Nonconfidential

March 2020
Forward Looking Statements

Any statements, other than statements of historical facts, made in this presentation regarding our future financial or business performance, conditions, plans, prospects, trends, or strategies and other financial and business matters; our ability to obtain additional financing; the estimated size of the market for our product candidates, the timing and success of our development and commercialization of our anticipated product candidates; and the availability of alternative therapies for our target market, are, or may be deemed, forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “could,” “should,” “would,” “anticipate,” “believe,” “estimate,” “continue,” “design,” “expect,” “intend,” “plan,” “potential,” “predict,” “seek” or the negative of these words and similar expressions and their variants may identify forward-looking statements.

These forward-looking statements reflect management’s current expectations, are based on certain assumptions and involve certain risks and uncertainties, which change over time. Our actual results may differ materially from the results discussed in these forward-looking statements due to various factors. Important factors that may cause actual results to differ materially from the results discussed in these forward-looking statements include, but are not limited to, risks related to securing and maintaining relationships with collaborators; risks relating to our clinical trials; risks relating to the commercialization, if any, of our proposed product candidates (such as marketing, regulatory, product liability, supply, competition, and other risks); dependence on the efforts of third parties; dependence on intellectual property; and risks related to our cash resources and ability to obtain working capital to fund our proposed operations. Further information regarding on the factors that could affect our business, financial conditions and results of operations are contained our filings with the U.S. Securities and Exchange Commission, which are available at www.sec.gov. These forward-looking statements represent management’s expectations as of the date hereof only, and we specifically disclaim any duty or obligation to update forward-looking statements as a result of subsequent events or developments, except as required by law.
Projecting the Future for Resmetirom

We believe that ...

- Based on our strong Phase 2 and extension study results and the powering of both Phase 3 studies, we have a high degree of confidence that:
  - In MAESTRO-NASH, we will achieve:
    - The primary endpoint of NASH resolution; and
    - The key secondary endpoints of at least a 1-stage improvement in fibrosis and statistically significant LDL-cholesterol lowering

- In MAESTRO-NAFLD-1, we will generate:
  - Sufficient additional safety data to support a Subpart H filing for NASH;
  - Convincing data for noninvasively diagnosing and evaluating improvements in NASH resulting from resmetirom therapy; and
  - Further convincing evidence supporting the potential for resmetirom to provide cardio-protection via lowering of LDL-C and multiple atherogenic lipids and clearing the liver of fat

- Realization of these outcomes will significantly differentiate resmetirom’s product profile from competing drugs and dramatically enhance the Company’s strategic value proposition

- In parallel with execution of the Phase 3 programs, we plan to:
  - Build the internal capability to launch the product in the U.S.; and
  - Seek appropriate commercial partnerships for global product launch
Madrigal has Initiated MAESTRO-NASH, Phase 3 in NASH Fibrosis and MAESTRO-NAFLD-1

Madrigal is focused on the development of its pipeline of THR-β agonists for the treatment of NASH

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Pre-Clinical</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Upcoming Catalysts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resmetirom (MGL-3196)</td>
<td>Treatment of Nonalcoholic Steatohepatitis (NASH) With Fibrosis Stage 2-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▸ Phase 3 MAESTRO-NASH, recruiting</td>
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<tr>
<td>Thyroid Hormone Receptor-β (THR-β) Agonist</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>▸ Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Safety, Lipids and NASH Biomarker study, recruiting</td>
</tr>
<tr>
<td>MGL-3745 THR-β Agonist</td>
<td>NASH and Hyperlipidemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-Alcoholic Fatty Liver Disease (NAFLD) Ranges from Simple Steatosis (NAFL) to NASH, a Progressive Form of Liver Disease

- **DISEASE**
  - NAFLD results from accumulation of excess fat within the liver (steatosis) unrelated to alcohol use
  - Some patients with NAFLD have NASH (nonalcoholic steatohepatitis)

- **INCIDENCE**
  - 25 – 30% of all adults in Western countries have NAFLD
  - NASH afflicts 3 – 12% of the U.S. population. In certain populations such as diabetics fat in the liver is virtually always NASH.

