Madrigal’s MGL-3196 Achieves Primary Endpoint in Patients with Biopsy-proven Non-alcoholic Steatohepatitis (NASH) in Phase 2 Clinical Trial

-- Statistically significant improvement in the relative decrease in liver fat in patients treated with MGL-3196 compared with placebo, determined by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) at 12-weeks, the primary end point in this Phase 2 proof-of-concept trial--

-- Statistically significantly more MGL-3196 than placebo treated patients achieved clinically relevant (at least 30%) liver fat reduction at 12 weeks relative to baseline MRI-PDFF--

-- Statistically significant improvements in drug-treatment group compared to placebo in low-density lipoprotein cholesterol (LDL-C), triglycerides and lipoprotein (a) (Lp(a)); these lipids when elevated are associated with increased cardiovascular risk--

-- Statistically significant improvements in liver enzymes in drug-treatment group, with very good all subject tolerability, few serious adverse events, none related to MGL-3196--

-- Clinical trial continues blinded with potential for correlating improvement in non-invasive imaging test (MRI-PDFF at 12 and 36 weeks) with improvement in repeat liver biopsy obtained at 36 weeks--

- Conference call scheduled for 8:30 AM Eastern Time today -

Conshohocken, PA – December 6, 2017 – Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) today announced positive top-line results from a Phase 2 clinical trial in patients with biopsy-proven non-alcoholic steatohepatitis (NASH). In this trial, MGL-3196, a first-in-class, oral, once-daily, liver-directed, thyroid hormone receptor (THR) \( \beta \) -selective agonist, demonstrated statistically significant results for the primary endpoint, the percent change in hepatic fat versus placebo as measured by MRI-PDFF, a non-invasive imaging test. Recent published data have shown a high correlation of the reduction of liver fat of 30% or more as measured by MRI-PDFF to improvement in NASH on liver biopsy.

<table>
<thead>
<tr>
<th>Numbers of patients</th>
<th>ALL MGL-3196</th>
<th>HIGH MGL-3196**</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of patients</td>
<td>78</td>
<td>44</td>
<td>38</td>
</tr>
<tr>
<td>Relative change in MRI-PDFF (% change from baseline, median)</td>
<td>-36.3%</td>
<td>-42.0%</td>
<td>-9.6%</td>
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<tr>
<td>Significance relative to placebo</td>
<td>p&lt;0.0001</td>
<td>p&lt;0.0001</td>
<td></td>
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</tbody>
</table>
Percentage of patients attaining ≥30% liver fat reduction
| Significance relative to placebo |
|-------------------------------|------------------|------------------|
| 60.3%                         | 75.0%            | 18.4%            |
| p<0.0001                      | p<0.0001         |                  |

**Prespecified group of patients (44/78) with relatively higher MGL-3196 drug levels**

Statistically significant reductions in ALT and AST were observed in MGL-3196 treated patients; greater reductions in ALT and AST, statistically significant relative to placebo, were observed in the prespecified group of 44/78 patients with relatively higher MGL-3196 drug levels. In drug-treated relative to placebo patients, statistically significant improvements were also seen in multiple secondary endpoints considered to be potentially clinically relevant in patients with NASH including LDL-C, triglycerides, apolipoprotein B (ApoB), and Lp(a).

MGL-3196 has been well-tolerated with mostly mild AEs, and a few moderate AEs, the numbers of which are balanced between placebo and drug-treatment groups. There are no adverse effects of MGL-3196 on safety laboratory or vital sign parameters. There have been three serious adverse effects in the study, all considered unrelated to MGL-3196.

The on-going study remains blinded. Safety, efficacy of NASH resolution by biopsy, and repeat MRI-PDFF will be assessed at 36 weeks. Multiple inflammatory and fibrosis serum biomarkers at 12 and 36 weeks are being and will be assessed.

"NASH is a common liver disease in the United States, with a growing prevalence, for which no FDA approved treatment is yet available," said Dr. Stephen Harrison, M.D., Principal Investigator of the study as well as Medical Director for Pinnacle Clinical Research, San Antonio, Texas, and Visiting Professor of Hepatology, Oxford University. “These results suggest that a highly selective liver-directed, thyroid hormone receptor-β agonist may be able to effectively and safely treat patients with NASH. Importantly, the study is designed to allow correlations between efficacy in a non-invasive imaging test, MRI-PDFF at 12 and 36 weeks, and improvement in NASH on liver biopsy at 36 weeks.”

Rebecca Taub, M.D., Chief Medical Officer and Executive VP, Research & Development of Madrigal added, “Results from this study confirm what we have seen in both our preclinical and earlier clinical studies and support our long-standing confidence in the safety and potential therapeutic value of MGL-3196. We fully expect data at 36 weeks to confirm results seen at 12 weeks, and potentially show improvement in NASH on liver biopsy. We look forward to the presentation of the 12-week, Phase 2 results to the scientific and clinical community, and further development of MGL-3196 for treatment of patients with NASH.”

