# NGM313, a novel activator of β-klotho/FGFR1c, improves insulin resistance and reduces hepatic fat in obese, non-diabetic subjects

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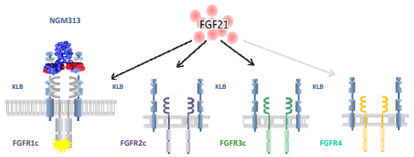
## BACKGROUND AND AIMS

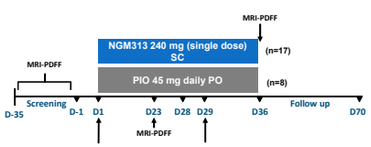
- NGM313 is a humanized, monoclonal antibody directed to β–Klotho that modulates activity of the β–Klotho/FGFR1c receptor complex [1-4]
  - Highly specific, no signaling through other receptor complexes
  - Does not compete with endogenous FGF21/FGF19 binding to β–Klotho/FGFR1c
  - Favorable effects on lipids and glucose metabolism, with a good safety profile in obese healthy volunteers
- FGF21 signals through the β–Klotho/FGFR1c, FGFR2c and FGFR3c receptor complexes to regulate glucose, energy and lipid homeostasis [5]
- FGF21 analogues have demonstrated changes in imaging and laboratory parameters supportive of improvements in patients with non-alcoholic steatohepatitis (NASH) [6]
- This study aims to compare the effects of a single dose of NGM313 *vs.* daily pioglitazone (45 mg), an insulin-sensitizer with modest efficacy in NASH [7-8], in insulin-resistant patients with NAFLD

### NGM313 Selectively Targets β–Klotho/FGFR1c




## METHODS

- Twenty-five insulin-resistant patients with NAFLD were randomized 2:1 to either a single dose of NGM313 240 mg SC (n=17) or pioglitazone (PIO) 45 mg QD (n=8) for 36 days
- Primary objectives
  - Change in insulin sensitivity from baseline to Day 29
  - Change in liver fat content from baseline to Day 36
- Whole-body insulin sensitivity was determined by a two-step hyperinsulinemic, euglycemic clamp [9] performed at Day 1 and Day 29
  - Step 1: low-dose insulin infusion (20 mU/m²/min)
  - Step 2: high-dose insulin infusion (60 mU/m²/min)
- Analyses were conducted using an ANCOVA model with treatment as a factor and the baseline variable as a covariate




## RESULTS

### Baseline Patient Characteristics

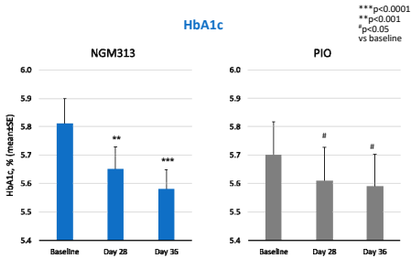
- We included males and females 18-65 years of age, fasting glucose ≤125 mg/dL, fasting insulin ≥10 µU/mL, BMI 30-43 kg/m², waist circumference >40 inches in males or >35 inches in females, NAFLD with ≥8% liver fat content as measured by magnetic resonance imaging-proton density fat fraction (MRI-PDFF)

| Parameter | NGM313 (n=17) ^ | PIO (n=8) |
|---|---|---|
| Age (years) | 41.9 ± 11.8 | 47.0 ± 10.2 |
| Male, n (%) | 10 (59%) | 5 (62%) |
| Female, n (%) | 7 (41%) | 3 (38%) |
| Weight (kg) | 106.0 ± 15.4 | 100.4 ± 18.7 |
| BMI (kg/m²) | 36.8 ± 3.1 | 33.7 ± 3.2 |
| Fasting Glucose (mg/dL) | 101.7 ± 9.6 | 101.5 ± 10 |
| Fasting Insulin (µU/mL) | 27.0 ± 13.9 | 20.0 ± 5.9 |
| Endogenous Glucose Production, Step 1 (mg/kg/min) | 0.5 ± 0.2 | 0.7 ± 0.2 |
| Endogenous Glucose Production, Step 2 (mg/kg/min) | 0.1 ± 0.2 | 0.2 ± 0.1 |
| Glucose Disposal Rate, Step 1 (mg/kg/min) | 1.8 ± 0.9 | 1.5 ± 0.9 |
| Glucose Disposal Rate, Step 2 (mg/kg/min) | 6.1 ± 2.0 | 6.4 ± 1.8 |
| HbA1c (%) | 5.81 ± 0.37 | 5.70 ± 0.33 |
| MRI-PDFF (%) | 18.5 ± 6.4 | 17.3 ± 7.7 |

