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

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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>Mean age, years (SD)</td>
<td>47.3 (11.7)</td>
<td>51.8 (10.4)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>24 (58.5)</td>
<td>38 (45.2)</td>
</tr>
<tr>
<td>White</td>
<td>37 (90.2)</td>
<td>79 (94.0)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>22 (53.7)</td>
<td>37 (44.0)</td>
</tr>
<tr>
<td>Diabetic, n (%)</td>
<td>13 (31.7)</td>
<td>35 (41.7)</td>
</tr>
<tr>
<td>Mean BMI (SD)</td>
<td>33.6 (5.8)</td>
<td>35.8 (6.2)</td>
</tr>
<tr>
<td>Mean ALT</td>
<td>60.1 (32.8)</td>
<td>50.0 (29.2)</td>
</tr>
<tr>
<td>PRO-C3</td>
<td>16.2 (8.3)</td>
<td>17.8 (10.3)</td>
</tr>
<tr>
<td>ELF</td>
<td>9.2 (1.0)</td>
<td>9.2 (0.88)</td>
</tr>
<tr>
<td>Mean LDL-C</td>
<td>116.9 (30.0)</td>
<td>111.3 (30.4)</td>
</tr>
<tr>
<td>Mean Triglycerides (TG)</td>
<td>161.1 (75.2)</td>
<td>178.5 (82.4)</td>
</tr>
<tr>
<td>Mean MRI-PDFF*</td>
<td>19.8 (6.7)</td>
<td>20.7 (7.0)</td>
</tr>
<tr>
<td>Mean NAS</td>
<td>4.8 (1.1)</td>
<td>4.9 (1.0)</td>
</tr>
<tr>
<td>Fibrosis stage** 1, n (%)</td>
<td>19 (46.3)</td>
<td>47 (55.9)</td>
</tr>
<tr>
<td>2-3, n (%)</td>
<td>20 (48.8)</td>
<td>36 (42.8)</td>
</tr>
</tbody>
</table>

* Patients with both baseline and week 12 assessments; **F0 placebo=2 (4.9); MGL-3196=1 (1.2) were included in all analyses.
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%

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 of 36 Week Phase 2 Trial

**Extension Study**

- The Extension study includes 14 former placebo patients with persistently mildly to markedly elevated liver enzymes from the Main 36 Week study, ~ two thirds F2/F3
- 16 former MGL-3196 patients (dose increased to 80 or 100 mg)
- Noninvasive end points, only
- To optimize exposure, all patients in the Extension study received 80 or 100 mg per day of MGL-3196, a higher average dose than in the 36 Week study to move all patients into the “high exposure” category
- Highly significant reduction in lipids including LDL-C, ApoB and triglycerides
- Well tolerated, few AEs, improvement in liver enzymes from baseline
- No increase in GI AEs observed in the 30 patients in the Extension study

**Former Placebo Patients**

- Percent Change
  - ApoB: -21
  - LDL-C: -23
  - TGs: -29
  - ALT: -31
  - AST: -21
  - GGT: -33
  - SHBG: 120
### Extension Study: Reduction in Liver Fat on MRI-PDFF

#### Former Placebo Patients

<table>
<thead>
<tr>
<th></th>
<th>≥30% Fat Reduction (%)</th>
<th>Relative Fat Reduction (%)</th>
<th>Absolute Fat Reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main</td>
<td>7</td>
<td>1.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Extension</td>
<td>87</td>
<td>-50</td>
<td>-10</td>
</tr>
</tbody>
</table>

#### All Extension Patients

Graph showing reduction in liver fat over time for former placebo and former 3196 main patients.

**Graph Legend:**
- **Main**
- **Extension**

- Former placebo
- Former 3196 Main
NASH Extension Study

- Former placebo patient, diabetic on multiple medications whose ALT was ~200 IU/L during the Main study
- Following initiation of MGL-3196 at Week 36, rapid decrease in liver fat, improvement in liver imaging (Perspectum) normalized corrected T1 (measure of liver inflammation), 85% decrease in liver enzymes
Week 36: Sustained Robust Lipid Lowering

Significant sustained lowering effect in multiple atherogenic lipids

MGL-3196 compared with placebo; all analyses and cutoffs were prespecified; based on prespecified mITT; placebo n=39; MGL-3196 n=79 (LOCF)
Week 36: Liver Enzymes

**ALT**

- Week 36, 40% reduction in ALT in MGL-3196 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)

**AST**

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

**GGT**

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

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

All analyses were prespecified. Baseline elevated ALT =45 male, 30 female. GGT shown as % change from baseline, females and males have different normal GGT ranges, placebo n=39; MGL-3196, n=79, LOCF
Week 36: NASH Liver Biopsy Endpoints

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

![Graph showing NAS reduction](image)

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

![Graph showing NASH resolution](image)

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; Prespecified: Excluded patients with >9.5% weight loss from NR
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.
Week 36: Change in Fibrosis Score on Liver Biopsy

- 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 \( \geq 1 \)-pt reduction in fibrosis score at Week 36. Based on pathology score, fibrosis was reduced by \( \geq 1 \) point in 29% of MGL-3196 treated patients vs. 23% in placebo.

[Graph showing SHG scores and percentage of biopsies with different scores]
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.
Unlike statins or some thyromimetic compounds, MGL-3196 does not elevate liver enzymes

- Other companies’ thyromimetcs increased liver enzymes in healthy volunteers, often after a single dose, and liver enzymes were still increasing after 2 weeks of treatment
- Thyroid hormone given at 5X replacement dose does not elevate liver enzymes
- No increase in ALT in two weeks of treatment with doses of 50-200 mg of MGL-3196 in healthy volunteers, despite significant LDL cholesterol lowering