Madrigal EASL Investor Event & Webcast

June 25, 2022[1]

[1]Slide 12, 24 added on June 28th 2022

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).

Madrigal Pharmaceuticals

EASL™ The Home of Hepatology

THE INTERNATIONAL LIVER CONGRESS™

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, presentations of data from, or outcomes 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; projections or objectives for obtaining accelerated or full approval for resemtirom for non-cirrhotic NASH patients and NASH patients with compensated cirrhosis; optimal dosing levels for resmetirom; projections regarding potential future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment and/or biomarker effects with resmetirom; the potential 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, as 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 or improvement 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 "accelerate," "achieve," "allow," "anticipates," "be," "believes," "can," "continue," "could," "demonstrate," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "hopeful," "inform," "intends," "may," "might," "on track," "planned", "planning," "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will achieve," "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, and patients with different disease states, than our prior studies; limitations associated with early stage or 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, 2021, our Quarterly Report on form 10-Q for the Quarter ended March 31, 2022, and in our other filings with the SEC.*

Agenda

Introduction	Paul Friedman, M.D., Chief Executive Officer
Review of Resmetirom Data Presentations at EASL	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
Q&A	

Opening Remarks

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Phase 2 & 3 NASH Clinical Trials
Ongoing: MAESTRO-NASH, MAESTRO-NAFLD-1, & MAESTRO-NAFLD-OLE

Compound/ Indication	Clinical Trial	Preclinical	Phase 1	Phase 2	Phase 3	Description
Resmetirom (MGL-3196) THR-β Agonist **Treatment of NASH**	Phase 2 MGL-3196-05 NCT02912260		**Completed**			■ **Phase 2: MRI-PDFF, biopsy – endpoints met**[1] • 36-week with 36-week OLE
	Phase 3 MAESTRO-NASH NCT03900429		**Recruiting**			■ **Phase 3: Treatment of NASH with Fibrosis** • Up to 2000 patients; double-blind 80, 100 mg, placebo • 52-week serial liver biopsy, Subpart H approval based on 900 F2-F3 patients • 54-month outcomes (liver events)
	Phase 3 MAESTRO-NAFLD-1 (presumed NASH) NCT04197479		**Ongoing (Cirrhosis arm and OLE)**			■ **Phase 3: Treatment of NASH** • >1200 patients • *52-week safety, lipids, NASH biomarker & imaging* • *Double-blind arms, 80, 100 mg, placebo* • *Open-label arms: non-cirrhotic 100 mg; NASH cirrhotic* • *OLE (MAESTRO-NAFLD-OLE – 52-week patient roll-over from NAFLD-1. Safety, Lipids, & NASH biomarker/imaging study)*

MAESTRO Phase 3 trials provide a comprehensive data set to support accelerated approval of resmetirom for treatment of NASH with significant liver fibrosis

MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OLE, open-label extension;THR, thyroid hormone receptor.

1. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024.

Multiple Presentations at EASL's International Liver Congress

Late-breaking presentation: *"Primary data analyses of MAESTRO-NAFLD-1, a 52 week double-blind placebo-controlled phase 3 clinical trial of resmetirom in patients with NAFLD"* [Saturday, June 25 at 3:00 PM. Presenter: Stephen Harrison]

Oral presentations:

- *"Impact of resmetirom-mediated reductions in liver volume and steatosis compared with placebo on the quantification of fibrosis using second harmonic generation in a serial liver biopsy study"* [Thursday, June 23 at 4:00 PM. Presenter: Dean Tai]
- *"Utility of FIB-4 thresholds to identify patients with at-risk F2-F3 NASH based on screening data from a 2000 patient biopsy confirmed cohort of resmetirom Phase 3 clinical trial, MAESTRO-NASH"* [Saturday, June 25 at 9:15 AM. Presenter: Jörn Schattenberg]
- *"Biomarkers, imaging and safety in a well-compensated NASH cirrhotic cohort treated with resmetirom, a thyroid hormone receptor beta agonist, for 52 weeks"* [Saturday, June 25 at 5:45 PM. Presenter: Stephen Harrison]

Posters:

- *"A higher Fibrosis-4 (FIB-4) score is associated with higher healthcare costs and hospitalizations in patients with nonalcoholic steatohepatitis"* [Presenter: Elliot Tapper]
- *"Retrospective AI-based measurement of NASH histology (AIM-NASH) analysis of biopsies from Phase 2 study of Resmetirom confirms significant treatment-induced changes in histologic features of non-alcoholic steatohepatitis"* [Presenter: Janani Iyer]

Madrigal Satellite Symposium: *"Identifying, Managing and Treating Patients with NASH and Significant Fibrosis – Current Practice and Future Perspectives"* [Thursday, June 23, 6:30 PM]

All times London

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Primary Data Analyses of MAESTRO-NAFLD-1:a 52-week Double-blind, Placebo-controlled Phase 3 Clinical Trial of Resmetirom in Patients With NAFLD

Stephen A. Harrison,[1] Rebecca A. Taub,[2] Guy W. Neff,[3] Sam Moussa,[4] Naim Alkhouri,[5] Mustafa R. Bashir[6]

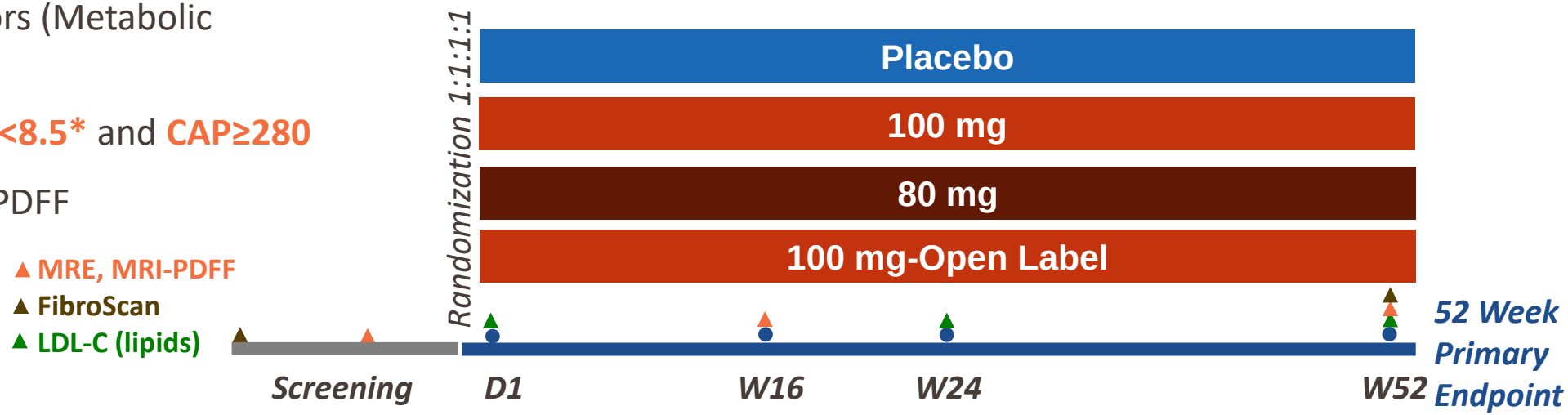
[1]University of Oxford, UK; Pinnacle Clinical Research, San Antonio, TX, USA; [2]Madrigal Pharmaceuticals, Conshohocken, PA, USA; [3]Covenant Metabolic Specialists, Sarasota, FL, USA; [4]University of Arizona College of Medicine, Tucson, AZ, USA; [5]Arizona Liver Health, Tucson AZ, USA; [6]Duke University Medical Center, Durham, NC, USA

