Madrigal Pharmaceuticals

MAESTRO-NAFLD-1 Topline Data Review

January 31st, 2022
8-9am EST

Resmetirom is an investigational therapy and has not been approved by the FDA (or any other regulatory authority). Resmetirom is only available for use in a clinical trial setting (ClinicalTrials.gov NCT03900429, NCT04197479).

NASDAQ: MDGL

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, that are based on our beliefs and assumptions and on information currently available to us but are subject to factors beyond our control. Forward-looking statements include but are not limited to statements or references concerning: our clinical trials, including the anticipated timing of disclosure or presentations of data from our trials; research and development activities; market size and patient treatment estimates for NASH and NAFLD patients; the timing and results associated with the future development of our lead product candidate, MGL-3196 (resmetirom); our primary and secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; plans, objectives and timing for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to FDA; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment or biomarker effects with resmetirom; the efficacy and safety of resmetirom for non-cirrhotic NASH patients and cirrhotic NASH patients; ex-U.S. launch/partnering plans; the predictive power of liver fat reduction measured by non-invasive tests on NASH resolution with fibrosis reduction or improvement; the predictive power of liver fat liver volume changes or MAST scores for NASH and/or NAFLD patients; the effects of resmetirom's mechanism of action; the achievement of enrollment objectives concerning patient number, safety database and/or timing for our studies; the predictive power of NASH resolution and/or liver fibrosis reduction with resmetirom using non-invasive tests, including the use of ELF, FibroScan, MRE and/or MRI-PDFF; the ability to develop clinical evidence demonstrating the utility of non-invasive tools and techniques to screen and diagnose NASH and/or NAFLD patients; the predictive power of non-invasive tests generally, including for purposes of diagnosing NASH, monitoring patient response to resmetirom, or recruiting a NASH clinical trial; potential NASH or NAFLD patient risk profile benefits with resmetirom; the potential for resmetirom to become the best-in-class and/or first-to-market treatment option for patients with NASH and liver fibrosis; and our possible or assumed future results of operations and expenses, business strategies and plans, capital needs and financing plans, trends, market sizing, competitive position, industry environment and potential growth opportunities, among other things. Forward-looking statements: reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; and can be identified by terms such as "allow," "anticipates," "be," "believes," "continue," "could," "demonstrate," "design," "estimates," "expects," "forecasts," "future," "goal," "hopeful," "inform," "intends," "may," "might," "planned", "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will be," "would" or similar expressions and the negatives of those terms. Although management presently believes that the expectations reflected in such forward-looking statements are reasonable, it can 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: our clinical development of resmetirom; enrollment uncertainties, generally and in relation to COVID-19-related measures that may be continued for an uncertain period of time or implemented; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that include substantially more patients than our prior studies; limitations associated with early stage, non-placebo controlled study data; the timing and outcomes of clinical studies of resmetirom; 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 submissions filed or furnished 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. We specifically discuss these risks and uncertainties in greater detail in the section entitled "Risk Factors" in our Annual Report on Form 10-K for the year ended December 31, 2020, as well as in our other filings with the SEC.

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Agenda

1.	**Introduction**	Paul Friedman, M.D., Chief Executive Officer
2.	**MAESTRO-NAFLD-1 Topline Data**	Becky Taub, M.D., Chief Medical Officer and President of R&D Stephen Harrison, M.D., Medical Director for Pinnacle Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and Principal Investigator of the MAESTRO studies
3.	**Q&A**	

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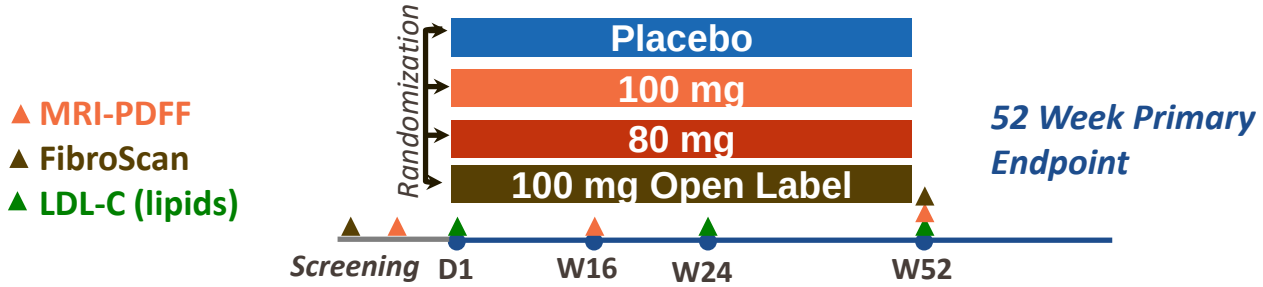
MAESTRO-NAFLD-1 Topline Data Review

