Madrigal Pharmaceuticals, Inc.

NASDAQ: MDGL
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.
Madrigal Investment Highlights

MGL-3196: First-in-Class THR-β Agonist

• Phase 2 once-daily oral, liver-directed thyroid hormone receptor-β agonist (THR-β); efficacy and safety profile validated by preclinical and clinical data

Large & Underserved Markets in NASH & Genetic Lipid Disorders

• Initial indications are NASH and familial hypercholesterolemia; possibility to expand indications with either MGL-3196 or pre-clinical backup MGL-3745

Multiple Possible Value-Creating Catalysts over Next 18 Months

• Phase 2 NASH and HeFH trials initiated; other potential clinical trial initiation and data readouts throughout 2017 for NASH, HeFH & HoFH

Expected Funding to Key Inflection Points

• Cash resources sufficient to reach key clinical inflection points in NASH, HeFH & HoFH (~$40M at 9/30/2016)

Seasoned Management Team

• Experienced management team with proven track record in drug discovery, development and commercialization; expertise in liver diseases
Madrigal Leadership

- Combined company is led by an experienced management team with multiple successful NDA/EMAs and marketed products

- **Paul Friedman, M.D. - Chairman and CEO**
  - Former CEO of Incyte Pharmaceuticals; former President of DuPont Pharmaceuticals Research R & D

- **Rebecca Taub, M.D. - Chief Medical Officer, Executive Vice President, R&D**
  - Founder of Madrigal
  - Led teams that discovered Eliquis and MGL-3196, Madrigal’s lead compound
  - Recognized expert in liver regeneration and diseases of the liver

- **Marc Schneebaum - Chief Financial Officer, Senior Vice President**
  - SVP, CFO of Synta since 2014
  - Over 20 years of executive operational experience in the biotechnology and health care sector
MGL-3196, a First-in-Class Liver-Directed THR-β Agonist

- We believe MGL-3196 is the first bona fide THR-β selective molecule
  - β-selectivity and liver targeting are key to beneficial metabolic actions of thyroid hormone (triglyceride, cholesterol lowering and treatment of NASH) and avoiding safety issues
  - Discovery of MGL-3196 and backups at Roche utilized a novel functional assay that went beyond what previous companies had done (simple receptor binding assay)
    - Earlier compounds from other companies, purported to be THR-β selective, show no functional selectivity in this assay and, like thyroid hormone, activate the THR-α receptor equally well as the β receptor
  - MGL-3196: excellent safety; unlike another company’s earlier thyroid receptor agonist, no cartilage findings in chronic toxicology or ALT increases in human studies
Why MGL-3196 for NASH?

We believe that MGL-3196 will treat the underlying disease in NASH patients

- Hypothyroidism at the level of the thyroid gland is at least twice as common in individuals with NASH as in the general population* and increases the risk of of nonalcoholic fatty liver disease** (*Clinical Gastroenterology, 2003; 37(4):340-343; **J Clin Endocrinol Metab. 2016; 101(8):3204-3211)
- Liver-specific hypothyroidism, present in human NASH, is caused by degradation of thyroid hormone (increased deiodinase (DIO) 3 produced by stellate cells) in the NASH liver (Endocrinology. 2014; 155(11):4591-4601)
  - Treatment with MGL-3196 should normalize hepatic thyroid function
- MGL-3196 has pleiotropic effects characteristic of an “ideal” NASH drug
  - Potentially improves components of the metabolic syndrome, including insulin resistance & dyslipidemia
  - Potentially improves components of fatty liver disease (lipotoxicity/inflammation)
- NASH patients with advanced fibrosis have increased CV risk and primarily die of CV (not liver) disease (Hepatology. 2015; 61:1547-54, Gastroenterology, 2015; 149:389-97)
  - MGL-3196 lowers LDL-cholesterol and may provide CV benefit to NASH patients
- Treating NASH, rather than fibrosis, is key to addressing the disease
  - Recent FDA guidance indicates resolution of NASH, without reducing fibrosis, is an approvable endpoint
  - Recognition that liver fibrosis will decrease with time after NASH resolves (similar to reduction of fibrosis as the liver regenerates after cure of HCV)
MGL-3196: Improved Safety Profile Relative to T3

Thyroid hormone (T3, thyroxine) treatment may cause osteoporosis

Significantly reduced bone mineral density with T3
MGL-3196: Data Supports Improvement in Liver Health