NASDAQ: MDGL

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

Inclusion/Exclusion

- ≥3 metabolic risk factors (Metabolic Syndrome)
- FibroScan **kPa ≥ 5.5 & <8.5*** and **CAP≥280**
- **≥8 % liver fat** on MRI-PDFF



- 1143 presumed NASH patients enrolled in the USA (~80 sites)
  - 972 randomized to double-blind arms
  - 171 open label patients (recruitment completed July 1, 2020)

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

*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

MAESTRO-NAFLD-1 Objectives & Endpoints

- **Primary Safety Objective** – 52 weeks
  - 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

- **Key Secondary Efficacy Objectives** (hierarchical control):
  - **LDL-c** : % change from baseline – *at Week 24*
  - **ApoB** : % change from baseline – *at Week 24*
  - Hepatic fat fraction (**MRI-PDFF**): % change from baseline – *at Week 16*
  - **Triglycerides** : % change from baseline in the subgroup of patients with baseline TG ≥150 mg/dL – *at Week 24*
  - **FibroScan** CAP and VCTE: change from baseline – *at Week 52*

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Baseline Characteristics Double Blind population (mITT – n=943[1])

Baseline Characteristic	Resmetirom 100 mg OL n=171	Resmetirom 80 mg n=320	Resmetirom 100 mg n=314	Placebo n=309
Age mean (SD)	55.6 (11.5)	56.2 (11.7)	56.2 (11.5)	55.7 (12.2)
Male n, (%)	55 (32)	141 (44.1)	142 (45.2)	146 (47.2)
Hispanic or Latino n, (%)	52(30)	105 (32.8)	103 (32.8)	118 (38.2)
BMI, kg/m^2 mean (SD)	36.1(6.3)	35.4 (6.0)	35.4 (6.4)	35.2 (5.8)
Type 2 Diabetes n, (%)	82(48)	156 (48.8)	152 (48.4)	156 (50.5)
Hypertension n, (%)	117(68)	243 (75.9)	237 (75.5)	238 (77.0)
Hypothyroid n, (%)	75 (44%)	37(11.3%)	37 (11.4%)	37 (11.3%)
ASCVD risk score, % mean (SD)	11.6 (12)	12.7 (11.5)	12.3 (11.8)	13.7 (12.9)
FibroScan, VCTE kPa mean (SD)	7.7 (3.3)	7.33 (4.4)	7.28 (4.2)	7.55 (5.6)
CAP mean (SD) (SD)	342.0(35.5)	339.3 (32.9)	341.1 (34.0)	344.1 (33.6)
MRI-PDFF, % fat fraction	17.8 (7.0%)	17.60 (6.6)	17.98 (7.3)	17.83 (6.9)
MRE, kPa**,** mean (SD)	2.8 (0.9)	2.6(0.5)	2.6 (0.6)	2.6 (0.5)
FIB-4 mean (SD)	1.0 (0.6)	1.0 (0.4)	1.0 (0.5)	1.1 (0.5)
ALT, IU/L mean (SD)	36.9 (24.2)	36.9 (22.9)	36.2 (23.7)	37.8 (28.4)
AST, IU/L mean (SD)	26.4 (15.3)	25.1 (12.3)	25.1 (12.2)	26.3 (15.3)
GGT, IU/L mean (SD)	46.9 (55.0)	46.1 (41.0)	41.5 (31.8)	49.9 (62.1)
LDL cholesterol, mg/dL mean (SD)	115.2(41.0)	111.3 (37.8)	109.1 (36.4)	105.9 (36.9)
ApoB, mg/dL mean (SD)	101.1 (28.4)	97.7 (26.3)	95.4 (24.9)	94.5 (27.0)
Triglycerides, mg/dL mean (SD)	183.6 (86.2)	176.2 (94.5)	173.7 (93.7)	187.3 (120.6)

[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 Double-Blind Arms

Safety population	Resmetirom 80 mg n=327	Resmetirom 100 mg n=324	Placebo n=318
At least one TEAE	**289 (88.4)**	**279 (86.1)**	**260 (81.8)**
Grade 1	99 (30.3)	99 (30.6)	92 (28.9)
Grade 2	164 (50.2)	151 (46.6)	139 (43.7)
TEAE ≥ Grade 3 Severity	25 (7.6)	29 (9.0)	29 (9.1)
Related TEAE >= Grade 3 Severity	1(0.3)	1(0.3)	2 (0.6)
At least one Serious TEAE	**20 (6.1)**	**24 (7.4)**	**20 (6.3)**
AE discontinuations from study	**8 (2.4)**	**9 (2.8)**	**4 (1.3)**
Related AE discontinuations from study	**5 (1.5)**	**6 (1.9)**	**3 (0.9)**
GI AE discontinuations from study	5 (1.5)	6 (1.9)	2 (0.6)

- In the 100 mg resmetirom open-label arm, 94% & 89% completed key efficacy endpoints at Weeks 24 & 52, respectively
- Drop-out rate due to AEs was 1.2%

AE (adverse event); TEAE (treatment emergent adverse event); NCI (National Cancer Institute); CTCAE (Common Terminology Criteria for Adverse Events);

AEs ≥5% MAESTRO-NAFLD-1 Double-blind

Preferred Term	80 mg N = 327	100 mg N = 324	Placebo N = 318	All N = 969
Diarrhea	77 (23.5)	101 (31.2)	44 (13.8)	222 (22.9)
Nausea	39 (11.9)	59 (18.2)	25 (7.9)	123 (12.7)
Abdominal pain	14 (4.3)	23 (7.1)	14 (4.4)	51 (5.3)
COVID-19	27 (8.3)	27 (8.3)	27 (8.5)	81 (8.4)
Urinary tract infection	21 (6.4)	20 (6.2)	23 (7.2)	64 (6.6)
Arthralgia	24 (7.3)	27 (8.3)	21 (6.6)	72 (7.4)
Pain in extremity	16 (4.9)	18 (5.6)	16 (5.0)	50 (5.2)
Back pain	17 (5.2)	18 (5.6)	14 (4.4)	49 (5.1)
Headache	22 (6.7)	27 (8.3)	24 (7.5)	73 (7.5)
Fatigue	21 (6.4)	15 (4.6)	13 (4.1)	49 (5.1)