"These positive results from the first of our two Phase 3 MAESTRO trials support our conviction that resmetirom has the potential to be the first medication approved for the treatment of patients with NASH and liver fibrosis."

- ***Paul A. Friedman, M.D., Chairman and Chief Executive Officer***

Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled with 100 mg Open Label Arm



Comparator/Arms

- Randomized 1:1:1:1 resmetirom 80, 100 mg , placebo, open label 100 mg
- 1143 presumed NASH patients enrolled in the USA (~80 sites)
  - 972 randomized to double-blind arms; 171 open label patients completed randomization of this arm July 1, 2020
- Additional ongoing cohorts include well compensated NASH cirrhosis open label arm (n>150); some additional screen fail patients from MAESTRO-NASH with F2-F3 stage fibrosis and NAS<4

Inclusion/Exclusion

- Requires 3 metabolic risk factors (Metabolic Syndrome)
- FibroScan (VCTE) kPa≥ 5.5 and ≤8.5, CAP≥280, except at sites not participating in MAESTRO-NASH where FibroScans ≥ 5.5 kPa (no upper limit) were allowed; includes MAESTRO-NASH patients who screen fail at the biopsy stage
- ≥8 % liver fat on MRI-PDFF

A "Real-life" NASH Study with Non-invasive Monitoring of Patient Response

MAESTRO-NAFLD-1 Patients and Endpoints

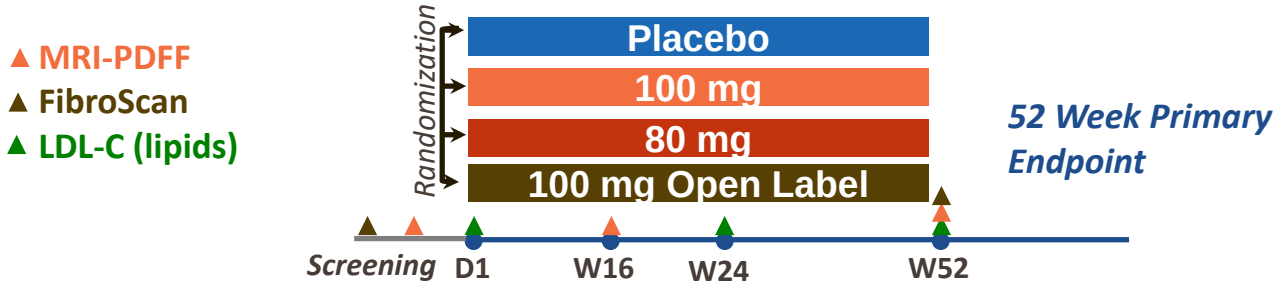
- A total of 171 subjects were randomized to the open label non-cirrhotic resmetirom 100 mg 52-week open label arm. All were included in the safety population; 94% and 89% completed key efficacy endpoints at Weeks 24 and 52, respectively. Drop out rate secondary to AEs was 1.2%
- A total of 972 patients were randomized in the double blind arms; 969 patients, safety population; 943 patients, mITT population for evaluation of key secondary and other endpoints
- The study remains blinded at the individual patient level; treatment groups are unblinded in topline data. As prespecified, if an assessment had <25 patients across all treatment groups, the output was suppressed, to prevent any possibility of individual patient unblinding
  - Site data are collected, final checks ongoing

MAESTRO-NAFLD-1 Objectives

- Primary safety objective: to evaluate the safety and tolerability of once-daily, oral administration of 80 or 100 mg resmetirom versus matching placebo as measured by: Incidence of Adverse Events [Time Frame: 52 weeks]

