In a Placebo Controlled 36 Week Phase 2 Trial, Treatment with MGL-3196 Compared to Placebo Results in Significant Reductions in Hepatic Fat (MRI-PDFF), Liver Enzymes, Fibrosis Biomarkers, Atherogenic Lipids, and Improvement in NASH on Serial Liver Biopsy

Dr. Stephen A. Harrison, Dr. Cynthia D. Guy, Dr. Mustafa Bashir, Dr. Juan Pablo Frias, Dr. Naim Alkhouri, Dr. Seth Baum, Dr. Rebecca Taub, Dr. Cynthia A. Moylan, Dr. Meena B. Bansal, Dr. Brent A. Neuschwander-Tetri, Dr. Sam Moussa
Mechanism of Action: The Importance of Liver THR-β in NASH

In humans, thyroid hormone receptor-β (THR-β) agonism:
- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

MGL-3196
- THR-β selective molecule with proven safety and efficacy in more than 300 subjects and patients treated
  - No exposure outside the liver or activity at the systemic THR-α receptor
- Pleiotropic effects with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly)
  - Reduction of liver fat through breakdown of fatty acids, normalization of liver function

Sinha and Yen Cell Biosci (2016) 6:46
Study Design: Randomized, Double-Blind, PBO Controlled Trial

Comparator/Arms
- 2:1 MGL-3196 to placebo
- 125 patients enrolled in USA, 18 sites
- MGL-3196 or placebo, oral, once daily; dose 80 mg (+/-20 mg dose adjustment possible at Week 4 )

Inclusion/Exclusion
- NASH on liver biopsy: NAS ≥4 with fibrosis stage 1-3
- ≥10% liver fat on MRI-PDFF
- Includes diabetics, statin therapy, representative NASH population
Study Endpoints

- Primary endpoint
  - Relative reduction of liver fat (MRI-PDFF) at 12 weeks (at 36 weeks, secondary)

- Key secondary endpoints at 12, 36 weeks
  - Reduction (2-point on NAS) or resolution of NASH without worsening of fibrosis with at least a 2-pt reduction in NAS in MGL-3196-treated compared to placebo patients
  - One point reduction in fibrosis on liver biopsy
  - Numbers achieving ≥ 30% liver fat reduction at 12, 36 weeks; absolute liver fat reduction
  - Liver enzymes, fibrosis biomarkers and lipids at 12, 36 weeks

- Ongoing exploratory endpoint extension study in a subset of patients who completed the main 36 week study
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (41)</th>
<th>MGL-3196 (84)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, years (SD)</strong></td>
<td>47.3 (11.7)</td>
<td>51.8 (10.4)</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>24 (58.5)</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>37 (90.2)</td>
<td>79 (94.0)</td>
</tr>
<tr>
<td><strong>Hispanic/Latino</strong></td>
<td>22 (53.7)</td>
<td>37 (44.0)</td>
</tr>
<tr>
<td><strong>Diabetic, n (%)</strong></td>
<td>13 (31.7)</td>
<td>35 (41.7)</td>
</tr>
<tr>
<td><strong>Mean BMI (SD)</strong></td>
<td>33.6 (5.8)</td>
<td>35.8 (6.2)</td>
</tr>
<tr>
<td><strong>Mean ALT</strong></td>
<td>60.1 (32.8)</td>
<td>50.0 (29.2)</td>
</tr>
<tr>
<td><strong>PRO-C3</strong></td>
<td>16.2 (8.3)</td>
<td>17.8 (10.3)</td>
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<tr>
<td><strong>ELF</strong></td>
<td>9.2 (1.0)</td>
<td>9.2 (0.88)</td>
</tr>
<tr>
<td><strong>Mean LDL-C</strong></td>
<td>116.9 (30.0)</td>
<td>111.3 (30.4)</td>
</tr>
<tr>
<td><strong>Mean Triglycerides (TG)</strong></td>
<td>161.1 (75.2)</td>
<td>178.5 (82.4)</td>
</tr>
<tr>
<td><strong>Mean MRI-PDFF</strong></td>
<td>19.8 (6.7)</td>
<td>20.7 (7.0)</td>
</tr>
<tr>
<td><strong>Mean NAS</strong></td>
<td>4.8 (1.1)</td>
<td>4.9 (1.0)</td>
</tr>
<tr>
<td><strong>Fibrosis stage 1, n (%)</strong></td>
<td>19 (46.3)</td>
<td>47 (55.9)</td>
</tr>
<tr>
<td></td>
<td>20 (48.8)</td>
<td>36 (42.8)</td>
</tr>
</tbody>
</table>

* Patients with both baseline and week 12 assessments
Week 36: Sustained Reduction in Liver Fat on MRI-PDFF

**Main, 36 Week Study**
- Sustained statistically significant reduction in hepatic fat Week 12 to Week 36
- Placebo response generally related to weight loss ≥5%

**Absolute Fat Reduction (%)**

<table>
<thead>
<tr>
<th>Week</th>
<th>12</th>
<th>36</th>
<th>12</th>
<th>36</th>
<th>12</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1.6</td>
<td>-2.3</td>
<td>-7.6</td>
<td>-8.5</td>
<td>-8.8</td>
<td>-9.4</td>
</tr>
</tbody>
</table>

P value, placebo compared to MGL-3196; MGL-3196, n=78; placebo, n=38; prespecified high exposure (High Exp) n=44; F2/F3, placebo, n=19; MGL-3196, n=33
Extension Study: Reduction in Liver Fat on MRI-PDFF

**Extension Study**

Former 36 Week placebo patients treated with 80 or 100 mg MGL-3196 for 36 Weeks in an open label extension study (*bar graphs show all extension patients; study still ongoing*)

Noninvasive endpoints, only
Week 36: Sustained Robust Lipid Lowering

Significant sustained lowering effect in multiple atherogenic lipids

**Lipids (% Change from Baseline)**

- **LDL-C (BL>100)**: -22.3, p<0.0001
- **ApoB**: -21.9, p<0.0001
- **TGs**: -36, p<0.0001
- **Lp(a) (BL>=10)**: -36.8, p<0.001
- **ApoCIII**: -36.5, p<0.0001

Placebo corrected; p value, placebo compared to MGL-3196; MGL-3196, n=79; placebo, n=39
Week 36: Liver Enzymes

Statistically significant reductions in ALT, AST and GGT versus placebo; no change in bilirubin or alkaline phosphatase.