Paul Friedman, M.D., Chief Executive Officer of Madrigal, stated, “We are gratified to see clinical results that strongly suggest MGL-3196 has the potential to provide clinically meaningful improvement of NASH by targeting lipotoxicity and inflammation as well as by reduction of cardiovascular risk by lowering atherogenic lipids. These pleiotropic actions, coupled with the excellent safety profile we have seen in this trial, continue to suggest that MGL-3196 has the potential to address the root causes of the underlying disease process in NASH.”

**Conference Call and Webcast Information**
Madrigal will hold a conference call and webcast this morning at 8:30 a.m. ET. To access the conference call, please dial 833-660-2754 for domestic callers or 409-350-3497 for international callers. When prompted, provide the conference identification number, 5577478.
The conference call will also be webcast live and can be accessed at [http://www.madrigalpharma.com/newsroom/presentations/](http://www.madrigalpharma.com/newsroom/presentations/) in the “Events and Presentations” section of the Madrigal website.

If you are unable to participate, a replay of the conference call will be available on the website under [http://www.madrigalpharma.com/newsroom/presentations/](http://www.madrigalpharma.com/newsroom/presentations/).

**About the Phase 2 NASH Study**
The randomized, double-blind, placebo-controlled, multi-center Phase 2 study enrolled 125 patients 18 years of age and older with liver biopsy-confirmed NASH and included approximately 25 clinical sites in the United States. Patients were randomized to receive either placebo or MGL-3196 with twice as many patients receiving MGL-3196 as placebo. The starting dose in 3196-treated patients was 80 mg once a day. The study employed an adaptive dosing design whereby, in a blinded fashion, the dose could be adjusted by small amounts (i.e. 20 mg up or down) or remain at 80 mg in each 3196-treated patient based on a pharmacokinetic analysis of drug level performed in each patient at 2 weeks.

The primary endpoint of the study is the reduction of liver fat at 12 weeks compared with baseline (relative change), assessed by MRI-PDFF, with efficacy confirmed at the end of the trial (36 weeks) by repeat MRI-PDFF and conventional liver biopsy to examine histological evidence for the resolution of NASH. A total of 116 patients completed the 12 week MRI-PDFF; the 9 discontinuations were balanced between placebo and drug treated; 2/9 discontinuations were AE-related.

Other secondary endpoints include changes in clinically relevant biomarkers at 12 and 36 weeks, improvement in fibrosis by at least one stage with no worsening of steatohepatitis, and safety and tolerability. Results at 36-weeks are expected in the second quarter of 2018. Additional information about the study [NCT02912260] can be obtained at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov).

**About MGL-3196**
Among its many functions in the human body, thyroid hormone, through activation of its beta receptor, plays a central role in controlling lipid metabolism, impacting a range of health parameters from levels of serum cholesterol and triglycerides to the pathological buildup of fat in the liver. Attempts to exploit this pathway for therapeutic purposes in cardio-metabolic and liver diseases have been hampered by the lack of selectivity of older compounds for the thyroid hormone receptor (THR)-β, chemically-related toxicities and undesirable distribution in the body.

Madrigal recognized that greater selectivity for thyroid hormone receptor (THR)-β and liver targeting might overcome these challenges and deliver the full therapeutic potential of THR-β agonism. Madrigal believes that MGL-3196 is the first orally administered, small-molecule, liver-directed, truly β-selective THR agonist. MGL-3196 has demonstrated the potential for a broad array of therapeutically beneficial effects, improving components of both metabolic syndrome, such as insulin resistance and dyslipidemia, and fatty liver disease, including lipotoxicity and inflammation. These pleiotropic actions, coupled with an excellent safety profile, suggest that MGL-3196 could be the preferred treatment option for NASH.
About Madrigal Pharmaceuticals
Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL) is a clinical-stage biopharmaceutical company pursuing novel therapeutics that target a specific thyroid hormone receptor pathway in the liver, which is a key regulatory mechanism common to a spectrum of cardio-metabolic and fatty liver diseases with high unmet medical need. Madrigal’s lead candidate, MGL-3196, is a first-in-class, orally administered, small-molecule, liver-directed, thyroid hormone receptor (THR) β-selective agonist that is currently in Phase 2 development for NASH and HeFH. For more information, visit www.madrigalpharma.com.

Forward-Looking Statements
This communication contains “forward-looking statements” made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. Such statements contain words such as “expect,” “could,” “may,” “will,” “believe,” “estimate,” “continue,” “future,” or the negative thereof or comparable terminology and the use of future dates. Forward-looking statements reflect management’s current knowledge, assumptions, judgment and expectations regarding future performance or events. Although management believes that the expectations reflected in such statements are reasonable, they give no assurance that such expectations will prove to be correct and you should be aware that actual results could differ materially from those contained in the forward-looking statements. Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to, the company’s clinical development of MGL-3196, the timing and outcomes of clinical studies of MGL-3196, and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward-looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the occurrence of unanticipated events. Please refer to Madrigal’s filings with the U.S. Securities and Exchange Commission for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied.

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