- Key secondary efficacy objectives (hierarchical control): percent change from baseline in LDL-C; percent change from baseline in ApoB at Week 24; percent change from baseline in hepatic fat fraction by MRI-PDFF at Week 16; percent change from baseline in triglycerides (baseline >=150 mg/dL) at Week 24; change from baseline in FibroScan CAP and VCTE at Week 52

Study Design



- Visits were conducted every 4 weeks for 52 weeks on IP with a visit after 4 weeks of follow up off IP (Week 56)
- Laboratory and imaging assessments
  - Lipids and safety labs were collected at each visit
  - MRI-PDFF, MRE in patients with baseline MRE>=2.9 were conducted at Baseline, Week 16 and 52; A subset of patients had CT1
  - Special biomarkers (inflammation and fibrosis) were collected q 12 weeks
  - Baseline and Week 52 imaging included Dexa scan to measure bone mineral density and FibroScan (CAP and VCTE)
- The study was monitored q3 month by an unblinded data monitoring committee. Potential cardiovascular or hepatic events were evaluated by blinded adjudication committees
- Patients completing the study could enroll in a 52-week active treatment extension study (MAESTRO-NAFLD-OLE)

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COVID Impact

	Resmetirom 80 mg	Resmetirom 100 mg	Placebo
Randomized	(N=327)	(N=325)	(N=320)
Withdrawal by Subject (Other than AE)	49 (15.0)	32 (9.8)	39 (12.2)
Lost to Follow-up	24 (7.3)	22 (6.8)	16 (5.0)

- MAESTRO-NAFLD-1 was conducted from December 2019 to November 2021 during the height of the COVID pandemic
  - Enrollment was robust and exceeded original target of a total of 700 patients (double blind plus open label populations)
- Maximum study withdrawals occurred at the height of COVID infections (Nov 2020 to Feb 2021); enrollment was completed in October 2020
  - Withdrawals were not different according to randomized treatment in the double-blind arms
  - AE related withdrawals were uncommon (21 total AE-related withdrawals in the 56 week study period)
- Average COVID-related dose/visit interruption (COVID missed visit or COVID-related missed blister pack delivery) was 2 visits per patient
- MAESTRO-NASH serial liver biopsy study has not been significantly impacted by COVID-related issues or patient withdrawals
  - 5-6% withdrawal by subject/LTFU in 52 week time period, consistent with pre-COVID expectations

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Baseline Characteristics Double Blind population (mITT)

Baseline Characteristic	Resmetirom 80 mg	Resmetirom 100 mg	Placebo
Number (total = 943)[1]	320	314	309
Age (SD)	56.2 (11.7)	56.2 (11.5)	55.7 (12.2)
Male (%)	141 (44.1)	142 (45.2)	146 (47.2)
White (%)	284 (88.8)	278 (88.5)	276 (89.3)
Hispanic or Latino (%)	105 (32.8)	103 (32.8)	118 (38.2)
BMI (kg/m^2) at Baseline (SD)	35.4 (6.0)	35.4 (6.4)	35.2 (5.8)
Type 2 Diabetes (%)	156 (48.8)	152 (48.4)	156 (50.5)
Hypertension (%)	243 (75.9)	237 (75.5)	238 (77.0)
ASCVD risk score (SD)	12.7 (11.5)	12.3 (11.8)	13.7 (12.9)
LDL cholesterol, mg/dL (SD)	111.3 (37.8)	109.1 (36.4)	105.9 (36.9)
ApoB, mg/dL (SD)	97.7 (26.3)	95.4 (24.9)	94.5 (27.0)
Triglycerides, mg/dL (SD)	176.2 (94.5)	173.7 (93.7)	187.3 (120.6)
FibroScan VCTE (kPa (SD))	7.33 (4.4)	7.28 (4.2)	7.55 (5.6)
CAP (SD)	339.3 (32.9)	341.1 (34.0)	344.1 (33.6)
MRI-PDFF, % fat fraction (SD)	17.60 (6.6)	17.98 (7.3)	17.83 (6.9)

[1]Randomized with at least one post-baseline assessment, e.g. at least week 4; for imaging endpoints, baseline and at least one post baseline assessment; CAP, controlled attenuation parameter