- Most frequent AEs- GI Related (Diarrhea and Nausea)- Consistent with the Phase 2 study & MAESTRO-NAFLD-1 open-label arm, no increase in incidence of GI-related AEs after first 12 weeks of resmetirom treatment. Females had higher incidence of early nausea
- Consistent with Phase 2 data, minimal reduction in prohormone free T4 (due to liver effect) & no effect on active hormone free T3 or TSH; no increase in AEs associated with hyper or hypothyroidism

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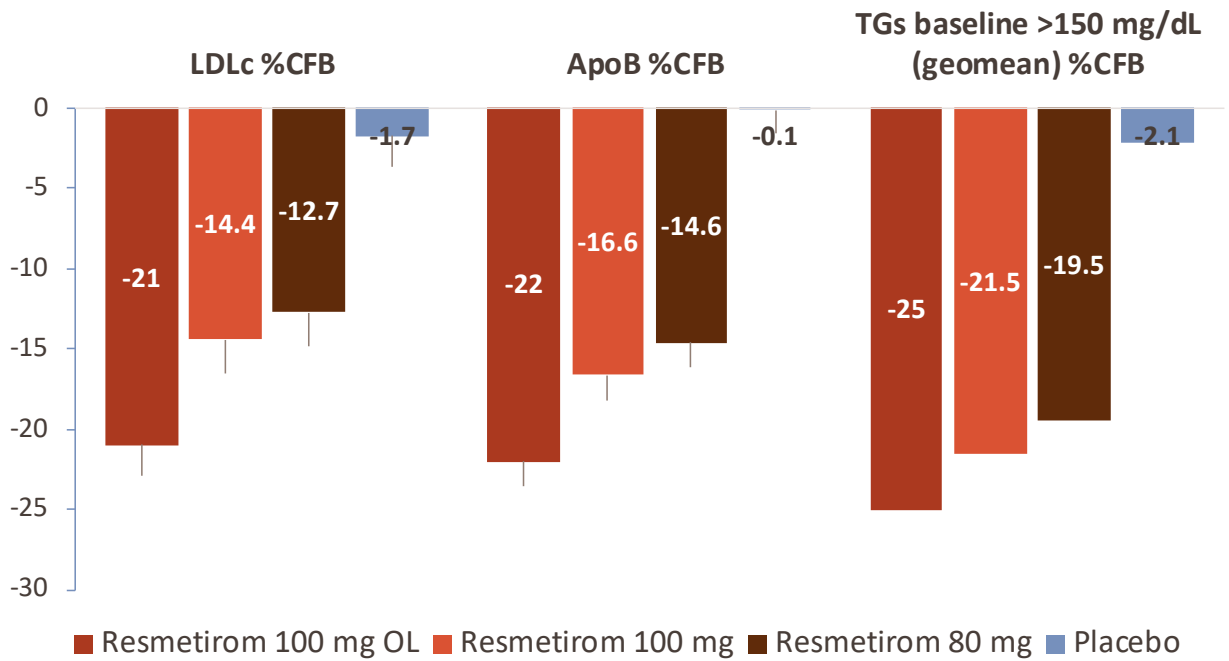
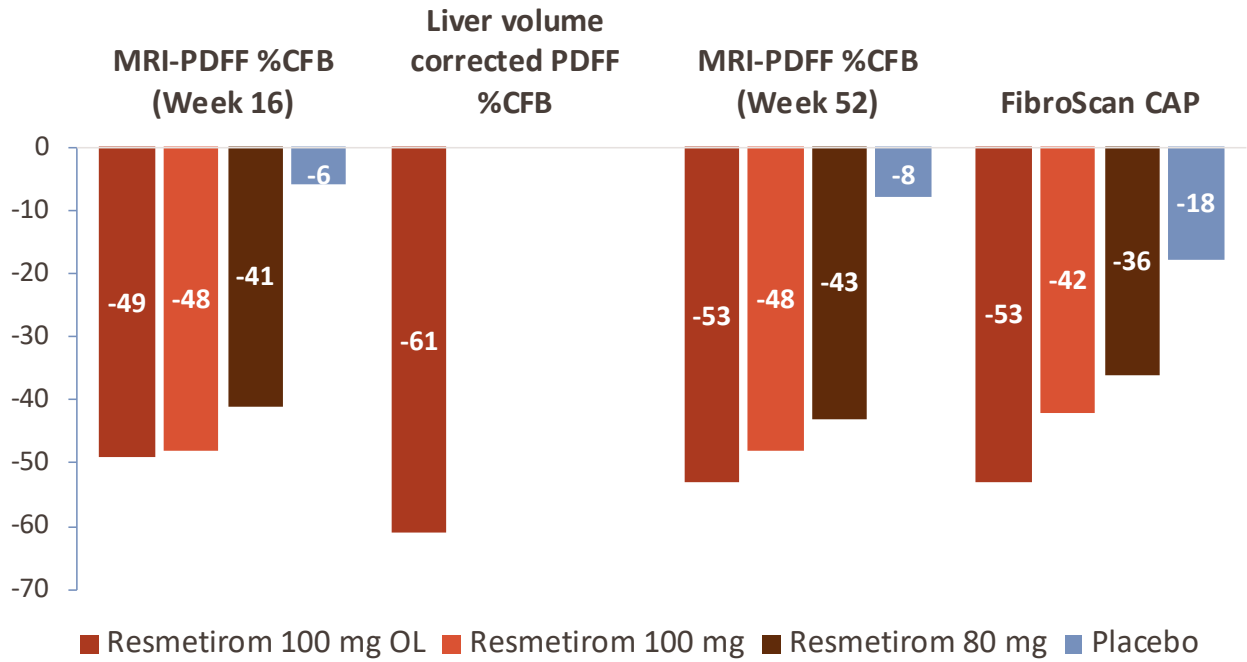
Key Secondary Endpoints





- Key secondary endpoints were achieved for both 80 and 100 mg dose groups ($p<0.0001$ for LDLc, ApoB, TGs, MRI-PDFF and CAP)
  - 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 not impacted by COVID-related dose interruptions (due to blister pack shortages) compared to 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

