NGM282 Rapidly Improves NAFLD Activity Score (NAS) and Fibrosis in 12 Weeks in Patients with Biopsy-Confirmed Nonalcoholic Steatohepatitis (NASH)

Results of a Phase 2 Multi-Center Dose Finding Study

NGM282 Targets Multiple Drivers of the Pathogenesis of NASH

Biologic activity established in multiple preclinical models of NASH demonstrating improvements in NAS, fibrosis and markers of hepatic injury.
NGM282 is an Engineered Variant of Human FGF19 in Development for NASH

• NGM282 has been evaluated in > 400 subjects
  • Completed Phase 2 studies in T2D, NASH, PBC and PSC
  • Potent target engagement across all study populations

• A 12-week Phase 2 randomized, placebo-controlled trial of NGM282 (3 mg and 6 mg) in biopsy-confirmed NASH subjects demonstrated:
  • Significant reduction in liver fat content (LFC) by MRI-PDFF
  • Rapid decreases in biomarkers relevant to resolution of NASH and improvement in fibrosis (ALT, AST, PRO-C3, ELF)
  • Favorable safety and tolerability profile consistent with prior studies

• Durable 6 week off-treatment effects observed in LFC, ALT and Pro-C3 reduction (Poster #LB-22)
• Data supported an exploratory 12-week study of NGM282 (1 mg and 3 mg) to assess the potential for early histologic changes on liver biopsy

1 Harrison et al. Lancet 2018 Mar 24;391(10126):1174-1185
**Study Design and Key Enrollment Criteria**

- Subjects enrolled with biopsy-confirmed NASH in this open-label trial
  - NAS ≥4 (at least 1 point in each component); Stage 1-3 fibrosis; LFC ≥ 8% (MRI-PDFF)
- Primary endpoint was the absolute change in LFC at W12
  - Clinically meaningful reduction ≥ 5% absolute LFC or ≥ 30% relative LFC
- Exploratory endpoint of change in liver histology at W12
  - Liver biopsy collected by a 16g needle
- Rosuvastatin (ROS 20 mg) started at W2 if LDL-C rise of 10 mg/dl observed
  - ROS dose titrated up to 40 mg at W4 to W8 if LDL-C remains above Baseline
### Baseline Demographics and Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NGM282 1 mg (n=24)</th>
<th>NGM282 3 mg ¹ (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>5/19</td>
<td>4/15</td>
</tr>
<tr>
<td>Age, Years</td>
<td>49.4 (10.7)</td>
<td>51.4 (12.6)</td>
</tr>
<tr>
<td>Liver Fat Content, % by MRI-PDFF</td>
<td>19.2 (7.1)</td>
<td>17.1 (5.6)</td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>92 (53)</td>
<td>82 (39)</td>
</tr>
<tr>
<td>AST, U/L</td>
<td>70 (39)</td>
<td>64 (32)</td>
</tr>
<tr>
<td>Fibrosis Stage</td>
<td>2.3 (0.8)</td>
<td>2.5 (0.8)</td>
</tr>
<tr>
<td>NAFLD Activity Score</td>
<td>5.4 (1.5)</td>
<td>5.7 (1.5)</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>103 (24)</td>
<td>97 (27)</td>
</tr>
<tr>
<td>Statin Naïve/Experienced</td>
<td>20/4</td>
<td>13/6</td>
</tr>
<tr>
<td>7α-hydroxyl-4-cholesten-3-one (C4), ng/ml</td>
<td>35.6 (27.0)</td>
<td>35.1 (24.2)</td>
</tr>
<tr>
<td>cT1, msec</td>
<td>918 (82)</td>
<td>891 (56)</td>
</tr>
</tbody>
</table>

- Analysis includes subjects that completed 12W of treatment with paired biopsies

¹ Previously presented at EASL 2018
Suppression of C4 and Serum Bile Acids by NGM282 Reflects Potent Target Engagement

**C4 Levels**

- **1 mg**
- **3 mg**

**Total Serum Bile Acids**

- **1 mg**
- **3 mg**

***P<0.001 vs baseline C4, 7α-hydroxyl-4-cholesten-3-one***
Significant Decrease in Absolute and Relative LFC by MRI-PDFF After 6 and 12 Weeks of NGM282

Liver Fat Content (LFC)

<table>
<thead>
<tr>
<th>Change From Baseline to Week 12</th>
<th>NGM282 1 mg (n=24)</th>
<th>NGM282 3 mg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI-PDFF (Absolute)</td>
<td>−10.9%***</td>
<td>−11.2%***</td>
</tr>
<tr>
<td>pts w/ ≥5% absolute change</td>
<td>92%</td>
<td>100%</td>
</tr>
<tr>
<td>pts normalized LFC¹</td>
<td>33%</td>
<td>63%</td>
</tr>
<tr>
<td>MRI-PDFF (Relative)</td>
<td>−57%***</td>
<td>−67%***</td>
</tr>
<tr>
<td>pts w/ ≥30% relative change</td>
<td>92%</td>
<td>100%</td>
</tr>
</tbody>
</table>