Upper panels: 24d study in 17 wk old DIO mice (po, qd) on high fat diet (HFD) 13 wks; lower panels: 24d study in 40 wk old DIO mice on HFD 35 wks

Liver Size

Liver Triglycerides

Insulin Tolerance Test (0.5 U/kg insulin)

ALT

Liver Fat (Histology)

MGL-3196
- Reduced hepatic triglycerides (>50%), normalized liver size
- Insulin sensitivity improved at all doses
- Reduced liver enzymes (ALT, AST)
- Improved liver histology, reduced NASH score
MGL-3196: Reduction of Key NASH, Fibrosis Pathway Genes at Human Comparable Drug Levels

25 week study in lean control mice and HFD mice treated with Vehicle, 0.1 to 3 mg/kg MGL-3196 or Rosiglitazone (3mg/kg)

<table>
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<th>Inflammation</th>
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<tbody>
<tr>
<td>MCP-1/CCL2</td>
</tr>
<tr>
<td>MIP-2α/CXCL2</td>
</tr>
<tr>
<td>MIP-2β/CXLCL3</td>
</tr>
<tr>
<td>A20/TNFαip3</td>
</tr>
<tr>
<td>CRP</td>
</tr>
<tr>
<td>Annexin 2</td>
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<tr>
<td>SAA1</td>
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<table>
<thead>
<tr>
<th>Fibrosis</th>
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</thead>
<tbody>
<tr>
<td>Collagen 1</td>
</tr>
<tr>
<td>Galectin-3</td>
</tr>
<tr>
<td>TIMP1</td>
</tr>
<tr>
<td>Collagen 4a2</td>
</tr>
<tr>
<td>SMA</td>
</tr>
<tr>
<td>Collagen 4a1</td>
</tr>
<tr>
<td>CTGF</td>
</tr>
<tr>
<td>Keratin 18</td>
</tr>
<tr>
<td>Collagen 3</td>
</tr>
<tr>
<td>Galectin-1</td>
</tr>
</tbody>
</table>

“HFD”, lane 1 mean HFD gene expression normalized to mean Lean; Lanes (2-7) mean gene expression normalized to mean of DIO; “Rosi” (rosiglitazone, 3 mg/kg, 24 wks)

Red, higher expression; blue decreased expression

TIMP1 tissue inhibitor metalloproteinase
CTGF connective tissue growth factor
SMA smooth muscle actin
SAA serum amyloid A
CRP C-reactive protein
THR-ß Agonism: Expected Direct Anti-Fibrotic Actions

• Fat deposition, lipotoxicity and resultant local inflammation are seen in NASH

• Hepatocyte dysregulation and damage ensue up to and including apoptosis. These perturbations lead to a profibrotic environment through:
  o Ongoing inflammation;
  o Production by the dysregulated / damaged / dying hepatocytes of profibrotic factors, with TGF-Beta among the most important

• Thyroid Hormone Receptor agonism has been shown to dampen inflammation in vivo and to inhibit TGF-Beta signaling in cell culture and in vivo

• In animal models of liver fibrosis, the extent of fibrosis is decreased by Thyroid Hormone administration and increased if Thyroid Hormone Receptor is knocked out.

• Thyroid Hormone Receptor Beta is the operative receptor in hepatocytes
THR-ß: Decreased Liver Fibrosis and Apoptosis

- THR-ß -/- mice have increased liver fibrosis with age
- Treatment with thyroid hormone reduces fibrosis in animal models of liver fibrosis PNAS 2016

Fig. 8. Genetic deletion of TRs causes spontaneous liver fibrosis in aged mice.

- THR-ß knockout and hypothyroid mice have delayed liver regeneration, increased apoptosis
MGL-3196: Long-term Dosing in Humans is Enabled

**Completed:**

- Single Ascending Dose (SAD) study

- Multiple Ascending Dose (MAD) study
  - Six dose cohorts, 36 total HV dosed daily with MGL-3196 (5, 20, 50, 80, 100, or 200 mg) and 12 with placebo for 14 days
    - Healthy volunteers with slightly elevated LDL cholesterol (> 110 mg/dL)
    - Well-tolerated, appeared safe at all doses tested
    - No effect on vital signs, heart rate, central thyroid axis, or liver enzymes