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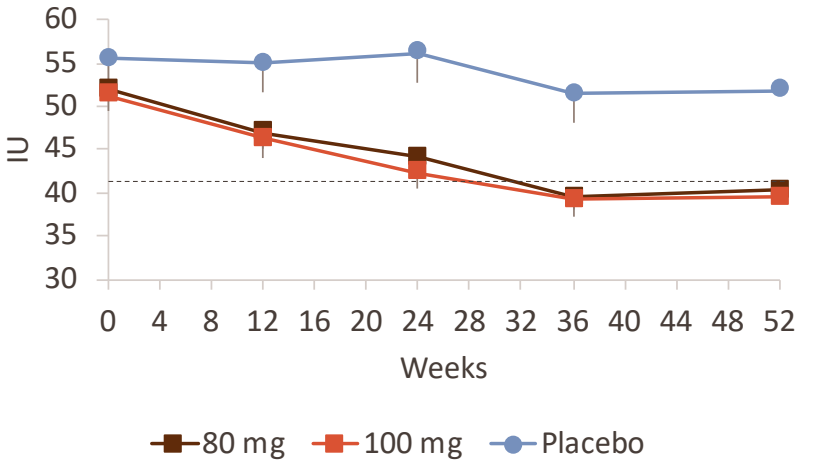
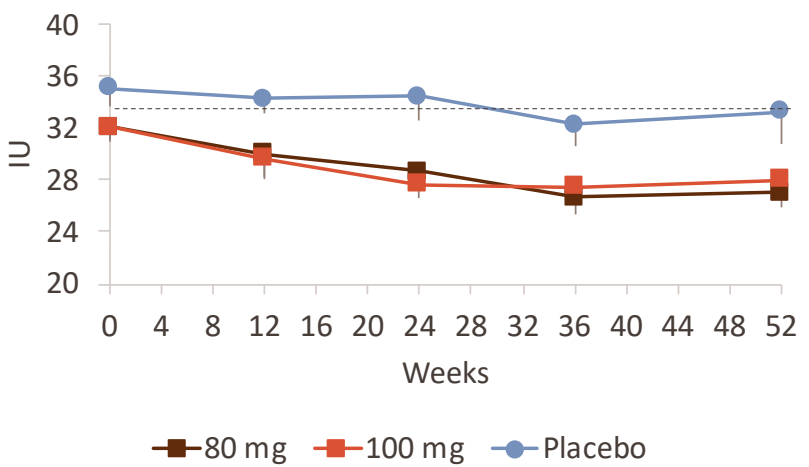
Liver Enzymes in the subgroup of patients with baseline ALT ≥30
80 mg (n=172) - 100 mg (n=164) - placebo (n=159)

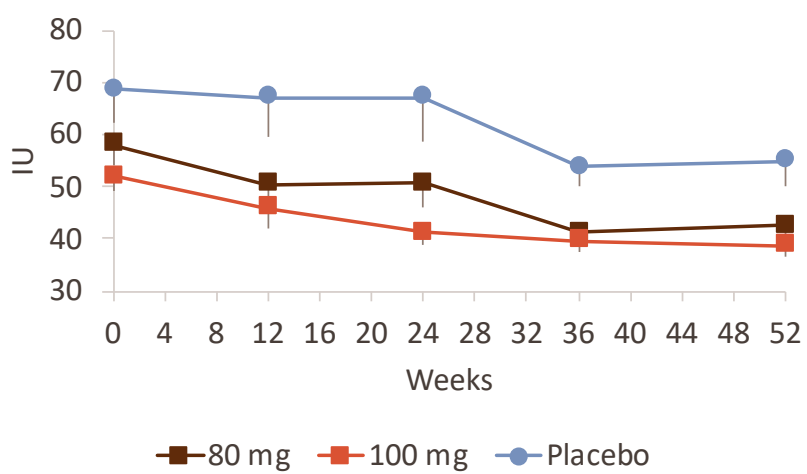
ALT



AST



GGT

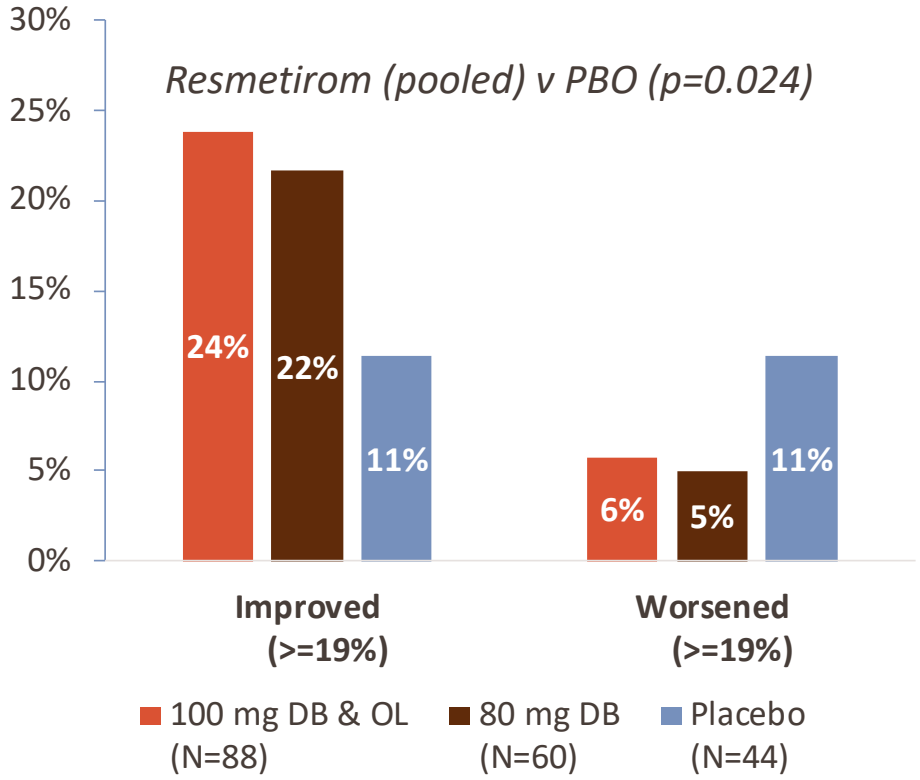


- Patients in the resmetirom 80 mg and 100 mg (double-blind) achieved reductions relative to placebo in:
  - ALT (p=0.002; <0.0001)
  - AST (p=0.028; 0.074)
  - GGT (p=0.039;0.021)
  - This was consistent with the 100 mg OL arm

