics by Fibrosis Stage at Baseline

<table>
<thead>
<tr>
<th></th>
<th>F2 at Baseline (n=44)</th>
<th>F3 at Baseline (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.5 (11.8)</td>
<td>57.3 (9.6)**</td>
</tr>
<tr>
<td>Female/Male</td>
<td>23/21</td>
<td>19/15</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>102.2 (26.3)</td>
<td>98.7 (20.5)</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>36.9 (8.1)</td>
<td>35.0 (5.9)</td>
</tr>
<tr>
<td>LFC (% by MRI-PDFF)</td>
<td>19.6 (6.4)</td>
<td>16.4 (5.3)*</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>69.2 (40.7)</td>
<td>65.4 (32.6)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>51.2 (26.4)</td>
<td>51.7 (26.9)</td>
</tr>
<tr>
<td>PRO-C3 (ng/mL)</td>
<td>15.6 (8.5)</td>
<td>20.3 (7.3)*</td>
</tr>
<tr>
<td>NAS</td>
<td>5.3 (1.2)</td>
<td>5.8 (1.0)</td>
</tr>
<tr>
<td><strong>Steatosis</strong></td>
<td>2.0 (0.9)</td>
<td>2.0 (0.8)</td>
</tr>
<tr>
<td><strong>Ballooning</strong></td>
<td>1.5 (0.5)</td>
<td>1.8 (0.4)*</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>1.8 (0.4)</td>
<td>2.0 (0.5)</td>
</tr>
</tbody>
</table>

→ Compared to F2 patients, F3 patients were older, had lower liver fat content, higher PRO-C3 levels, and more ballooning on biopsy

LFC, liver fat content as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)

**P<0.01, *P<0.05 vs F2**
Patients Receiving Aldafermin Achieved Liver Fat Response (≥5% Absolute Reduction) Irrespective of Baseline Fibrosis Stage

≥ 5% Reduction in Absolute Liver Fat Content

→ Compared to F2 patients, F3 patients appeared to have lower placebo response rate in LFC reduction (≥ 5% absolute LFC↓)

1 Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
Patients Receiving Aldafermin Achieved Liver Fat Response (≥30% Relative Reduction) Irrespective of Baseline Fibrosis Stage

≥ 30% Relative Reduction in Liver Fat Content¹

F2 at Baseline

Placebo (n=15)  Aldafermin (n=29)

Patients (%)  38% 74%  Δ = 36%

F3 at Baseline

Placebo (n=10)  Aldafermin (n=23)

Patients (%)  12% 56%  Δ = 44%

→ Compared to F2 patients, F3 patients appeared to have lower placebo response rate in LFC reduction (≥ 30% relative LFC↓)

¹ Liver fat content (LFC) as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
Aldafermin Produced Greater Placebo-Subtracted Anti-Fibrotic Response in F3 Patients than in F2 Patients

Fibrosis Improvement ≥ 1 Stage with No Worsening of NASH\(^1\)

\[\Delta = 13\%\]  \hspace{1cm}  \Delta = 30\%

\[\text{Patients (\%)}\]

\begin{array}{c|c|c}
  & F2 at Baseline & F3 at Baseline \\
  \hline
  \text{Patients (\%)} & 60\% & 60\% \\
  \hline
  \text{F2 at Baseline} & 44\% & 30\% \\
  \hline
  \text{Placebo} (n=13) & 31\% & 0\% \\
  \text{Aldafermin} (n=27) & \Delta = 13\% & \text{(n=9)} \\
  \hline
  \text{Placebo} (n=9) & \text{(n=23)} & \text{(n=23)} \\
  \hline
\end{array}

→ Compared to F2 patients, F3 patients appeared to have lower placebo response rate in fibrosis improvement

\(^1\) Defined as patients who have an improvement in liver fibrosis by ≥1 stage with no worsening of NASH (no worsening of steatosis, lobular inflammation or hepatocyte ballooning grade) from baseline to W24 (not powered for statistical significance)
**Aldafermin Produced Greater Placebo-Subtracted Anti-Fibrotic Response in F3 Patients than in F2 Patients**

Subpopulation: Patients Who Achieved ≥30% Relative Reduction in LFC

**Fibrosis Improvement ≥ 1 Stage with No Worsening of NASH**

<table>
<thead>
<tr>
<th>F2 at Baseline</th>
<th>F3 at Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% Placebo (n=5)</td>
<td>46% Aldafermin (n=13)</td>
</tr>
<tr>
<td>45% Aldafermin (n=20)</td>
<td>0% Placebo (n=1)</td>
</tr>
</tbody>
</table>

→ Compared to F2 patients, F3 patients appeared to have lower placebo response rate in fibrosis improvement among those who achieved ≥30% reduction in LFC

LFC, liver fat content as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)
Patients Receiving Aldafermin Had Reductions in ALT Irrespective of Baseline Fibrosis Stage

Mean % change in ALT

F2 at Baseline

- Placebo (n=15)
- Aldafermin (n=29)

Δ = −38%

F3 at Baseline

- Placebo (n=10)
- Aldafermin (n=23)

Δ = −52%
Patients Receiving Aldafermin Achieved Reduction in AST Irrespective of Baseline Fibrosis Stage

**AST**

**F2 at Baseline**

- Placebo (n=15)
- Aldafermin (n=29)

\[ \Delta = -30\% \]

**F3 at Baseline**

- Placebo (n=10)
- Aldafermin (n=23)

\[ \Delta = -41\% \]
Patients Receiving Aldafermin Achieved Reduction in PRO-C3 Irrespective of Baseline Fibrosis Stage

**PRO-C3**

### F2 at Baseline
- Placebo (n=15)
- Aldafermin (n=29)

\[ \Delta = -18\% \]

### F3 at Baseline
- Placebo (n=10)
- Aldafermin (n=23)

\[ \Delta = -29\% \]
Summary

• Aldafermin 1 mg produced robust fibrosis regression in F3 patients compared to placebo
  • At week 24, placebo-subtracted anti-fibrotic response rates were 13% in F2 patients compared to 30% in F3 patients

• Patients receiving aldafermin had reductions in liver fat content, ALT, AST and PRO-C3 irrespective of baseline fibrosis stage

• Placebo response rates in LFC reduction and fibrosis improvement were lower in F3 than in F2 patients, which may inform sample size estimation and trial design for future NASH trials

• These data support further studies of aldafermin in patients with NASH and advanced fibrosis
We thank all of the patients who participated in this study, and the investigators, study coordinators and staff for their support.