- **OUTCOME**
  - NAFLD leads to an increased risk of morbidity and mortality from:
    - Cardiovascular disease (leading cause of death for NAFLD patients)
    - Liver-related events
  - 11% of advanced NASH patients progress to cirrhosis over a 15 year period
Resmetirom Development Path Across the Spectrum of NAFLD/NASH

**NASH/NAFLD Spectrum**

- **1.3 million** F4
- **2.0 million** F3
- **3.4 million** F2
- **6.3 million** F1
- **3.5 million** F0
- **15 million** NAFLD with dyslipidemia, diabetes, metabolic syndrome

**CV Benefits**
- Fatty liver
- LDL-C
- ApoB
- Triglycerides
- Lp(a)

**Patient Numbers (US)**

- **Total US NAFLD:** (NASH plus NAFL) 83 million (2015)

**Phase 3 MAESTRO-NASH study:** NASH Resolution (primary), LDL-C, fibrosis (key secondary); Phase 4 (post-approval): cirrhosis and MACE

**MAESTRO-NAFLD-1 study:** Safety, Lipids, NASH biomarkers (no liver biopsy requirement)

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1 Estes et al; *Hepatology*, Vol. 67, No. 1, 2018
**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)

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**Resmetirom (MGL-3196)**

- THR-β selective molecule, once a day oral, with proven safety and efficacy in more than 400 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 mitochondrial and liver function

Resmetirom, First and Best-in-Class Liver-Directed THR-β Agonist

First bona fide THR-β selective molecule with key advantages

- Discovery of resmetirom utilized a novel in vitro functional assay, 28 fold THR-β selective with virtually no THR-α activity
  - Other thyromimetic compounds lacked beta selectivity in this assay
- In vivo preclinical and clinical data confirm resmetirom’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
  - Multiple Phase 1 studies completed, well-tolerated in clinical dosing, normal thyroid axis and vital signs, no liver enzyme increases (right panel)

Resmetirom: Non-invasive and Liver Biopsy Readouts (Lancet online)

- Reduces steatosis on biopsy
- At Phase 3 doses (80 or 100 mg/qd) clears more liver fat on MRI-PDFF than other agents, average 55% reduction
- About 90% of patients should clear ≥30% liver fat
  - ≥30% hepatic fat reduction predicts higher rates of NASH resolution & decreased fibrosis on biopsy
- Decreases ballooned hepatocytes on biopsy
- Stimulates mitochondrial biogenesis reducing hepatocyte dysfunction and death
- Reduces GGT and CK-18 markers of oxidative damage/ballooning
- Decreases inflammation on biopsy
- Continued, sustained decreases in elevated liver enzymes, many reaching normal levels (60% with ALT <30 by 36 weeks)
- Reduces reverse T3, a marker of inflammation
Resmetirom: Fibrosis, Non-invasive and Liver Biopsy Readouts

- Liver biopsy trend favoring resmetirom in Phase 2 (study was not powered for 1-point improvement in fibrosis)
  - 56% of patients who resolved NASH also resolved fibrosis, 61% of NASH resolvers achieved ≥ 1 point improvement in fibrosis

- Statistically significant reductions in multiple fibrosis markers including PRO-C3, ELF (P3NP, TIMP-1, hyaluronic acid) and increased adiponectin, most pronounced in patients with advanced fibrosis at baseline (F2 / F3)

- Half of F3 patients showed ≥ 1-point improvement in fibrosis, compared to no placebo F3 patients, using Second Harmonic Generation

- Reduction in fibrosis (kPa) on fibroscan

Phase 3 NASH study is >90% powered to show a 1-point improvement in fibrosis on biopsy

