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 in 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 follow-on MGL-3745

Multiple Possible Value-Creating Catalysts over Next 18 Months

- Phase 2 NASH & HeFH trials initiated; enrollment completed for NASH trial, nearing completion for HeFH. HoFH pilot study planned.

Expected Funding to Key Inflection Points

- Cash resources sufficient past key clinical inflection points in NASH and HeFH and into 2019 (~$67M at 6/30/2017, incl. $35M June financing)

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/MAAs 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
The Importance of Liver THR-β in NASH

We believe that MGL-3196, a selective THR-β agonist, will treat the underlying disease in NASH patients

- The THR-β receptor mediates the beneficial effects of thyroid hormone in the liver, on LDL-cholesterol and triglycerides, fatty liver and insulin sensitivity
  - Lipid benefits of liver THR-β established by decades of clinical experience
- The liver is hypothyroid in NASH: treatment with MGL-3196 should normalize hepatic thyroid function
  - 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 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)
- MGL-3196 has pleiotropic effects characteristic of an “ideal” NASH drug, with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooned, pre-apoptotic hepatocytes, fibrosis (both directly and indirectly)
- 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
  - 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, a First-in-Class Liver-Directed THR-β Agonist

- We believe MGL-3196 is the first bona fide THR-β selective molecule with key advantages over previous companies’ analogues
  - 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
  - *in vivo* data confirm MGL-3196’s high liver uptake and preclinical safety: no heart, bone/cartilage, or brain uptake; safe in long-term animal toxicology studies
    - Avoids activity at the systemic THR-α receptor (increased heart rate, osteoporosis)
    - Unlike other company’s earlier thyroid receptor agonists, no cartilage findings in chronic toxicology or liver enzyme increases in human studies
MGL-3196: Improved Safety Profile Relative to T3

24d study in 40 week old diet-induced obese (DIO) mice on High Fat Diet (HFD) for 38 weeks

Thyroid hormone (T3, thyroxine) treatment may cause osteoporosis

Significantly reduced bone mineral density with T3

BMJ 2011;342:d2238

p<.05*
p<.01**
P<.001***
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 3 mg/kg

• 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)

**Inflammation**
- MCP-1/CCL2
- MIP-2α/CXCL2
- MIP-2β/CXCL3
- A20/TNFαip3
- CRP
- Annexin 2
- SAA1

**Fibrosis**
- Collagen 1
- Galectin-3
- TIMP1
- Collagen 4a2
- SMA
- Collagen 4a1
- CTGF
- Keratin 18
- Collagen 3
- Galectin-1

“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-β 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:
  • Ongoing inflammation;
  • Production by the dysregulated / damaged / dying hepatocytes of profibrotic factors, with TGF-β among the most important

• Thyroid hormone receptor agonism has been shown to dampen inflammation in vivo and to inhibit TGF-β 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 receptors are knocked out (PNAS 113: 3451, 2016)

• THR-β is the operative receptor in hepatocytes
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
Lipid Lowering in Additional Phase 1 Studies

In Phase 1 studies, 38 healthy volunteers were dosed with one-two days of a statin and multiple daily doses (9-11) of MGL-3196 (100 or 200 mg).

Robust lipid lowering was observed (up to 60% LDL-C), subjects reaching an average LDL-C of 70 mg/dL, ApoB of 59 mg/dL.

Consistent with MAD data, subjects with higher MGL-3196 exposures did not demonstrate more lipid lowering.

Baseline (BL); triglycerides (TG) (all) or >150 mg/dL at BL; Lp(a) shown only for subjects with measurable BL Lp(a)
# Phase 2 Proof-of-Concept NASH Protocol

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Details</th>
</tr>
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<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>
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<tr>
<td><strong># Patients</strong></td>
<td>117</td>
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<td><strong>Centers</strong></td>
<td>~30, USA</td>
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<tr>
<td><strong>Treatment duration</strong></td>
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</table>

## Inclusion/Exclusion
- NASH on liver biopsy
- 10% liver fat on MRI-PDFF
- 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
- NASH biomarkers and lipids at 12, 36 weeks
- Repeat MRI-PDFF at 36 weeks
- Liver biopsy at 36 weeks - reduction/resolution of NASH in patients on drug; reduction of fibrosis
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)


- First regularly scheduled DSMB meeting held May 2017 to review data from the Madrigal NASH Phase 2 trial
  - DSMB recommended to continue the trial with no changes to the protocol

_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._
Strong Positioning in NASH Landscape

- 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
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, HoFH and most HeFH not achieving treatment goals on standard care
- Significant commercial opportunity for MGL-3196 in HoFH, refractory HeFH
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

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

* Endocrinology 2012 Nov;153(11):5143-9
** Lancet Diabetes Endocrinol2014; 2: 455–63
## Phase 2 HeFH Clinical Trial Protocol