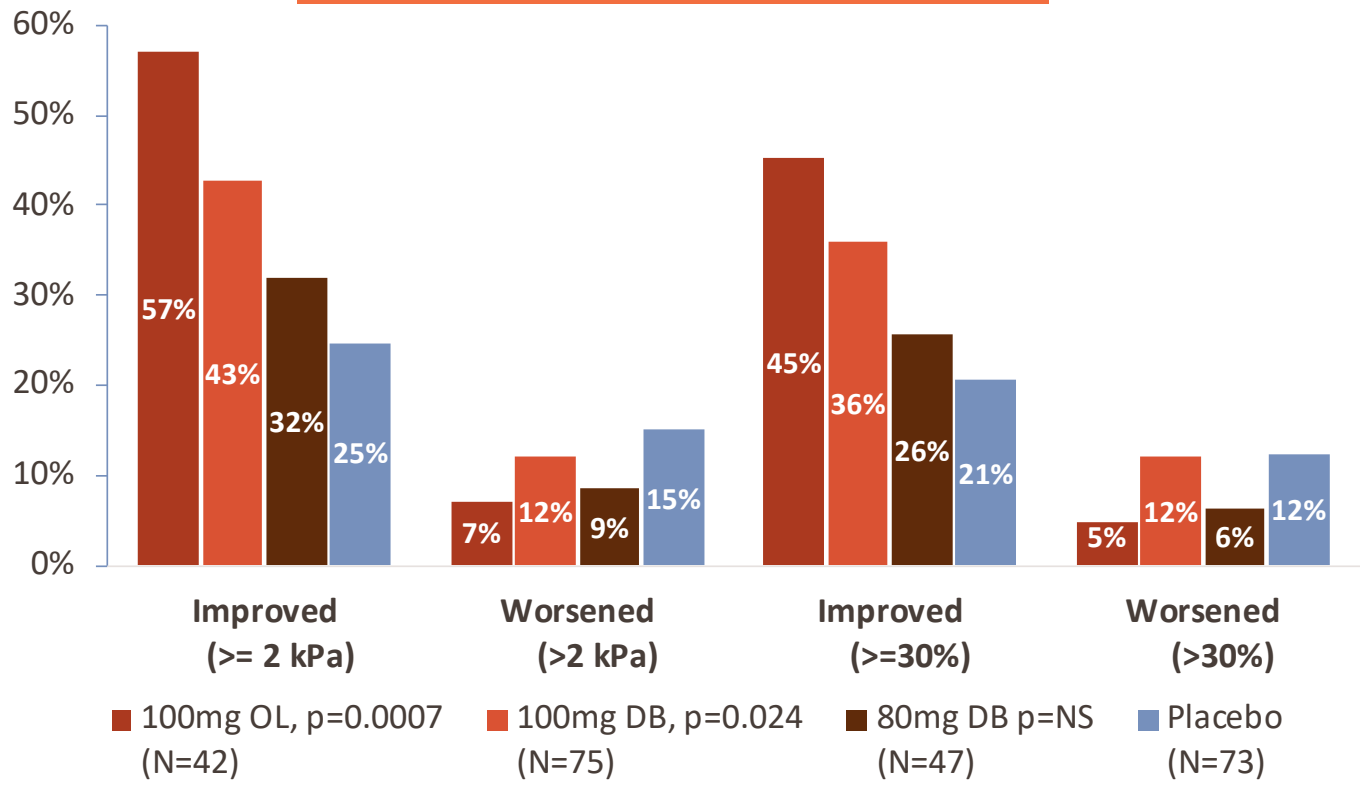
- ALT increases ≥3 times the upper limit of normal occurred in 0.61% in the resmetirom 80 mg group, 0.31% in the 100 mg group and 1.6% of patients in the placebo group

Fibroscan and MRE, Liver Stiffness Measure (LSM), Change at Week 52

MRE, baseline LSM >=2.9 kPa



Fibroscan, baseline VCTE >=7.2 kPa



- In this study most patients did not have baseline LSM on FibroScan or MRE that met criteria for analysis
- Although directionally showing a resmetirom treatment effect at 100 mg, mean change was not significantly different for FibroScan LSM
- Responder analyses were conducted to reduce the influence of highly variable (inaccurate) measurements and showed statistically significant response in resmetirom compared with placebo

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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; MAESTRO-NAFLD-1 achieved the primary endpoint
- **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
- Limitation of the study was the early fibrosis stage of MAESTRO-NAFLD-1 patients
- 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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Biomarkers, Imaging, & Safety in a Well-compensated NASH Cirrhotic Cohort Treated With Resmetirom, a Thyroid Hormone Receptor Beta Agonist, for 52 Weeks

Stephen A. Harrison,[1] Kris V. Kowdley,[2] Rebecca A. Taub,[3] Naim Alkhouri,[4] Guy W. Neff[5]

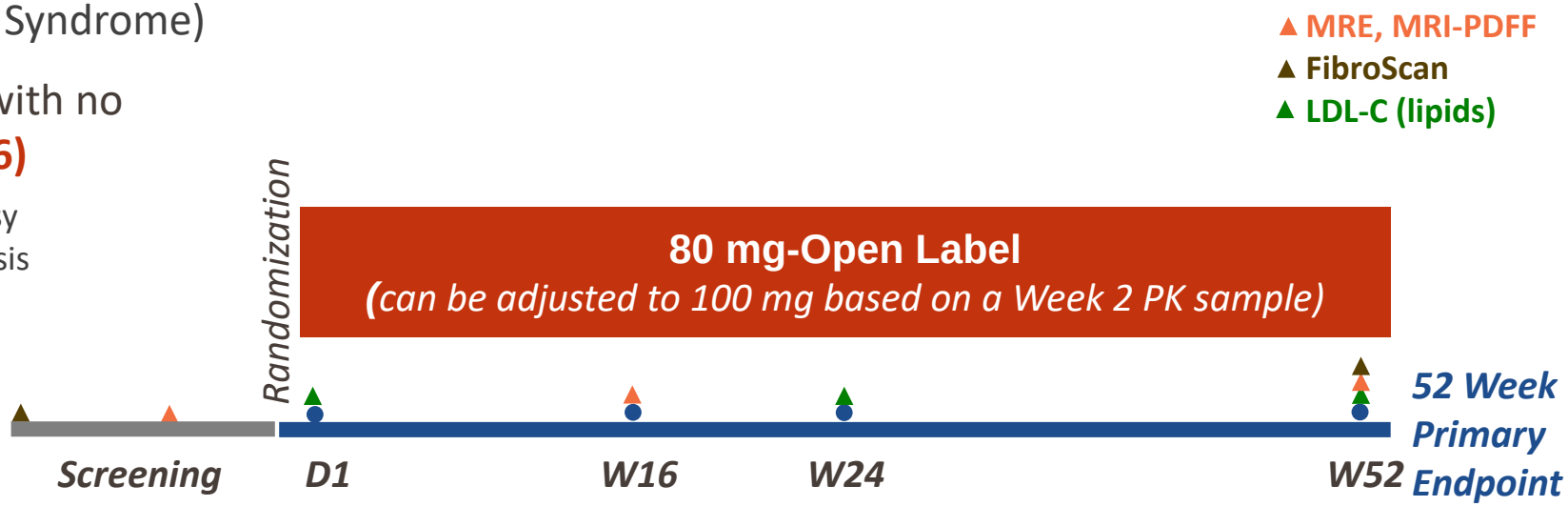
[1]University of Oxford, United Kingdom & Pinnacle Clinical Research, San Antonio, TX, USA; [2]Liver Institute Northwest, Seattle, WA, USA; [3]Madrigal Pharmaceuticals, Conshohocken, PA, USA; [4]Arizona Liver Health, Tucson, AZ, USA; [5]Covenant Metabolic Specialists, Sarasota, FL, USA

Presented at The International Liver Congress; 22-26 June 2022; London, United Kingdom.