¹ Normalized LFC defined as absolute MRI-PDFF ≤5%

***P<0.001 vs baseline
Rapid Decreases in ALT and AST Supportive of a Reduction in Hepatic Inflammation

Change From Baseline to Week 12

<table>
<thead>
<tr>
<th></th>
<th>NGM282 1 mg (n=24)</th>
<th>NGM282 3 mg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/L)</td>
<td>−64***</td>
<td>−53***</td>
</tr>
<tr>
<td>ALT (Relative)</td>
<td>−67%***</td>
<td>−60%***</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>−42***</td>
<td>−37***</td>
</tr>
<tr>
<td>AST (Relative)</td>
<td>−57%***</td>
<td>−52%***</td>
</tr>
</tbody>
</table>

***P<0.001 vs baseline
Fibrogenesis Marker Pro-C3 is Significantly Reduced by NGM282 as Early as Week 6

**PRO-C3 Levels**

![Graph showing PRO-C3 levels at baseline, week 6, and week 12 for 1 mg and 3 mg of NGM282.](image)

**Change From Baseline to Week 12**

<table>
<thead>
<tr>
<th></th>
<th>NGM282 1 mg (n=24)</th>
<th>NGM282 3 mg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-C3 (Absolute)</td>
<td>-4.5** ng/mL</td>
<td>-11.1* ng/mL</td>
</tr>
<tr>
<td>Pro-C3 (Relative)</td>
<td>-22%***</td>
<td>-33%**</td>
</tr>
</tbody>
</table>

***P<0.001, **P<0.01, *P<0.05 vs baseline

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Dashed line indicates Pro-C3 levels in healthy volunteers

*Nielsen et al., Am J Transl Res 2013;5:303-315*
Enhanced Liver Fibrosis (ELF) Scores are Significantly Reduced by NGM282

- ELF scores have been shown to associate with disease progression in 2 Phase 2b trials of simtuzumab in patients with NASH and advanced fibrosis.

- Increase in ELF from baseline was associated with progression to cirrhosis.

**ELF Score and Components**

<table>
<thead>
<tr>
<th>Change From Baseline to Week 12</th>
<th>NGM282 1 mg (n=24)</th>
<th>NGM282 3 mg (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELF</td>
<td>−0.31***</td>
<td>−0.56***</td>
</tr>
<tr>
<td><strong>Hyaluronic Acid (ng/mL)</strong></td>
<td>0.7</td>
<td>−19.0</td>
</tr>
<tr>
<td><strong>PIIINP (ng/mL)</strong></td>
<td>−3.1***</td>
<td>−3.1**</td>
</tr>
<tr>
<td><strong>TIMP-1 (ng/mL)</strong></td>
<td>−39.6***</td>
<td>−42.7***</td>
</tr>
</tbody>
</table>

*1 Sanyal et al., EASL 2017

***P<0.001, **P<0.01 vs baseline
Reduction in cT1 on Multi-Parametric MRI is Consistent with Other Non-Invasive Markers

**Correlation of cT1 and Disease Severity**

<table>
<thead>
<tr>
<th></th>
<th>Mean Corrected T1 (cT1; ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Fibrosis</td>
<td>≥ 950</td>
</tr>
<tr>
<td>Decreased Liver-Related Events</td>
<td>≤ 875</td>
</tr>
<tr>
<td>No Fibrosis</td>
<td>≤ 800</td>
</tr>
</tbody>
</table>

**Representative Images**

(a patient from the NGM282 3 mg group)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>W6</th>
<th>W12</th>
</tr>
</thead>
</table>

**cT1 Values**

- **1 mg**
  - W6: -64***
  - W12: -78***

- **3 mg**
  - W6: -52***
  - W12: -72***

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1 Banerjee et al, J Hepatol. 2014; 60(1): 69-77
2 Data on file, Perspectum Diagnostics
Translation of Non-Invasive Efficacy into Histological Response at W12

• Significant reductions across non-invasive parameters for NASH at W12

• Conducted biopsy at Week 12 to assess the translation of early potent effects into changes in NASH-related histopathology and fibrosis

• Blinded biopsies at Baseline and Week 12 were assessed by an independent hepatopathologist at Duke University

• Biopsy samples were collected with a 16g needle; core length of > 15 mm with sufficient tissue and portal tracts for assessment
Decrease Across All NASH Histological Parameters with NGM282 at W12

**NAS HISTOLOGICAL RESPONSE AT W12**

**1 mg**
- NAS: 75% improved, 17% no change, 8% worsened
- Steatosis: 67% improved, 33% no change
- Inflammation: 33% improved, 46% no change
- Ballooning: 42% improved