*Schuppan 2018 https://doi.org/10.1016/j.matbio.2018.04.006
Phase 2 NASH Study Design: Randomized, Double-Blind, PBO Controlled

Comparator/Arms
- 2:1 Resmetirom to placebo
- 125 patients enrolled in USA, 18 sites
- Resmetirom 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
Phase 2 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 resmetirom-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

- **Completed 36 week extension study in 30 patients who completed the main 36 week study**
## Baseline Characteristics—a Representative NASH Population

<table>
<thead>
<tr>
<th></th>
<th>Placebo (41)</th>
<th>Resmetirom (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); resmetirom=1 (1.2) were included in all analyses
Safety

**AEs**

- AEs, mostly mild, a few moderate, balance between groups. Increase in resmetirom treated relative to placebo in loose stools, typically a single episode, only at the beginning of therapy, GI AEs not increased over placebo in Phase 1 or NASH extension study.
- No lab abnormalities or other AEs were increased in resmetirom compared with placebo patients.
- 7 SAEs, distributed between placebo and drug-treated, all single occurrences, none related.

**Safety Biomarkers**

- No symptoms, clinical signs or laboratory findings of either hyper or hypothyroidism in over 400 subjects and patients dosed with resmetirom.
- No effects on thyroid axis hormones, bone mineral density (up to 1.5 years), heart rate, QTc, other CV biomarkers or diabetes biomarkers.
- Small (<3%, not statistically significant) reduction in diastolic BP at Week 36 in resmetirom patients, consistent with reduced liver fat.

One patient in the Phase 2 NASH study had autoimmune hypothyroidism (Hashimoto’s thyroiditis), which was present at baseline. As a result of asymptomatic TSH elevations caused by the Hashimoto’s thyroiditis, the patient remained in the clinical trial on thyroxine. Patients with thyroid disorders including those on thyroxine for hypothyroidism are allowed in resmetirom clinical trials because of resmetirom’s excellent safety profile, liver targeting and beta selectivity.
Dose-related Sustained Reduction in Liver Fat on MRI-PDFF

Main, 36 Week Phase 2 Study
- Sustained statistically significant reduction in hepatic fat Week 12 to Week 36
- Placebo response generally related to weight loss ≥5%

36 Week Phase 2 Extension Study
- Thirty patients, 14 former placebo patients were treated with resmetirom, 80-100 mg for an additional 36 weeks
- Well tolerated, excellent safety, lipid and liver enzyme responses

P value, placebo compared to resmetirom; resmetirom, n=78; placebo, n=38; extension study shown for former pbo patients, 3 took 100 mg, 11/14, 80 mg.
### MRI-PDFF Relative Fat Reduction (%)

<table>
<thead>
<tr>
<th>Target</th>
<th>Disease</th>
<th>Weeks</th>
<th>Treatment dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF19</td>
<td>NASH</td>
<td>12</td>
<td>Pbo 0 (n=27), NGM28 2</td>
</tr>
<tr>
<td>THR-β</td>
<td>NASH</td>
<td>36</td>
<td>Res 60/80 (n=74)</td>
</tr>
<tr>
<td>FXR</td>
<td>NASH</td>
<td>72</td>
<td>Res 80/100 (n=23)</td>
</tr>
<tr>
<td>FGF21</td>
<td>NAFLD</td>
<td>16</td>
<td>OCA/pb 25 (n=40/3)</td>
</tr>
<tr>
<td>ACC</td>
<td>NAFLD</td>
<td>12</td>
<td>Peg 10 sc (n=25)</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Early NAFLD</td>
<td>24</td>
<td>Lira 1.2 sc (n=68)</td>
</tr>
<tr>
<td>THR-β</td>
<td>Early NAFLD</td>
<td>12</td>
<td>Pegbo 9 10qod (n=13)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline fat fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.8</td>
</tr>
<tr>
<td>18.1</td>
</tr>
<tr>
<td>19.8</td>
</tr>
<tr>
<td>20.6</td>
</tr>
<tr>
<td>18</td>
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<tr>
<td>18–20</td>
</tr>
<tr>
<td>21</td>
</tr>
<tr>
<td>18</td>
</tr>
<tr>
<td>13.7</td>
</tr>
<tr>
<td>15.9</td>
</tr>
<tr>
<td>17.3</td>
</tr>
<tr>
<td>13.2</td>
</tr>
<tr>
<td>18.1</td>
</tr>
</tbody>
</table>

