NGM313, a Novel Activator of β-Klotho/FGFR1c: A Single Dose Significantly Reduces Steatosis (Liver Fat by MRI-PDFF), Inflammation (ALT, AST) and Fibrogenic Activity (Pro-C3) in NAFLD Subjects

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NGM313 Selectively Targets β-Klotho/FGFR1c to Modulate the Insulin Sensitizing Effects of FGF21

- FGF21 Analogs: Demonstrated Clinical Efficacy in Metabolic Syndrome/NASH
- Important Regulator of Glucose and Lipid Homeostasis
- Pathway Complements Existing Therapeutic Classes (e.g., GLP-1, DPP-IV)

- Highly Specific, No Signaling Through Other Receptors
- Reduced Immunogenicity vs. Ligand Analogs
- Does Not Compete with Endogenous FGF21 / FGF19 Binding to FGFR1c

β-Klotho (KLB)/FGFR1c: A Validated Pathway

NGM313

• Allosteric Agonistic Monoclonal Antibody with Long Half-life
NGM313 is a Monoclonal Antibody Activator of β-Klotho/FGFR1c in Development for NASH

• NGM313 has completed Phase 1 studies in normal subjects\(^1\)-\(^2\)
  – Single ascending dose: 4-week treatment
  – Multiple ascending dose: 12-week treatment

• NGM313 has demonstrated favorable safety and tolerability profile in Phase 1 studies:\(^1\)-\(^3\)
  – No significant lab, vital sign or adverse event signals observed
  – No evidence for changes in blood pressure or gastrointestinal symptoms

• A single dose of NGM313 produced rapid, robust and significant decreases in TG and increases in plasma adiponectin, consistent with insulin-sensitizing action\(^1\)-\(^3\)

• Data support Phase 1b metabolic study in insulin-resistant NAFLD subjects

\(^1\) DePaoli et al. NASH-TAG Conference 2019
\(^2\) NGM Data on File
\(^3\) DePaoli et al. AASLD Conference 2018
Twenty-five insulin-resistant patients with NAFLD were randomized 2:1 to either a single dose of NGM313 240 mg SC or pioglitazone 45 mg QD for 36 days.

Inclusion criteria included fasting glucose <125 mg/dL, fasting insulin >10 mIU/mL, BMI >30 kg/m² and NAFLD with ≥8% liver fat content by MRI-PDFF.

Primary objectives:
- Change in **insulin sensitivity** from baseline to Day 29
- Change in **liver fat content (LFC)** from baseline to Day 36
Baseline Demographics and Patient Characteristics

One subject declined to complete the Day 28 and Day 29 procedures and was excluded from the pharmacodynamic analysis; all patients were included in the safety analysis.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NGM313 (n=17)</th>
<th>Pioglitazone (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41.9 ± 11.8</td>
<td>47.0 ± 10.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>106.0 ± 15.4</td>
<td>100.4 ± 18.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.8 ± 3.1</td>
<td>33.7 ± 3.2</td>
</tr>
<tr>
<td>Fasting Glucose (mg/dL)</td>
<td>101.7 ± 9.6</td>
<td>101.5 ± 10.0</td>
</tr>
<tr>
<td>Fasting Insulin (mU/mL)</td>
<td>27.0 ± 13.9</td>
<td>20.0 ± 5.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.81 ± 0.37</td>
<td>5.70 ± 0.33</td>
</tr>
<tr>
<td>Hepatic Fat Fraction (%)</td>
<td>18.4 ± 6.4</td>
<td>17.3 ± 7.7</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>105 ± 25</td>
<td>111 ± 41</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>39 ± 8</td>
<td>42 ± 10</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>148 ± 91</td>
<td>136 ± 61</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>30.7 ± 14.0</td>
<td>43.0 ± 24.4</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>20.7 ± 6.3</td>
<td>23.0 ± 10.9</td>
</tr>
</tbody>
</table>

Shown are mean ± SD

*One subject declined to complete the Day 28 and Day 29 procedures and was excluded from the pharmacodynamic analysis; all patients were included in the safety analysis.*
Robust Lowering of HOMA-IR is Consistent with the Insulin-Sensitizing Action of NGM313

NGM313, 240 mg

Pioglitazone, 45 mg QD

***p<0.0001 vs baseline
NGM313 Lowered HbA1c and Fasting Glucose Levels

**HbA1c**

- Baseline
- Day 28

**Fasting Glucose**

- Baseline
- Day 28

**p<0.001**

* p<0.01

# p<0.05 vs baseline
A Single Dose of NGM313 Resulted in Significant Reductions in Absolute and Relative Liver Fat Content

### Relative Change in LFC, % (LS Mean±SE)

<table>
<thead>
<tr>
<th></th>
<th>Day 23</th>
<th>Day 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>8 / 16 (50%)</td>
<td>10 / 16 (63%)</td>
</tr>
<tr>
<td>PIO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 / 8 (13%)</td>
<td>2 / 8 (25%)</td>
</tr>
</tbody>
</table>