- Phase 1 studies dosing MGL-3196 with statins

- Series of GLP toxicology and CMC studies support all indications
  - Manufacturing and product formulation
  - Chronic toxicology package
  - Phase 2-enabling
MGL-3196: Robust LDL and Triglyceride Lowering in 14 Day Multiple Dose Phase 1 Study

Once daily oral treatment led to highly significant and dose-dependent up to ~30% reduction of apolipoprotein B (ApoB), total, LDL, non-HDL cholesterol; Strong trends in triglyceride reduction up to 60%; Near maximal effect at 80mg dose.
### Strong Positioning in NASH Landscape

<table>
<thead>
<tr>
<th>Target compound</th>
<th>NAS Score</th>
<th>Fibrosis Score</th>
<th>Liver Lipids</th>
<th>NASH Prevention</th>
<th>Insulin Sensitivity</th>
<th>LDL</th>
<th>TGs</th>
<th>CV Risk</th>
<th>Side Effects</th>
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<tbody>
<tr>
<td>FXR</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>↑</td>
<td>—</td>
<td>↑LDL-C</td>
<td>Pruritus</td>
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<tr>
<td>Anti-fibrotic</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>PPARα/δ</td>
<td>Well-tolerated</td>
</tr>
<tr>
<td>Anti-inflam</td>
<td>✔</td>
<td>?</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>?</td>
<td>Well-tolerated</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>↓</td>
<td>↓</td>
<td>PPAR</td>
<td>CHF, ↓ bone, ↑ weight</td>
</tr>
<tr>
<td>MGL-3196</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>↓</td>
<td>↓</td>
<td>CV Benefit</td>
<td>Well-tolerated</td>
</tr>
</tbody>
</table>

- Pleiotropic and cardio-beneficial actions position MGL-3196 as potential best-in-class NASH therapeutic
- Opportunities for differentiation from other NASH agents
- Efficacy on NASH and cardiovascular endpoints position MGL-3196 to be used in combination with anti-fibrotic and/or anti-inflammatory agents
# Phase 2 Proof-of-Concept NASH Protocol

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
<td>MGL-3196</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Blinded 2:1</td>
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<tr>
<td><strong>Stage</strong></td>
<td>Ph2</td>
</tr>
<tr>
<td><strong># Patients</strong></td>
<td>117</td>
</tr>
<tr>
<td><strong>Centers</strong></td>
<td>TBD</td>
</tr>
<tr>
<td><strong>Treatment duration</strong></td>
<td>36 weeks</td>
</tr>
</tbody>
</table>

**Inclusion/Exclusion**
- NASH on liver biopsy
- Include diabetics, statin therapy

**Comparator/Arms**
- MGL-3196 or Placebo, once daily

**Primary Endpoint**
- Reduction of liver fat (MRI-PDFF) at 12 weeks

**Secondary Endpoints**
- Biomarkers at 12, 36 weeks
- Liver biopsy at 36 weeks - reduction/resolution of NASH in patients on drug
MGL-3196 Phase 2 NASH Study: Likelihood of Success

- Excellent correlation between decline in fat content on MRI-PDFF and NAS score, steatosis and ballooning on biopsy (Ther. Adv. Gastroenterol. 2016; 9:692-701)


*We believe that the impressive preclinical NASH animal and human lipid lowering effects coupled with the excellent safety profile point to a high probability of success*
Unmet Needs in FH, a Severe Genetic Dyslipidemia

Severe Debilitating Dyslipidemia

- HeFH and HoFH caused primarily by inactivating mutations in LDL receptor
- Early onset cardiovascular disease, HoFH < age 20

Prevalence

- 1/200-1/500 HeFH; 1/250,000-1/1,000,000 HoFH
- Higher frequency in certain genetically homogeneous populations

Novel Therapeutic Approaches Needed

- Despite current and newer therapies (i.e. PCSK9 ab), HoFH and many HeFH (severe HeFH) not achieving treatment goals
- Significant commercial opportunity for MGL-3196 in HoFH, refractory HeFH
Current Challenges in Treatment of FH

**HoFH**
- Most patients still not reaching LDL-C goal
- Newer agents, Lomitapide (Juxtapid, MTPi) and Mipomersen (Kynamro, anti-ApoB) may have safety issues
  - Both carry FDA label warning*, hepatotoxicity
  - Increased ALT and hepatic fat
- Elevated Lp(a) remains an issue