ACC, acetyl-CoA carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; Lira, liraglutide; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; Pbo, placebo; Peg, pegbelfermin; sc, subcutaneous; THR, thyroid hormone receptor. Harrison SA. Lancet. 2018;391:1174–85; Harrison AASLD 2018; Loomba AASLD 2017; Sanyal AJ. Lancet. 2018;392:2705–717; Loomba R. Gastroenterology. 2018;155:1463–1473; Petit JM. J Clin Endocrinol Metab. 2017;102:407–15; Loomba AASLD 2018.
## MRI-PDFF Absolute Fat Reduction (%)

<table>
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<tr>
<th>Target</th>
<th>Disease</th>
<th>Weeks</th>
<th>Treatment dose (mg)</th>
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<tbody>
<tr>
<td>FGF19</td>
<td>NASH</td>
<td>12</td>
<td>Pbo 0 (n=27)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NGM28 2 3 sc (n=27)</td>
</tr>
<tr>
<td>THR-β</td>
<td>NASH</td>
<td>36</td>
<td>Pbo 0 (n=33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Res 60/80 (n=74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Res 80/100 (n=23)</td>
</tr>
<tr>
<td>FXR</td>
<td>NASH</td>
<td>72</td>
<td>OCA/pb 25 (n=40/38)</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>16</td>
<td>Peg 10 sc (n=25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pbo 0 (n=26)</td>
</tr>
<tr>
<td></td>
<td>NAFLD</td>
<td>12</td>
<td>GS-0976 20 (n=46)</td>
</tr>
<tr>
<td></td>
<td>Early NAFLD</td>
<td>24</td>
<td>Lira 1.2 sc (n=68)</td>
</tr>
<tr>
<td></td>
<td>Early NASH</td>
<td>12</td>
<td>Peg 10 sc (n=25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pbo 0 (n=12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>VK280 9 10 qod (n=13)</td>
</tr>
</tbody>
</table>

**Baseline fat fraction**:
- FGF19: 16.8, 18.1
- THR-β: 19.8, 20.6
- FXR: 18
- FGF21: 18–20
- ACC: 21, 18
- GLP-1: 13.7, 15.9
- THR-β: 17.3, 13.2

**Absolute fat reduction (%)**:
- FGF19: -9.7, -11.5
- THR-β: -2.3, -8.5
- FXR: -3.4, -6.8
- FGF21: -1.3
- ACC: -6.4
- GLP-1: -1.1
- THR-β: -8.5

ACC, acetyl-CoA carboxylase; FGF, fibroblast growth factor; FXR, farnesoid X receptor; GLP-1, glucagon-like peptide-1; Lira, liraglutide; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; OCA, obeticholic acid; Pbo, placebo; Peg, pegbelfermin; sc, subcutaneous; THR, thyroid hormone receptor. Harrison SA. *Lancet*. 2018;391:1174–85; Harrison AASLD 2018; Loomba AASLD 2017; Sanyal AJ. *Lancet*. 2018;392:2705-717; Loomba R. Gastroenterology. 2018;155:1463–1473; Petit JM. *J Clin Endocrinol Metab*. 2017;102:407–15; Loomba AASLD 2018.
**NASH Resolution:** Ballooning = 0; Inflammation = 0,1; No worsening of fibrosis stage

