MGL-3196, a selective thyroid hormone receptor-beta agonist, significantly decreases hepatic fat in NASH patients at 12 weeks, the primary endpoint in a 36 week serial liver biopsy study

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Mechanism of Action: The Importance of Liver THR-β in NASH

- MGL-3196 has pleiotropic effects with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly).

- THR-β agonists reduce liver fat through breakdown of fatty acids, and stimulate mitochondrial biogenesis in the NASH liver, thereby reducing lipotoxicity and improving liver function.

- In human NASH, the liver has relatively low THR-β activity, exacerbating mitochondrial dysfunction and lipotoxicity.

- THR-β may have direct hepatic anti-fibrotic effects in that THR agonism has been shown to dampen inflammation in vivo and to inhibit TGF-β signaling in cell culture and in vivo.

In humans THR-β agonism:
- Lowers LDL-cholesterol
- Lowers triglycerides
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

Sinha and Yen Cell Biosci (2016) 6:46
MGL-3196, a First-in-Class Liver-Directed THR-β Agonist

First bona fide THR-β selective molecule with key advantages

- Discovery of MGL-3196 utilized a novel in vitro functional assay
  - Additional selectivity conferred by highly specific uptake into liver, avoiding any systemic thyroid receptor effects

- in vivo preclinical and clinical data confirm MGL-3196’s high liver uptake and safety
  - Avoids activity at the systemic THR-α receptor (no increased heart rate, osteoporosis)
  - Long-term animal studies completed: no cartilage/bone findings in chronic toxicology
  - Tested in more than 160 subjects in Phase 1 studies and 150 patients in Phase 2 studies
  - MGL-3196 well-tolerated in clinical dosing, normal thyroid axis and vital signs, no liver enzyme increases

- Lipid lowering
  - Robust, pleiotrophic anti-atherogenic lipid lowering properties
  - In In Phase 1 healthy volunteer and Phase 2 heterozygous familial cholesterolemia (HeFH) studies lowered LDL-cholesterol (LDL-C) up to 30%, apolipoprotein B (ApoB) 28%, lipoprotein(a) Lp(a) up to 40% and triglycerides (TGs) up to 40%
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, once daily; starting dose 80 mg per day, +/-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

- **Secondary, exploratory biomarker and imaging endpoints**
  - Numbers achieving ≥ 30% liver fat reduction at 12 weeks; absolute liver fat reduction
  - NASH, fibrosis biomarkers and lipids at 12, 36 weeks; multi-parametric imaging substudy
  - Repeat MRI-PDFF at 36 weeks

- **Secondary, exploratory liver biopsy endpoints at 36 weeks**
  - Reduction (2-point on NAS) or resolution of NASH without worsening of fibrosis in MGL-3196-treated compared to placebo
  - One point reduction in fibrosis
  - Reduction in components of NASH

- **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>
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<tr>
<td><strong>White</strong></td>
<td>37 (90.2)</td>
<td>79 (94.0)</td>
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<tr>
<td><strong>Hispanic/Latino</strong></td>
<td>22 (53.7)</td>
<td>37 (44.0)</td>
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<tr>
<td><strong>Diabetic, n (%)</strong></td>
<td>13 (31.7)</td>
<td>35 (41.7)</td>
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<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>Mean AST</strong></td>
<td>38.2 (21.2)</td>
<td>35.7 (17.8)</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 TGs</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 n, % 0-1</strong></td>
<td>21 (51.2)</td>
<td>48 (57.1)</td>
</tr>
<tr>
<td></td>
<td>20 (48.8)</td>
<td>36 (42.8)</td>
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</tbody>
</table>

*Patients with both baseline and week 12 assessments*
Primary endpoint was met: Relative change in MRI-PDFF (% change from baseline (median)) and absolute fat reduction were both highly significant.

Prespecified high exposure MGL-3196 patients achieved a 75% response for ≥30% liver fat reduction.

No effect of MGL-3196 on body weight; 5 out of the 7 placebo patients who achieved ≥ 30% fat reduction lost ≥5% body weight.

*compared with placebo **within group p-value
Fat Reduction Relative to NAS/Fibrosis Stage

MGL-3196 reduces liver fat effectively in both early and advanced NASH fibrosis.