Shown are mean ± SD
^ One subject declined to complete the Day 28 and Day 29 procedures and was excluded from the pharmacodynamic analysis; one subject attended all visits but declined Day 29 clamp procedure; all patients were included in the safety analysis

### HbA1c and Glucose

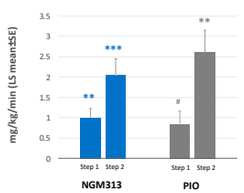
- Hemoglobin A1c (HbA1c) levels were reduced following treatment with a single dose of NGM313
- Fasting glucose concentrations were also reduced by NGM313



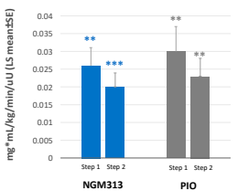

### Glucose Disposal

- A single dose of NGM313 significantly increased glucose disposal rate (GDR), indicating marked improvement in whole-body insulin sensitivity
- Consistent with the robust insulin-sensitizing activity, NGM313 also increased the ratio of GDR and insulin (M/I), glucose metabolic clearance rate (MCR), and Insulin Sensitivity Index ($SI_{clamp}$, calculated from 2-step clamp)
- The pronounced insulin-sensitizing effect of NGM313 is comparable to pioglitazone

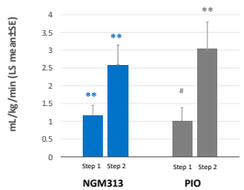
Change in GDR from Baseline



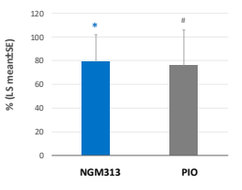

Change in M/I from Baseline




Change in MCR from Baseline




%Change in $SI_{clamp}$ from Baseline

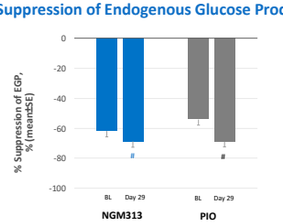



***p<0.0001, **p<0.001, *p<0.01, #p<0.05 vs baseline

### Endogenous Glucose Production

- At Day 29, suppression of endogenous glucose production (EGP) was enhanced by both NGM313 and PIO during low-dose insulin infusion

Suppression of Endogenous Glucose Production

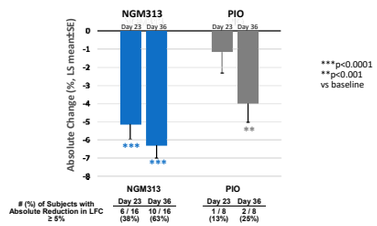



#p<0.05
vs baseline (BL)

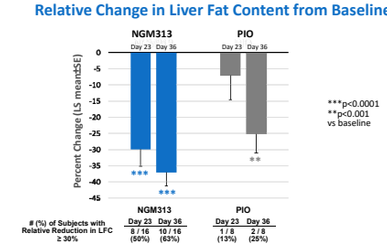
### Liver Fat Content

- We measured liver fat content by MRI-PDFF at Day 1, Day 23 and Day 36
- A single dose of NGM313 resulted in reductions from baseline in absolute liver fat content of 6.3%, and relative reduction of 37%, at Day 36
- 63% patients in the NGM313 group achieved ≥30% reduction in liver fat content after a single dose at Day 36
- Additionally, significant reductions in serum ALT, AST, triglycerides and LDL-C, and an increase in HDL-C, were observed with NGM313 therapy [1, 3]

Change in Liver Fat Content from Baseline




Relative Change in Liver Fat Content from Baseline




### NGM313 Safety

- All AEs were mild in severity
- No SAEs or Grade 2/3/4 AEs
- No pattern or organ system AEs of note
- No hypoglycemia
- Most common AEs (>10%) were injection site reaction (12%) and increased appetite (12%)
- No evidence of safety issues that have been 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 [4]