<table>
<thead>
<tr>
<th>Treatment dose (n)</th>
<th>Weeks</th>
<th>Target</th>
<th>Baseline NAS</th>
<th>Baseline Fibrosis</th>
<th>Reduces NAS ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pbo 0 mg (n=404)</td>
<td>72</td>
<td>FXR</td>
<td>F1–3</td>
<td>F1–3</td>
<td></td>
</tr>
<tr>
<td>OCA 25 mg (n=407)</td>
<td></td>
<td>PPARαδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pbo 0 mg (n=76)</td>
<td>52</td>
<td>PPARαδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elafibranor 120 mg (n=75)</td>
<td>52</td>
<td>PPARαδ</td>
<td>4.9*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pbo 0 mg (n=40)</td>
<td>52</td>
<td>PPARαδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aramchol 600 mg (n=78)</td>
<td>52</td>
<td>PPARαδ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pbo 0 mg (n=34)</td>
<td></td>
<td>THR-β</td>
<td>4.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MGL-3196 60–80 mg (n=73)</td>
<td>36</td>
<td>THR-β</td>
<td></td>
<td>F1–3</td>
<td></td>
</tr>
<tr>
<td>3196 PDFF+ 60–80 mg (n=46)</td>
<td></td>
<td>THR-β</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *included NAS=3
- 36

*Fatty/bile acid SCD inh

**Table Notes:**
- NAS, NAFLD activity score
- OCA, obeticholic acid
- Pbo, placebo
- PDFF, proton density fat fraction
- PPAR, peroxisome proliferator-activated receptor
- THR, thyroid hormone receptor

For elafibranor only enrolled patients with NAS>3 at baseline were evaluated for NASH resolution

*Younossi ZM. EASL 2019 (F1–F3 population); Ratziu Gastroenterology 2016;150:1147–1159; Ratziu AASLD 2018; Harrison AASLD 2018.
NASH Resolution: "Non-NASH" or Ballooning=0; no worsening of fibrosis

GLP-1, glucagon-like peptide-1; Lira, liraglutide; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; Pbo, placebo; PPAR, peroxisome proliferator-activated receptor. sc, subcutaneous.

Correlation of Decrease in Hepatic Fat (MRI-PDFF) with NASH Resolution on Liver Biopsy

- Patients who were not MRI-PDFF Responders (≥30% fat reduction) had a low rate of NASH resolution (left panel).
- In both resmetirom (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: 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), blind to treatment code.

- Using SHG, resmetirom 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 resmetirom 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.
Fibroscan and Fibrosis Biomarker Changes at Week 36 (Extension)

Markers of fibrosis (kPa, kilopascals) liver stiffness on fibroscan, fibrosis (PRO-C3 and adiponectin) showed statistically significant improvement during the 36 Week Extension study.

BL, baseline, * baseline value; for PRO-C3, the original baseline was used for patients on resmetirom in the Main study; for patients on placebo in the Main study, the Extension study baseline was used.
# Phase 3/4: Resmetirom MAESTRO-NASH Trial: Recruiting

## Study Overview

<table>
<thead>
<tr>
<th>Study Overview</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>MGL-3196 (resmetirom)</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Blinded 1:1:1</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td>Phase 3/4</td>
</tr>
<tr>
<td><strong>Number of Patients</strong></td>
<td>Phase 3: 900 Phase 4: up to 2000</td>
</tr>
<tr>
<td><strong>Centers</strong></td>
<td>~150, USA; EU</td>
</tr>
<tr>
<td><strong>Treatment Duration</strong></td>
<td>52 Weeks; 4.5 years</td>
</tr>
</tbody>
</table>

## Inclusion/Exclusion
- NASH on liver biopsy: NAS≥4, high risk F1, F2/3

## Comparator/Arms
- Resmetirom 80 or 100 mg or Placebo, once daily

## Primary Endpoint
- Phase 3: Liver biopsy at 52 weeks - resolution of NASH associated with a ≥2 pt reduction in NAS and no worsening of fibrosis
- Phase 4: reduction in liver related events or progression to cirrhosis