### # (%) of Subjects with Relative Reduction in LFC ≥ 30%

<table>
<thead>
<tr>
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<th>Day 23</th>
<th>Day 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313</td>
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<td></td>
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<td>10 / 16 (63%)</td>
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<tr>
<td></td>
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<td>2 / 8 (25%)</td>
</tr>
</tbody>
</table>

### # (%) of Subjects with Absolute Reduction ≥ 5% LFC

<table>
<thead>
<tr>
<th></th>
<th>Day 23</th>
<th>Day 36</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 / 16 (38%)</td>
<td>10 / 16 (63%)</td>
</tr>
<tr>
<td>PIO</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 / 8 (13%)</td>
<td>2 / 8 (25%)</td>
</tr>
</tbody>
</table>

**p<0.0001  
**p<0.001  
*p<0.01 vs baseline

PIO, pioglitazone  
LFC, liver fat content
NGM313 Produced a Favorable Lipid Profile

- Administration of a single dose of NGM313 resulted in a favorable lipid profile in patients with NAFLD
  - ↓Triglycerides, ↑HDL-C, ↓LDL-C

### Triglycerides

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313 (n=16)</td>
<td>150±50</td>
<td><strong>130±40</strong></td>
</tr>
<tr>
<td>Pioglitazone (n=8)</td>
<td>160±50</td>
<td>140±40</td>
</tr>
</tbody>
</table>

### HDL-C

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313 (n=16)</td>
<td>40±5</td>
<td>*<strong>30±4</strong></td>
</tr>
<tr>
<td>Pioglitazone (n=8)</td>
<td>35±5</td>
<td>45±5</td>
</tr>
</tbody>
</table>

### LDL-C

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGM313 (n=16)</td>
<td>90±5</td>
<td><strong>70±5</strong></td>
</tr>
<tr>
<td>Pioglitazone (n=8)</td>
<td>100±5</td>
<td>90±5</td>
</tr>
</tbody>
</table>

**p<0.0001  
**p<0.001  
*p<0.01  
#p<0.05 vs baseline
Decreases in ALT and AST Suggest Potential for Improvement in Hepatic Injury and Inflammation by NGM313

**ALT**

- NGM313 (n=16)
- Pioglitazone (n=8)

**AST**

- NGM313 (n=16)
- Pioglitazone (n=8)

***p<0.0001, **p<0.001
* p<0.01 vs baseline
Fibrosis Marker Pro-C3 is Significantly Reduced by NGM313 But Not Pioglitazone

- Pro-C3 measures a neo-epitope of type III collagen during collagen formation and reflects fibrogenic activity.¹

- PRO-C3 increases with fibrosis stage and is independently associated with advanced fibrosis in patients with NAFLD.²

¹ Nielsen et al., Am J Transl Res 2013;5:303-315
² Daniels et al., Hepatology 2018; doi: 10.1002
Numerically Less Weight Gain in Subjects Treated with NGM313 than Pioglitazone

Body Weight Change from Baseline to Day 28

<table>
<thead>
<tr>
<th>Change from Baseline, Kg (LS mean±SE)</th>
<th>NGM313 (n=16)</th>
<th>Pioglitazone (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td></td>
<td>2.0</td>
</tr>
</tbody>
</table>

* p<0.01
# p<0.05 vs baseline
Summary of NGM313 Safety and Tolerability

• Favorable safety and tolerability profile consistent with other NGM313 studies
  – No new safety signals identified
• All AEs were mild in severity
• No SAEs or Grade 3/4 AEs
• No pattern or organ system AEs of note
• Most common AEs (>10%) were increased appetite (12%)
• No evidence of safety issues that were associated with FGF21 analogues in clinical development
  – No significant change in blood pressure
  – A previously conducted multiple-ascending dose study showed no significant change in bone mineral density or bone turnover markers ¹

¹ NGM data on file
NGM313 Demonstrates Significant Improvements in Multiple Non-Invasive Markers of NASH

• Administration of a single dose of NGM313 resulted in robust **reductions in liver fat content** in obese, insulin-resistant, non-diabetic subjects with NAFLD
  – 5.1% (Day 23) and 6.3% (Day 36) reduction in absolute liver fat content
  – 30% (Day 23) and 37% (Day 36) relative reduction in liver fat content

• NGM313 also demonstrated robust metabolic effects on insulin sensitivity and lipid homeostasis
  – Improved insulin sensitivity
  – Reduced HbA1c and fasting glucose levels
  – Lowered triglycerides and LDL-C
  – Raised levels of HDL-C

• Safe and well-tolerated

• These data support advancing NGM313 to Phase 2b studies in patients with biopsy-proven NASH with or without type 2 diabetes
Acknowledgments

We thank all of the patients who participated in this study, and the investigators, study coordinators, and staff for their support and assistance.