## Summary

| | NGM313, 240 mg x 1 | PIO, 45 mg QD |
|---|---|---|
| **Δ Glucose Disposal Rate (mg/kg/min) Day 29** | | |
| Step 1 (low insulin infusion) | 1.0 ± 0.2*** | 0.8 ± 0.3* |
| Step 2 (high insulin infusion) | 2.0 ± 0.4*** | 2.6 ± 0.5*** |
| **Δ %Suppression of Endogenous Glucose Production Day 29** | | |
| Step 1 (low insulin infusion) | 8.2% ± 3.3%* | 11.3% ± 4.6%* |
| Step 2 (high insulin infusion) | −4.6% ± 4.3% | 12.5% ± 5.9%* |
| **Δ MRI-PDFF (Absolute, %) Day 23** | −5.1 ± 0.8***# | −1.2 ± 1.2 |
| **Δ MRI-PDFF (Relative, %) Day 23** | −29.9 ± 5.2***# | −7.1 ± 7.4 |
| *% patients with ≥ 30% relative↓* | *50%* | *13%* |
| **Δ MRI-PDFF (Absolute, %) Day 36** | −6.3 ± 0.7*** | −4.0 ± 1.0** |
| **Δ MRI-PDFF (Relative, %) Day 36** | −37.1 ± 4.1*** | −25.2 ± 5.8*** |
| *% patients with ≥ 30% relative↓* | *63%* | *25%* |
| **Δ Triglycerides (mg/dL) Day 28** | −68.3 ± 8.3***# | −27.2 ± 11.7* |
| **Δ LDL-C (mg/dL) Day 28** | −15.8 ± 3.8*** | −6.4 ± 5.3 |
| **Δ HDL-C (mg/dL) Day 28** | 7.4 ± 1.1*** | 4.8 ± 1.6** |
| **Δ HbA1c (%) Day 28** | −0.14 ± 0.03*** | −0.10 ± 0.04* |
| **Δ Glucose (mg/dL) Day 28** | −5.0 ± 1.3*** | −4.8 ± 1.8* |
| **Δ HOMA-IR Day 28** | −2.6 ± 0.4*** | −3.1 ± 0.6*** |
| **Δ ALT (U/L) Day 28** | −5.7 ± 1.4*** | −9.4 ± 2.0*** |
| **Δ AST (U/L) Day 28** | −3.4 ± 0.7*** | −2.7 ± 0.9** |
| **Δ Weight (kg) Day 28** | 1.2 ± 0.5* | 2.1 ± 0.6** |
| **Δ Pro-C3 (ng/mL) Day 28** | −1.4 ± 0.5*# | 1.5 ± 0.8 |

***p<0.001, **p<0.01, *p<0.05 vs baseline; #p<0.05 vs PIO

## CONCLUSION

- NGM313 was safe and well tolerated in obese, insulin-resistant, non-diabetic subjects with NAFLD
- Administration of a single dose of NGM313 produced robust metabolic effects
  - Improved whole-body insulin sensitivity (↓EGP, ↑GDR, ↑MCR, ↑$SI_{clamp}$)
  - Reduced HbA1c and fasting glucose levels
  - Reduced ALT and AST
  - Favorable effects on lipid profile (↓triglycerides, ↓LDL-C, ↑HDL-C)
- NGM313 has also demonstrated significant reductions in liver fat content
  - 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 has potential to be an effective treatment for non-alcoholic steatohepatitis and type 2 diabetes

*1. DePaoli et al., AASLD 2018; 2. DePaoli et al., NASH-TAG 2019; 3. DePaoli et al., EASL 2019; 4. NGM data on file; 5. Kliewer et al., Am J Clin Nutr. 2010;91:254S-257S; 6. Sanyal et al., Lancet 2018;392:2705-2717S; 7. Belfort et al., N Engl J Med. 2006;355:2297-307; 8. Cusi et al., Ann Intern Med. 2016;165:305-15; 9. Krentz et al., Methods for Quantifying Insulin Sensitivity. Springer 2015.*

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Author disclosures on file at ADA