<table>
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<th>Study</th>
<th>Study Details</th>
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<td>Drug</td>
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<td>Design</td>
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<tr>
<td>Stage</td>
<td>Ph2</td>
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<td># Patients</td>
<td>105</td>
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<td>Centers</td>
<td>13, Europe</td>
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<tr>
<td>Treatment duration</td>
<td>12 weeks</td>
</tr>
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</table>

**Inclusion/Exclusion**
- HeFH on maximally tolerated statins (typically high dose), ezetimibe

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

**Primary Endpoint**
- LDL cholesterol lowering

**Secondary Endpoints**
- TGs, Lp(a), ApoB lowering
- Safety
Potential Near and Longer-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 initiation:
• Ph2 in HeFH: 12-week clinical trial (initiated)

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

2018

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

NASDAQ: MDGL
Back Up Slides
NASH: High Prevalence and Significant Mortality

- NASH was coined over 40 years ago, to describe fatty changes with lobular hepatitis on liver biopsy in the absence of a history of alcoholism
  - NAS score: ballooned hepatocytes, steatosis, inflammation
  - Fibrosis score: Stage 1-3; cirrhosis, stage 4
- Improved non-invasive imaging and biomarker tests allow for possibilities to diagnosis and monitor NASH
- Increased prevalence of NASH because of epidemic of obesity and metabolic syndrome (obesity, hypertension, dyslipidemia, insulin resistance/diabetes)
- NASH is associated with significant mortality from liver and CV disease
  - NASH is expected to become the leading cause of liver transplant
- No approved therapies, first line consists of lifestyle modification

~5% of the US population has NASH

NAFLD is the most common liver disease world-wide
~25% of US population

Rapid progression, <2 years 25% of NASH
Stage 3 progress to cirrhosis

<table>
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<tr>
<th>Mortality in NAFLD/NASH</th>
<th>NAFLD</th>
<th>NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year Survival</td>
<td>Normal</td>
<td>67%</td>
</tr>
<tr>
<td>10-year Survival</td>
<td>Normal</td>
<td>38%</td>
</tr>
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</table>
MGL-3196 Agonism of Hepatic THR-β

- In livers of euthyroid individuals T3 induces about half the maximal transcriptional activity of THR-beta.

- MGL-3196 can further beneficially increase this transcriptional activity as we have shown in euthyroid animal models and humans.

- Interestingly, systemic hypothyroidism, at the level of the thyroid gland itself, leads to increases in plasma lipids (LDL-C and triglycerides) and increases the risk of nonalcoholic fatty liver disease.

- In fact, actual NASH is at least twice as common in hypothyroid individuals as in the general population.

- Further, liver-specific hypothyroidism is present in human NASH, caused by degradation of thyroid hormone (increased deiodinase 3 produced by stellate and inflammatory cells) in the NASH liver.
  - In a vicious cycle this liver-specific hypothyroidism increases as NASH progresses.
  - Thus, MGL-3196, which is not affected by deiodinases, can increase transcriptional activity over an even broader range than in the non-NASH euthyroid state.
  - With MGL-3196-induced resolution of NASH, with the concomitant decrease in numbers and level of activation of stellate cells, normalization of hepatic thyroid function should occur.
THR-β: Decreased Liver Fibrosis and Apoptosis

- THR-β -/- mice have increased liver fibrosis with age
- Treatment with thyroid hormone reduces fibrosis in animal models of liver fibrosis (PNAS 113: 3451, 2016)

- THR-β knockout and hypothyroid mice have delayed liver regeneration, increased apoptosis (PLoS ONE 5(1): e8710, 2010)
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, standard care (statins, ezetimibe) most HeFH still not achieving goal
  - Even with PCSK9 inh 40% not at target
- 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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<tr>
<td>Conventional</td>
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<tr>
<td>Statins</td>
<td>Up to 28%</td>
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<tr>
<td>Ezetimibe</td>
<td>&lt;10%</td>
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<tr>
<td>LDL apheresis</td>
<td>20-40%</td>
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<table>
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<tr>
<th>New Treatment Options</th>
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<tbody>
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<td>Lomitapide</td>
<td>Up to 50%</td>
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<td>Mipomersen</td>
<td>25%</td>
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<tr>
<td>PCSK9 inh</td>
<td>23%</td>
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# Proposed Phase 2a HoFH Clinical Trial Protocol

<table>
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<tr>
<td><strong>Drug</strong></td>
<td>MGL-3196</td>
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<tr>
<td><strong>Inclusion/Exclusion</strong></td>
<td>HoFH on standard care, may include PCSK9ab, statins, ezetimibe</td>
</tr>
<tr>
<td><strong>Comparator/Arms</strong></td>
<td>Patient is his own control, MGL-3196 may be titrated</td>
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<tr>
<td><strong>Stage</strong></td>
<td>Ph2</td>
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<td><strong># Patients</strong></td>
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<td><strong>Centers</strong></td>
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<td><strong>Treatment duration</strong></td>
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<td><strong>Primary Endpoint</strong></td>
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