**within group p-value**
Reductions in Multiple Atherogenic Lipids

**Lipids**

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Placebo (n=39)</th>
<th>MGL-3196 (n=79)</th>
<th>High MGL-3196 (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp(a)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-HDL-C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGs</td>
<td></td>
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</tbody>
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**Biomarker Monitoring in Patients: Extension Study**

- Extension study: Open label study of eligible week 36 completers, all patients on MGL-3196
  - Dose adjustment based on biomarkers
  - Significant lipid lowering, correlating with sex hormone binding globulin (SHBG) increase
  - ApoB lowering equal to LDL-C, reflects lowering of LDL and VLDL particles; ApoB correlates with CV risk more than LDL-C level

- Significant (p<0.0001) reductions relative to placebo in multiple atherogenic lipids including LDL-cholesterol, Lp(a), Apo B and TGs
- Average reductions in LDL-C, ApoB and triglyceride reductions not maximal, many patients had drug exposures consistent with half-maximal lipid lowering effect

Lp(a), % change from baseline, other lipids absolute reductions (ng/ml); LDL-C>100 mg/dL, BL; Lp(a)>10 nmol BL; TGs Week 4, MGL-3196 patients on 80 mg dose; SE shown; ND, not determined
Multiparametric MRI Substudy

- Multiparametric MRI has been validated as a predictive test for NASH, and the CT1 predicts NAS on liver biopsy, particularly correlating with inflammation*
- Measures inflammation and liver fat across the whole liver
- MGL-3196 NASH substudy: evaluation of 17 patients with paired baseline and week 12 multiparametric scans
- MGL-3196 treated patients showed statistically significant improvements in MRI-PDFF and CT1

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Reduction at Week 12 of Liver Enzymes and Reverse T3, Markers of Inflammation

- Decrease in liver enzymes is correlated with improvement in NASH on serial liver biopsy
- Significant decrease in ALT, AST (within group MGL-3196); significant decrease in ALT (patients with ALT* elevations at baseline) and AST (p=0.04, 0.02, respectively) compared with placebo in high MGL-3196 patients
- Significant decrease in reverse T3 (p<0.0001), an inflammatory biomarker that is relatively increased in patients with NASH, particularly advanced NASH (doi: 10.1210/en.2014-1302) Clinical Gastroenterology and Hepatology 2018;16:123–131

*Baseline ALT, >=45 males; >=30 females

**within group p-value
Reduction of Fibrosis Biomarkers by MGL-3196

- Pro-C3 and ELF scores have been correlated with the liver fibrosis score on liver biopsy in NASH patients*
- MGL-3196 significantly decreases ELF and Pro-C3 (up to 40% relative to placebo) fibrosis biomarkers particularly in patients with > normal level at baseline reflective of more advanced baseline liver fibrosis

BL, baseline; elevated BL Pro-C3>=17.5 ng/ml; elevated BL ELF >= 9

**within group p-value

Safety Results

Study remains blinded, completion of dosing and follow up in 36 week study by end of April 2018. 

Very good all subject tolerability: mostly mild and a few moderate AEs, the numbers of which are balanced between placebo and drug-treated groups; 3 reported SAEs all unrelated to drug.

Only 2/9 discontinuations secondary to AEs.

No change in heart rate or other vital signs, significant decrease in blood pressure in MGL-3196-treated.

No change in thyroid axis.

Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>MGL-3196</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild n (%)</td>
<td>19 (46.3)</td>
<td>55 (65.5)</td>
</tr>
<tr>
<td>Moderate n (%)</td>
<td>7 (17.1)</td>
<td>18 (21.4)</td>
</tr>
<tr>
<td>Severe*</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Study is blinded; 3 SAEs, all unrelated.

**within group p-value
Conclusions

- Once daily MGL-3196 for 12 weeks compared with placebo significantly decreased hepatic fat in patients relative to placebo.

- Results from liver enzyme, inflammatory and fibrosis biomarker data, including a multiparametric MRI substudy are suggestive of an impact of MGL-3196 to reduce NASH and fibrosis.

- MGL-3196 significantly reduced blood pressure and multiple atherogenic lipids which provides support for potential cardiobeneficial effects in NASH patients who most frequently die of cardiovascular disease.

- MGL-3196 appeared safe and was well-tolerated.

- Histopathologic assessment by 36 week liver biopsy will allow for correlations with the baseline biopsy in addition to multiple 12 week and 36 week non-invasive imaging and biomarker assessments.