**3 mg**
- NAS: 84% improved, 11% no change, 5% worsened
- Steatosis: 74% improved, 26% no change
- Inflammation: 42% improved, 5% no change
- Ballooning: 53% improved, 42% no change

Mean change at W12 (SD):
- **1 mg**
  - NAS: -1.9 (1.7)
  - Steatosis: -1.0 (0.9)
  - Inflammation: -0.4 (0.6)
  - Ballooning: -0.5 (0.9)

- **3 mg**
  - NAS: -2.3 (1.8)
  - Steatosis: -1.1 (0.9)
  - Inflammation: -0.4 (0.7)
  - Ballooning: -0.7 (0.9)
Fibrosis at Week 12 in Patients Treated with NGM282 1 mg

Fibrosis Stage at Baseline
(% patients; 1 mg n=24)

- F1: 16%
- F2: 42%
- F3: 38%
- F4: 4%

Mean fibrosis stage = 2.3

Fibrosis Histologic Response at W12

- Improved: 25%
- No change: 58%
- Worsened: 17%

• Mean change from Baseline in fibrosis stage = −0.1
• One subject had a 2-stage improvement in fibrosis: F2 → F0
Rapid Regression of Fibrosis at Week 12 in Patients Treated with NGM282 3 mg

Fibrosis Stage at Baseline (% patients; 3 mg n=19)

- F4: 5%
- F3: 53%
- F2: 26%
- F1: 16%

Mean fibrosis stage = 2.5

Fibrosis Histologic Response at W12

- Improved: 42%
- No change: 47%
- Worsened: 11%

- Mean change from Baseline in fibrosis stage = −0.5
- Three subjects had a 2-stage improvement in fibrosis: all F3 → F1
NGM282 Histologic Response Aligns with Decreases Across Noninvasive Efficacy Markers

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>W6</th>
<th>W12</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4 (ng/ml)</td>
<td>12</td>
<td>&lt;0.9</td>
<td>&lt;0.9</td>
</tr>
<tr>
<td>LFC (MRI-PDFF)</td>
<td>28.9</td>
<td>15.2</td>
<td>14.9</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>153</td>
<td>54</td>
<td>41</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>95</td>
<td>44</td>
<td>35</td>
</tr>
<tr>
<td>PRO-C3 (ng/ml)</td>
<td>25.6</td>
<td>15.8</td>
<td>13.9</td>
</tr>
<tr>
<td>cT1 (msec)</td>
<td>922</td>
<td>799</td>
<td>775</td>
</tr>
</tbody>
</table>

Shown are representative data from a patient in the 3 mg group.
Cholesterol Changes Effectively Managed with Rosuvastatin

- Decreased C4 and increased LDL-C levels reflect potent CYP7A1 inhibition
- Lipid particle change primarily driven by increase in large LDL particles
- Significant reductions in serum triglycerides (1 mg: −25%; 3 mg: −34% at week 12)
NGM282 Safety and Tolerability in 1 mg and 3 mg Histology Cohorts

• Favorable safety and tolerability profile consistent with other NGM282 studies
  • No new safety signals identified

• Mild GI symptoms (loose/frequent stools and nausea) remain the most common treatment emergent adverse events
  • Majority were mild and resolved during treatment phase
  • Two subjects (1 mg) withdrew from treatment due to diarrhea

• GI symptoms were largely mitigated with separating the timing of injection around meals and decreasing meal size

• Five patients experienced SAEs, all unrelated to study drug \(^1\)

\(^1\)Pneumonia, pleurisy, chest pain (musculoskeletal), cardiac arrest (non-MI) in 3 mg cohort; renal mass in 1 mg cohort
NGM282 Demonstrate Improvements Across Histological and Noninvasive Endpoints for NASH

• Potent C4 and bile acid suppression consistent with FGF19 hormone activity
• Significant and clinically meaningful reductions across non-invasive markers of NASH-related disease
• Large % of patients demonstrated histological improvement at W12
• Unprecedented anti-fibrotic activity at W12 for NGM282
  • 1 mg: 6 of 24 (25%) subjects had ≥ 1 fibrosis stage reduction; 1 patient improved from F2 to F0 (2 stage improvement)
  • 3 mg: 8 of 19 (42%) subjects had ≥ 1 fibrosis stage reduction; 3 patients improved from F3 to F1 (2 stage improvement)
• Statin co-administration rapidly mitigates LDL-C elevations
  • Majority of NGM282-treated patients reach LDL-C levels below baseline within 4 weeks of initiating statin therapy
• Safe and well-tolerated consistent with other study populations
• Given that histological fibrosis stage correlates with liver-related clinical outcomes, these data support advancing NGM282 to 24W Ph2b study in NASH