Safety

	Resmetirom 80 mg	Resmetirom 100 mg	Placebo
Safety population	(N=327)	(N=324)	(N=318)
At least one TEAE	289 (88.4)	279 (86.1)	260 (81.8)
At least one Serious TEAE	20 (6.1)	24 (7.4)	20 (6.3)
TEAE ≥ Grade 3 Severity	26 (8.0)	29 (9.0)	29 (9.1)
AE discontinuations from study	All treatments combined, n=21; (2.17%)		
Maximum NCI CTCAE Severity Grade			
Grade 1	99 (30.3)	99 (30.6)	92 (28.9)
Grade 2	164 (50.2)	151 (46.6)	139 (43.7)
AEs over 10%			
Diarrhea*	76 (23.2)	101 (31.2)	44 (13.8)
Nausea*	38 (11.6)	59 (18.2)	25 (7.9)

*AE (adverse event); TEAE (treatment emergent adverse event); NCI (National Cancer Institute); CTCAE (Common Terminology Criteria for Adverse Events); *No diarrhea was seen in the multiple ascending dose study at doses up to 200 mg; the incidence of diarrhea was 2% and nausea 0% at the 100 mg dose across completed Phase 1 studies*

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Key Secondary Endpoints (mITT)

	Resmetirom 100 mg OL	Resmetirom 80 mg	p-value	Resmetirom 100 mg	p-value	Placebo
LDLc %CFB (SE) (Week 24)	-21 (1.9)	-12.7 (2.1)	<.0001	-14.4 (2.1)	<.0001	-1.7 (2.0)
ApoB %CFB (SE) (Week 24)	-22 (1.5)	-14.6 (1.5)	<.0001	-16.6 (1.6)	<.0001	-0.1 (1.5)
MRI-PDFF %CFB (Week 16)	-49%	-41%	<.0001	-48%	<.0001	-6%
Liver volume PDFF correction %CFB	-60%					
MRI-PDFF %CFB (Week 52)	-53%	-43%	<.0001	-48%	<.0001	-8%
Liver volume PDFF correction %CFB	-61%					
Triglycerides baseline >150 mg/dL, CFB (SE)	-65 (8.3)	-55.6 (8.6)	NA	-59 (6.5)	NA	-6.9 (16.1)
Triglycerides baseline >150 mg/dL (geomean) %CFB (95% CI)	-25 (3.1)	-19.5 (-27.0 to -11.1)	=.0005	-21.5 (-28.0 to -14.3)	<.0001	-2.1 (-10.6 to 7.4)

CFB (change from baseline); SE (standard error); APOB (Apolipoprotein B); MRI-PDFF (magnetic resonance imaging proton density fat-fraction); CI (confidence interval); OL, open label non-cirrhotic arm randomized concurrently with double-blind arms

- Hierarchically-controlled key secondary endpoints were achieved for both dose groups
  - Lipid reductions were numerically greater in the 100 mg open label treatment arm compared to the 100 mg double-blind arm. Patients in the open-label active 100 mg treatment arm were less impacted by COVID-related dose interruptions than double-blind patients
- MRI-PDFF reductions were robust even though some double-blind patients had COVID-related treatment interruptions prior to the Week 16 or 52 MRI-PDFFs

Safety database

- Based on patients dosed with at least 100 and/or 80 mg per day in completed and ongoing studies, resmetirom has dosed a number of subjects in relevant studies that we believe is consistent with ICH guidance for safety database for long-term treatment therapies (at least 1500 patients dosed for specified lengths at the top approved dose)

- Phase 1 studies
  - A total of 12 Phase 1 studies have been conducted

- Phase 2 studies
  - Two completed Phase 2 studies

- Phase 3 studies
  - MAESTRO-NASH, subpart H population
  - MAESTRO-NAFLD-1
  - MAESTRO-NAFLD-OLE, a 52-week extension study of MAESTRO-NAFLD-1

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Conclusions

- Resmetirom was safe and well-tolerated at the top dose of 100 mg as well as 80 mg in MAESTRO-NAFLD-1
- Key secondary endpoints were achieved in MAESTRO-NAFLD-1 at both dose groups
- Safety and efficacy are in line with expectations from Phase 2 liver biopsy study and randomized parallel open label 100 mg arm of MAESTRO-NAFLD-1
- Positive results from this trial support our conviction that resmetirom has the potential to be the first medication approved for treatment of patients with NASH and liver fibrosis

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Q&A

Thank You