## Key Secondary Endpoints
- LDL-C lowering
- ≥1 pt reduction in fibrosis with no worsening of NAS

## Other Secondary and Exploratory Endpoints
- Additional NASH biopsy endpoints
- Imaging MRI-PDFF
- Fibrosis biomarkers
Phase 3 Largely Replicates the Phase 2 Design at Higher Doses

<table>
<thead>
<tr>
<th>Phase 2 NASH</th>
<th>Phase 3 NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver biopsy confirmed NASH; NAS≥4 F1-3</td>
<td>NAS≥4, F2-F3, primary assessment; F1B</td>
</tr>
<tr>
<td>MRI-PDFF≥10% fat fraction</td>
<td>MRI-PDFF ≥8% fat fraction</td>
</tr>
<tr>
<td>Enrollment 125 1:2 placebo: resmetirom</td>
<td>Enrollment 900 1:1:1 placebo: 2 doses</td>
</tr>
<tr>
<td>Dose: 60, 80 mg once daily</td>
<td>Dose: <strong>80, 100 mg once daily</strong></td>
</tr>
<tr>
<td>36 Weeks</td>
<td>52 Weeks</td>
</tr>
<tr>
<td>Centers: USA, 30</td>
<td>Centers: Global, 150, primary USA</td>
</tr>
<tr>
<td>Primary endpoint: Relative reduction in liver fat on MRI-PDFF</td>
<td>Primary endpoint: NASH resolution with at least a 2-point reduction in NAS, no worsening of fibrosis <em>powered</em> &gt;&gt;90% to achieve endpoint</td>
</tr>
<tr>
<td>Secondary endpoints: 2-pt reduction in NAS</td>
<td>Key secondary endpoints:</td>
</tr>
<tr>
<td>LDL-C, other lipids</td>
<td>LDL-C <em>powered</em> &gt;&gt;90% to achieve endpoint</td>
</tr>
<tr>
<td>NASH resolution with at least a 2-point reduction in NAS and no worsening of fibrosis</td>
<td>At least a 1 stage reduction in fibrosis with no worsening of NAS <em>powered</em> &gt;90% to achieve endpoint</td>
</tr>
<tr>
<td>Multiple exploratory biomarkers for fibrosis, inflammation, imaging assessed in Phase 2 and 3</td>
<td>Phase 4: Clinical benefit, reduction in cirrhosis, liver related outcomes up to 4.5 years</td>
</tr>
</tbody>
</table>
Fatty Liver Associates with Overall CVD Mortality

Cumulative CVD Survival

- No fat in the liver
- Moderate fat accumulation
  - M1: HR 1.72 (CI 0.81-3.62)
  - M2: HR 1.40 (CI 0.65-3.00)
  - M3: HR 1.20 (CI 0.54-2.65)
- Severe fat accumulation
  - M1: HR 2.95 (CI 1.58-5.51) **
  - M2: HR 2.04 (CI 1.03-4.05) *
  - M3: HR 1.64 (CI 0.79-3.43)

Follow-up time (months)
CV Risk in NASH and NAFLD

- Strong association between NAFLD, particularly NASH fibrosis, and increased risk of CVD events and mortality
  - Death from CVD much more common than death from liver disease (Angulo, 2015)

- Patients with NAFLD have a pro-atherogenic lipid profile:
  - Increased triglycerides
  - Increased apolipoprotein B
  - Higher concentration of small dense LDL

- Fatty liver appears to confer an independent cardiovascular risk, potentially related to increased inflammation in NASH

- Thus, aggressive modification of CVD risk factors is mandatory in all patients with NAFLD
Week 36: Sustained Robust Lipid Lowering

Significant sustained lowering effect in multiple atherogenic lipids

-22.3
-27.6
-36
-36.8
-36.5

- Resmetirom is the only NASH therapeutic in advanced development able to lower lipids, consistent with regulatory approval for dyslipidemia; and also reduces fatty liver, an independent CV risk factor
- ApoB, not LDL-C is the major risk factor in CV disease
- NASH patients die of CV disease more frequently than liver disease