Phase 3 MAESTRO-NAFLD-1 Study Design: Well-compensated NASH Cirrhosis Open-Label Active Treatment Arm (n=180)

Inclusion/Exclusion

- ≥3 metabolic risk factors (Metabolic Syndrome)
- **Well-compensated NASH cirrhosis** with no history of decompensation **(CP-A 5-6)**
  - F4 fibrosis either historic or recent biopsy
  - or historic biopsy with NASH F2-F3 fibrosis & subsequent progression to cirrhosis
  - Clinical evidence NASH cirrhosis (few)



- Cohort 1 (n=105) has completed 52 weeks
- Cohort 2 (n=75) is ongoing
- Other than the addition of a Week 2 visit, the NASH cirrhotic 52-week protocol is identical to MAESTRO-NAFLD-1 non-cirrhotic protocol

CP-A, Child–Pugh A; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PK, pharmacokinetic.
ClinicalTrials.gov (NCT04197479): https://clinicaltrials.gov/ct2/show/NCT04197479?term=MAESTRO-NAFLD-1&draw=2&rank=1

Baseline Characteristics Consistent With F4 Fibrosis Population

	(n=105)
Demographics & Medical History	
Age, years	62.7 (9.0)
Sex, female	64%
BMI, kg/m^2	35.4 (7.4)
Hypertension	78%
Hypothyroid	31%
T2D	71%
ASCVD score, %	16.1 (0.1)
Labs	
ALT, IU/L	40.3 (26.9)
AST, IU/L	39.4 (24.9)
Platelet	158.2 (60.7)
Albumin, g/dL	4.2 (0.4)

	(n=105)
Biomarkers	
FIB-4	**2.9 (1.7)**
ELF, mg/dL	10.8 (1.2)
PRO-C3, ng/mL	45.3 (25.4)
FibroScan	
LSM, kPa	**24.3 (14.9)**
CAP	317.5 (59.1)
Imaging	
MRI-PDFF, %FF	8.1 (5.0)
MRE, kPa	**5.74 (209.1)**

Data are mean (SD) or %.
ALT, alanine aminotransferase; ASCVD, atherosclerotic cardiovascular disease; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; FIB-4, fibrosis-4; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes.

Severity of Cirrhosis Within CP-A Defined by Baseline MRI-PDFF*

	BL PDFF ≤5% (n=31)	BL PDFF >5%, <8% (n=28)	BL PDFF ≥8% (n=40)	P value (BL PDFF ≤5% vs ≥8%)
BL Parameters				
PDFF	3.8%	6.8%	12.8%	<0.0001
ALT, IU	**32.0**	**34.2**	**51.8**	**0.005**
AST, IU	38.7	33.7	44.6	NS
FIB-4	**3.7**	**2.7**	**2.5**	**0.006**
ELF	11.1	10.8	10.7	0.180
FibroScan TE, kPa	27.4	24.9	23.6	NS
MRE	6.1	5.8	5.5	NS
LV, cc	2160 (686)	2090 (573)	2563 (612)	**0.020**
SV, cc	**649 (299)**	**546 (274)**	**484 (230)**	**0.0038**
Markers of Cirrhosis Progression				
MELD	**8.8**	**8.0**	**7.5**	**0.005**
Bilirubin, mg/dL	**1.08**	**0.86**	**0.71**	**0.004**
Platelets	**133**	**152**	**175**	**0.002**
Albumin	4.0	4.2	4.3	**0.030**

- Similar to non-cirrhotic NASH patients, LV is greatly elevated in well-compensated NASH cirrhosis patients compared to normal
- Multiple parameters of more advanced cirrhosis observed in patients with BL PDFF ≤5%; as expected for more advanced portal hypertension,[1] platelet count was reduced & BL SV measured by MRI was increased in the cohort with BL PDFF ≤5%

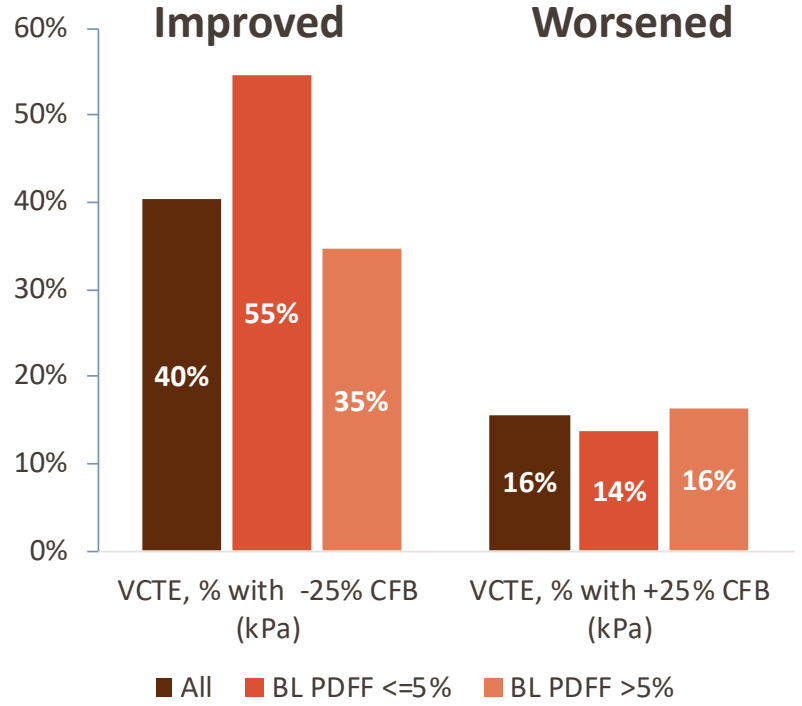
*Patients with no MRI-PDFF are not included.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BL, baseline; CP, Child-Pugh A; FIB-4, fibrosis-4; LV, liver volume; MELD, model for end-stage liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging- proton density fat fraction; NASH, nonalcoholic steatohepatitis; NS, not significant; PDFF, proton density fat fraction; SV, spleen volume.