**HeFH**
- In HeFH, PCSK9 inhibitors plus standard care (statins, ezetimibe) some HeFH still not achieving goal
- Further treatment opportunities include relative statin intolerance in some and elevated Lp(a)

<table>
<thead>
<tr>
<th>HoFH Lipid Lowering Therapy</th>
<th>LDL decrease</th>
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<tbody>
<tr>
<td>Conventional</td>
<td></td>
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<tr>
<td>Statins</td>
<td>Up to 28%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>LDL apheresis</td>
<td>20-40%</td>
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</table>

<table>
<thead>
<tr>
<th>New Treatment Options</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lomitapide</td>
<td>Up to 50%</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>25%</td>
</tr>
<tr>
<td>PCSK9 inh</td>
<td>23%</td>
</tr>
</tbody>
</table>

*In FH, we believe MGL-3196 will deliver additional LDL-C and Lp(a) lowering on top of conventional treatment*
MGL-3196: Unique and Complementary Lipid Lowering Profile

- **Thyroid pathway clinically validated and differentiated in FH**

- Both LDL receptor-dependent and –independent cholesterol lowering:
  - Stimulates cholesterol breakdown and elimination
  - Lowers ApoB and Lp(a)
  - Decreases levels of PCSK9 (human data) and angiopoietin-like protein 3 ANGPTL3 (gene expression)

- MGL-3196 lowers LDL in concert with statins in clinical & preclinical studies
- Thyroid agonists lower cholesterol in LDL receptor knockout mice*
- In Phase 3 trials in HeFH, an earlier THR agonist lowered LDL cholesterol and Lp(a)**
- MGL-3196 acts through a mechanism that potentially lowers Lp(a), a severely atherogenic particle that is elevated in FH

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* Endocrinology 2012 Nov;153(11):5143-9
** Lancet Diabetes Endocrinol 2014; 2: 455–63
# Proposed Phase 2 HeFH Clinical Trial Protocol

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<td>Ph2</td>
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<td># Patients</td>
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<td>Centers</td>
<td>TBD</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>12 weeks</td>
</tr>
</tbody>
</table>

### Inclusion/Exclusion
- FH on low, high dose statins, ezetimibe

### Comparator/Arms
- MGL-3196 or Placebo, once daily

### Primary Endpoint
- LDL cholesterol lowering

### Secondary Endpoints
- TGs, Lp(a), ApoB lowering
- Safety
# Proposed Phase 2a HoFH Clinical Trial Protocol

<table>
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<tbody>
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<tr>
<td>Design</td>
<td>Open label</td>
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<tr>
<td>Stage</td>
<td>Ph2</td>
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<td># Patients</td>
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<tr>
<td>Centers</td>
<td>6</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>12 weeks</td>
</tr>
<tr>
<td></td>
<td><strong>Inclusion/Exclusion</strong></td>
</tr>
<tr>
<td></td>
<td>• HoFH on standard care, may include PCSK9ab, statins, ezetimibe</td>
</tr>
<tr>
<td></td>
<td><strong>Comparator/Arms</strong></td>
</tr>
<tr>
<td></td>
<td>• Patient is his own control</td>
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<tr>
<td></td>
<td>• MGL-3196 may be titrated</td>
</tr>
<tr>
<td></td>
<td><strong>Primary Endpoint</strong></td>
</tr>
<tr>
<td></td>
<td>• LDL cholesterol lowering</td>
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<tr>
<td></td>
<td><strong>Secondary Endpoint</strong></td>
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<tr>
<td></td>
<td>• TGs, Lp(a), ApoB lowering</td>
</tr>
<tr>
<td></td>
<td>• Safety</td>
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Potential Near and Long-term Value Drivers

2016

Clinical trial initiated:
• Ph2 in NASH: 12 week MRI-PDFF with 36-week liver biopsy

Completed Previously:
• MGL-3196 long-term toxicology studies
• MGL-3196 dosed with statins in Ph1 studies (2015-2Q2016)

2017

Clinical trial initiations:
• Ph2 in HeFH: 12-week clinical trial (initiated)
• Ph2a in HoFH: 12-week clinical trial

Potential Data Readouts:
• Ongoing safety assessment, Phase 2 trials
• Ph2 topline results in HeFH
• Ph2 topline results in NASH (12 weeks)

2018

Potential Data Readouts:
• Ph2 topline results in NASH (liver biopsy)
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Thank you

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