Lipids (% Change from Baseline)

Resmetirom compared with placebo; all analyses and cutoffs were prespecified; based on prespecified mITT; placebo n=39; Resmetirom n=79 (LOCF)
### Study Overview

<table>
<thead>
<tr>
<th>Drug</th>
<th>Resmetirom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>1:1:1:1</td>
</tr>
<tr>
<td>Stage</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Number of Patients</td>
<td>700</td>
</tr>
<tr>
<td>Centers</td>
<td>50, USA</td>
</tr>
<tr>
<td>Treatment Duration</td>
<td>12 months</td>
</tr>
</tbody>
</table>

### Study Details

#### Inclusion/Exclusion
- NASH/NAFLD (presumptive NASH, not NAFL)
  - Most patients not at target on standard care treatment (LDL-C ≥100 or TGs>150; ≥ 70 mg/dL in patients with CV disease, very high risk diabetics)
- Eligibility: fibroscan, NASH on biopsy
- Excludes advanced patients F2/F3 NAS≥4 who qualify for MAESTRO-NASH

#### Comparator/Arms
- Resmetirom 80, 100 mg or Placebo, once daily; open label 100 mg arm in up to 100 patients

#### Study key endpoints
- Safety, including safety biomarkers (e.g. liver enzymes)
- LDL cholesterol
- ApoB, TGs, Lp(a),
- MRI-PDFF (fatty liver)
- Fibrosis biomarkers
## Strong Positioning in NASH Landscape

<table>
<thead>
<tr>
<th>Target compound</th>
<th>NASH res</th>
<th>Fibrosis reduction</th>
<th>Liver Fat</th>
<th>NASH Prevention</th>
<th>Insulin Sensitivity</th>
<th>LDL</th>
<th>TGs</th>
<th>CV Risk</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>FXR—FGF-19</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>✓</td>
<td>✓</td>
<td>↑LDL-C</td>
<td>Pruritus (FXR)</td>
</tr>
<tr>
<td>Anti-fibrotic (e.g. selonsertib)</td>
<td>—</td>
<td>?</td>
<td>—</td>
<td>×</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Unknown</td>
</tr>
<tr>
<td>PPARαδ</td>
<td>✓</td>
<td>×</td>
<td>—</td>
<td>?</td>
<td>✓</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>PPARα/δ</td>
</tr>
<tr>
<td>Anti-steatotic (ACC; SCD; GLP-1)</td>
<td>✓</td>
<td>?</td>
<td>✓</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>or ↑</td>
<td>Liver risk? Well-tolerated</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>PPAR</td>
</tr>
<tr>
<td>Resmetirom</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>↓</td>
<td>↓</td>
<td>—</td>
<td>CV Benefit Well-tolerated</td>
</tr>
</tbody>
</table>

- Once a day oral medication, pleiotropic and cardio-beneficial actions position resmetirom as potential best-in-class NASH therapeutic
- Differentiated from other NASH agents
- Efficacy on NASH and cardiovascular endpoints position resmetirom to be used in combination with anti-fibrotic, anti-steatotic and/or anti-inflammatory agents
Catalysts: Our Expectations for Development Timing

Completed Milestones:

- Positive topline data from Phase 2 trial of resmetirom for HeFH
- Positive 36-week topline liver biopsy data from Phase 2 trial of resmetirom for NASH

2018

- Completion of 36 Week NASH Extension Study
- Initiation of Phase 3 Study MAESTRO-NASH
- Initiation of Phase 3 Study MAESTRO-NAFLD-1
- Phase 2 NASH publication, Lancet

2019

2020

- Publications and meeting presentations
- Ongoing NASH Phase 3 milestones
- Topline data from open label arm MAESTRO-NAFLD-1