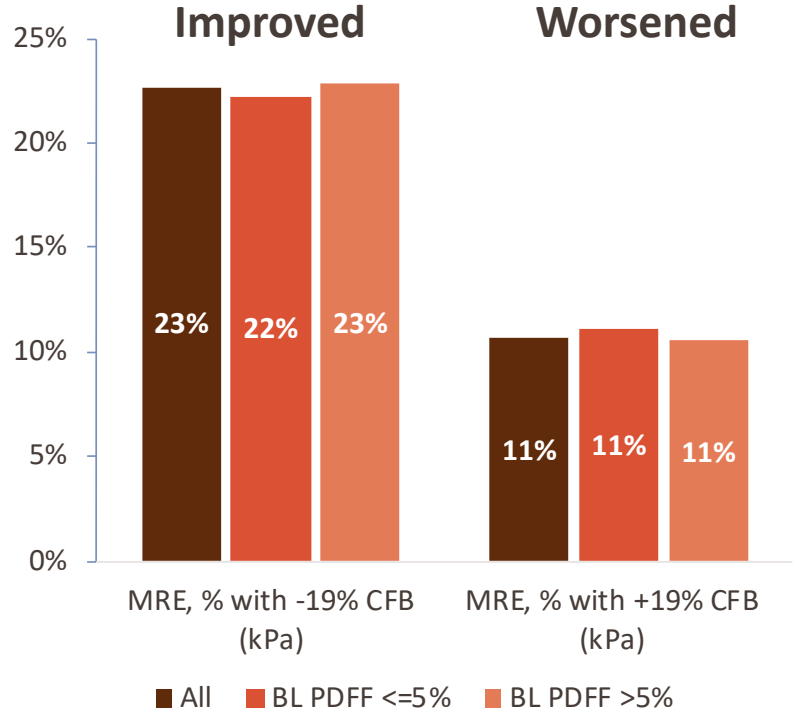
1. Yu S, et al. *PLoS One*. 2021;16(12):e0260774.

Resmetirom-mediated Changes to Fibrosis Imaging (Week 52)

FibroScan



MRE

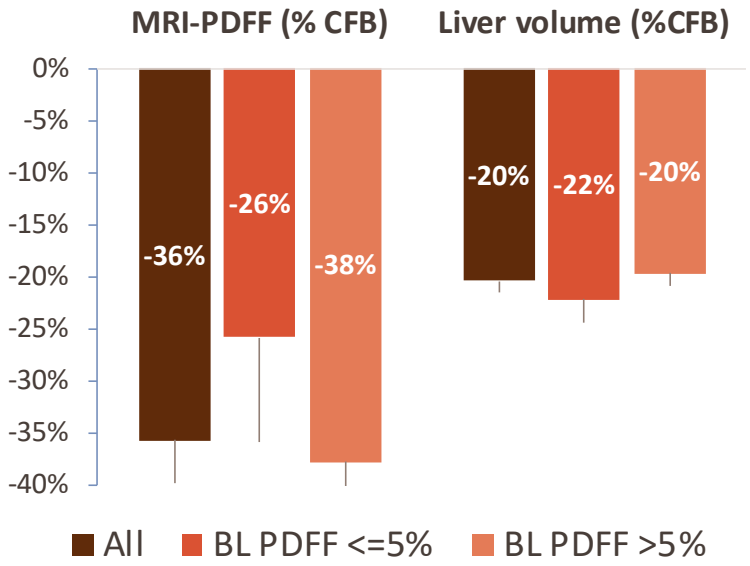


- Largest reduction in VCTE (mean, 9 kPa) in the most advanced group (BL PDFF ≤5%)
- Similar improvements were observed in MRE

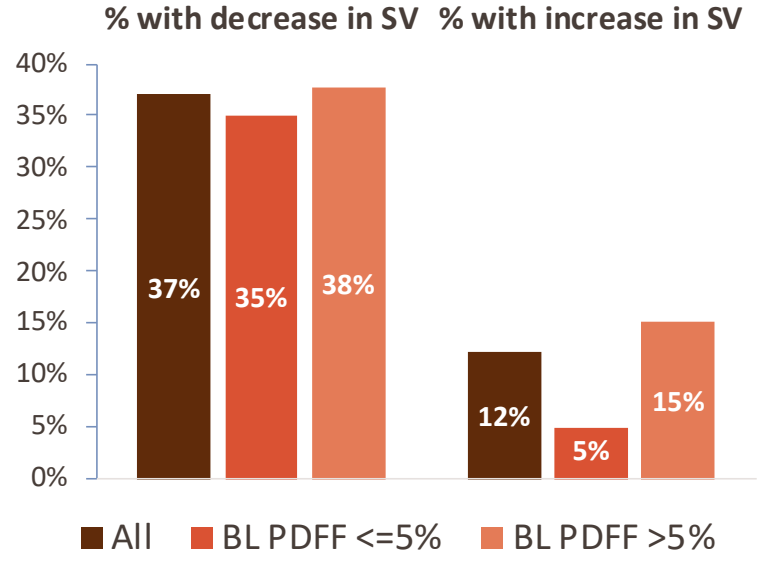
BL, baseline; CFB, change from baseline; MRE, magnetic resonance elastography; PDFF, proton density fat fraction; VCTE, vibration-controlled transient elastography.

Resmetirom-mediated Changes to MRI-PDFF, LV, & SV at Week 52

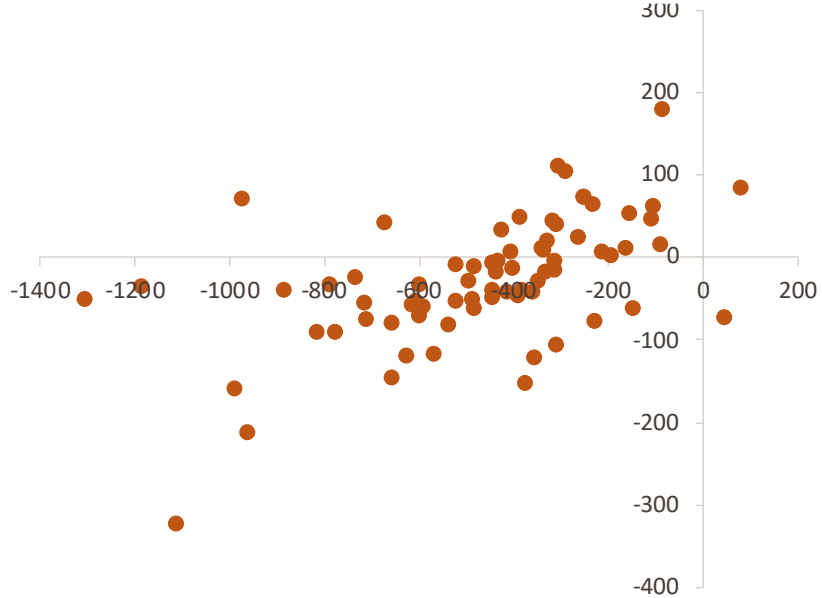
CFB (%CFB) in MRI-PDFF & LV



Percentage of Patients at Week 52 with ≥10% Change in SV



CFB in LV (x-axis) vs CFB in SV (y-axis)