Week 36, 40% reduction in ALT in patients with elevated baseline (p=0.01), and all MGL-3196 relative to placebo patients (p=0.002).

At Week 36, 60% of MGL-3196 patients with ALT <30 vs 37% of placebo (p=0.03).

Week 36, statistically significant AST reduction in MGL-3196 vs placebo (% change and absolute change) p=0.002.

Week 36, statistically significant GGT reduction MGL-3196 vs placebo (% change and absolute change) p=0.002.

Baseline elevated ALT =45 male, 30 female. GGT shown as % change from baseline, females and males have different normal GGT ranges.
**Week 36: NASH Liver Biopsy Endpoints**

**2-Point NAS Reduction**

with at least a 1-pt reduction in ballooning or inflammation
(% of liver biopsies)

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<tr>
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<th>% of Biopsies</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>32</td>
<td>0.09</td>
</tr>
<tr>
<td>MGL-3196 (all)</td>
<td>51</td>
<td>0.006</td>
</tr>
<tr>
<td>MGL-3196 (high exp)</td>
<td>65</td>
<td>0.02</td>
</tr>
<tr>
<td>MGL-3196, MRI responder</td>
<td>47</td>
<td>0.02</td>
</tr>
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</table>

2-pt reduction in NAS in placebo patients was correlated with body weight loss.

**NASH Resolution**

ballooning=0, inflammation =0, 1 with at least 2-point reduction in NAS
(% of liver biopsies)

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<td>0.003</td>
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In MGL-3196 treated patients with NASH resolution, 50% had fibrosis resolution (F=0).

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MRI Responder; ≥ 30% fat reduction on Week 12 MRI-PDFF High Exp., n=44; 2-pt NAS reduction; MGL-3196, n=73, placebo n=34; NASH Resolution, prespecified endpoint: at least 2-pt reduction in NAS; ballooning=0, inflammation=0, 1, <9.5% weight loss;
Correlation of Decrease in Hepatic Fat (MRI-PDFF) with Improvement in Ballooning and Inflammation on Liver Biopsy

- Patients who were not MRI-PDFF Responders (≥30% fat reduction) had a low rate of NASH resolution (left panel).
- In both MGL-3196 (correlation coefficient 0.42) (right panel) and placebo (correlation coefficient 0.58) % relative change in MRI-PDFF was correlated with reduction in ballooning plus inflammation scores on liver biopsy (steatosis score removed).
Week 36: Reduction of Fibrosis, Biomarkers

ELF, CK-18 and Pro-C3 scores, biomarkers correlated with liver fibrosis stage, were statistically significantly reduced in MGL-3196 treated, especially in patients with advanced fibrosis at baseline.

Second Harmonic Generation (SHG) microscopy provides automated fully quantitative assessment of fibrosis on liver biopsy slides based on unique architectural features of collagen.

SHG score was generated and aligned with the pathologist baseline score (baseline, r=0.76), (left panel), blinded to treatment code.

Using SHG, MGL-3196 treated compared with placebo showed a statistically significant ≥1-pt reduction in fibrosis score at Week 36. Based on pathology score, fibrosis was reduced by ≥ 1 point in 29% of MGL-3196 treated patients vs. 23% in placebo.

https://doi.org/10.1371/journal.pone.0199166

Week 36 pathology scores and treatment code were not provided to SHG readers.
Safety and Additional Biomarkers

- **AEs**
  - AEs, mostly mild, a few moderate, balance between groups. Increase in MGL-3196 treated relative to placebo in loose stools, typically a single episode, only at the beginning of therapy
  - No lab abnormalities or other AEs were increased in MGL-3196 compared with placebo patients
  - 7 SAEs, distributed between placebo and drug-treated, all single occurrences, none related

- **Safety Biomarkers**
  - No effects on TSH, bone mineral density, heart rate, QTc, other CV biomarkers or diabetes biomarkers
  - Small (<3%, not statistically significant) reduction in diastolic BP at Week 36 in MGL-3196 patients, consistent with reduced liver fat

- **Inflammation Biomarker**
  - Sustained statistically significant reduction in reverse T3
    - Reverse T3 is a marker of inflammation. Elevations in reverse T3 may be indicative of high hepatic thyroid hormone degradation, in NASH, potentially caused by activated stellate cells
Conclusions

In a Phase 2 36 week serial liver biopsy study in patients with NASH fibrosis stage 1-3, patients treated with MGL-3196 as compared with placebo showed:

- Sustained statistically significant reduction in liver fat on MRI-PDFF in MGL-3196 treated as compared with placebo patients

- Sustained statistically significant lowering of multiple atherogenic lipids including LDL-C, ApoB, triglycerides, ApoCIII and Lp(a)

- Statistically significant lowering and normalization of liver enzymes; overall safety

- Statistically significant resolution of NASH that is correlated with reduction in liver fat on MRI-PDFF and provides evidence for efficacy at a registrational endpoint for Phase 3 development in NASH
Acknowledgements

We are grateful to the patients and staff who made this study possible.