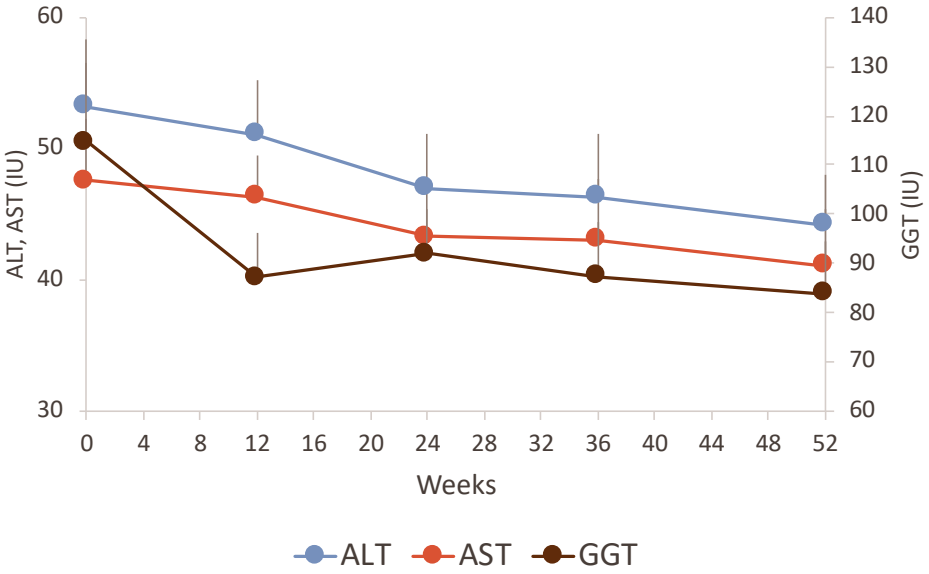


- 73% of patients, independent of baseline cirrhosis severity, had ≥15% reduction in LV at Week 52
- SV changes were more variable than PDFF & LV reductions & were thus evaluated as a responder analysis (based on percentage of patients with ≥10% reduction or ≥10% increase in SV)
- **Strong correlation between LV & SV change** (especially in the more advanced group with BL PDFF ≤5%)

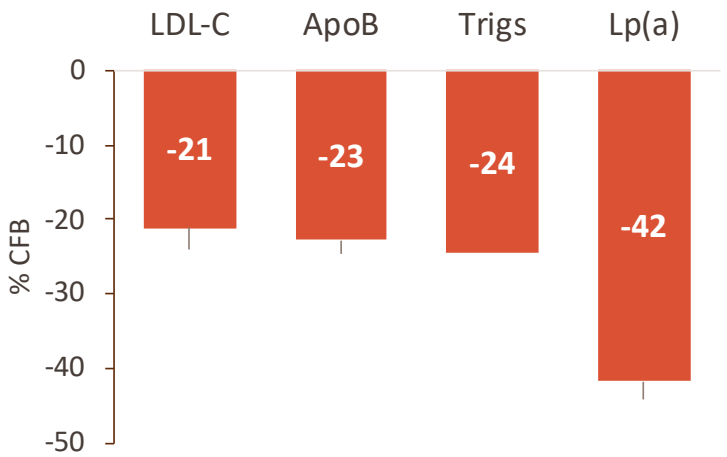
BL, baseline; CFB, change from baseline; LV, liver volume; MRI-PDFF, magnetic resonance imaging- proton density fat fraction; PDFF, proton density fat fraction; SV, spleen volume.

Liver Enzymes & CV Effects of Resmetirom

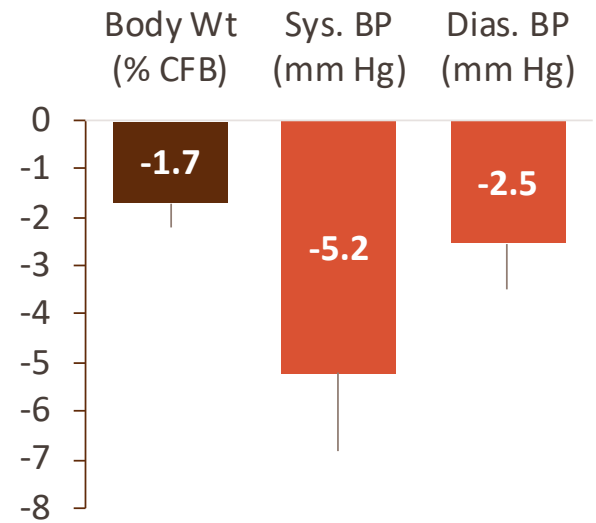
Liver Enzymes



Lipids



Vital Signs



- Reductions in liver enzymes & atherogenic lipids were similar across all patient subgroups
- Decreases in SBP & DBP, consistent with effects in non-cirrhotic NASH patients, independent of cirrhosis severity

Baseline ALT>=30 IU; ALT, alanine aminotransferase; apoB, apolipoproteinB; AST, aspartate aminotransferase; CFB, change from baseline; CV, cardiovascular; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; SBP, systolic blood pressure.

Safety Summary

	% of Patients
Any TEAE	**94**
Severity	
Grade 1	23.1
Grade 2	56.5
≥ Grade 3	11.4
Preferred Term	
Diarrhea	33.3
Nausea	25.0
UTI	16.7
COVID-19	12
Arthralgia	10.2
Fatigue	12.3
TEAE Leading to Study Discontinuation	**2.8**
Drug-related TEAE Leading to Study Discontinuation	**0**

- **No difference between cirrhosis severity groups or compared with non-cirrhotic NASH patients**
  - Most common AEs were mild, intermittent loose stools or nausea at initiation of resmetirom therapy
  - Low percentage (~15%) primarily GI AEs were considered related
- **No central thyroid axis changes**
  - Small decreases (~10%) in prohormone FT4 consistent with previous studies, no changes in active hormone FT3 or TSH
  - No hyper- or hypothyroid symptoms
  - Similar PD changes in euthyroid patients compared with patients with pre-existing hypothyroidism on thyroxine treatment

Database is not locked; AE results are preliminary.
AE, adverse event; FT3, free triiodothyronine; FT4, free thyroxine; GI, gastrointestinal; NASH, nonalcoholic steatohepatitis; PD, pharmacodynamic; TEAE, treatment-emergent adverse event; TSH, thyroid-stimulating hormone; UTI, urinary tract infection.

Conclusions

- In CP-A NASH cirrhotic patients, **resmetirom 80-100 mg daily for 52 weeks**:
  - was **safe and well tolerated** (mostly mild GI AEs at the beginning of resmetirom treatment)
  - **reduced MRI-PDFF, LDL-C, & other atherogenic lipids**
  - **reduced FibroScan CAP & VCTE as well as MRE (kPa)**
  - **statistically significantly reduced LV by an average of ~20%**

- Limitations of the study include lack of placebo control group
- This study provides foundation for MAESTRO-NASH Outcomes, a Phase 3 trial in well-compensated CP-A NASH cirrhosis patients that will initiate in the next few months

AE, adverse event; CAP, controlled attenuation parameter; CP-A, Child-Pugh A; GI, gastrointestinal; LDL-C, low-density lipoprotein cholesterol; LV, liver volume; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; VCTE, vibration-controlled transient elastography.

Madrigal Pharmaceuticals

Q&A

Thank You