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April 2021

Forward Looking Statements

Any statements, other than statements of historical facts, made in this presentation are, or may be deemed, forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Examples of these forward-looking statements include those concerning: our primary and secondary study endpoints and supportive data for resmetirom, and the potential for achieving such endpoints and projections and accelerated approval objectives; competitive positioning; the estimated size and diagnosis and treatment rates for our target patient market; projected clinical utility for resmetirom; U.S. launch and market positioning projections; our study and development timelines; 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, 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 the following summary risks described in our Annual Report on Form 10-K filed with the SEC on February 25, 2021: risks related to securing and maintaining relationships with collaborators; risks relating to conducting our clinical trials including trials substantially larger than our previous 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 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.

Projecting the Future for Resmetirom

We believe that …

- Based on our strong Phase 2 and extension study results and the powering of both Phase 3 studies, we have a high degree of confidence that:
  - In MAESTRO-NASH, we will achieve:
    - The primary endpoint of NASH resolution; and
    - The key secondary endpoints of at least a 1-stage improvement in fibrosis and statistically significant LDL-cholesterol lowering
- In MAESTRO-NAFLD-1 (non-invasively diagnosed NASH), we will generate:
  - Sufficient additional safety data to support an accelerated approval filing for NASH;
  - Convincing data for noninvasively diagnosing and evaluating improvements in NASH resulting from resmetirom therapy; and
  - Further evidence supporting the potential for resmetirom to clear the liver of fat, reduce fibrosis and provide cardio-protection via lowering of LDL-C and multiple atherogenic lipids
- There is a high unmet need for approved NASH drugs based on published literature and supported by Madrigal's recent market research with physicians and payers
- Resmetirom has the potential to be first-to market in NASH; Madrigal is building the strategy, organization and infrastructure to commercialize resmetirom

Phase 3 NASH Clinical Trials, *Ongoing*: MAESTRO-NASH and MAESTRO-NAFLD-1

Compound/ Indication	Clinical Trial	Pre-Clinical	Phase 1	Phase 2	Phase 3	Description
Resmetirom (MGL-3196) Thyroid Hormone Receptor-β (THR-β) Agonist **Treatment of Nonalcoholic Steatohepatitis (NASH)**	**Phase 2 MGL-3196-05** NCT02912260	Completed				■ MRI-PDFF, liver biopsy: endpoints achieved[1] • 36 week with 36 week open-label extension
	Phase 3 MAESTRO-NASH NCT03900429	Recruiting →				■ Treatment of NASH with Fibrosis Stage 2-3 • Serial liver biopsy • 52 week Phase 3; 54 month outcomes
	Phase 3 MAESTRO-NAFLD-1 (presumed NASH) NCT04197479	Ongoing →				■ Treatment of NASH • *Safety, Lipids and NASH biomarker and imaging study* • *52 week* • *Enrollment of double-blind arms completed* • *Open label 100 mg arm; includes NASH cirrhotics*

MAESTRO Phase 3 trials provide a comprehensive data set to support efficacy and safety, consistent with regulatory requirements to support accelerated approval of resmetirom for treatment of patients with NASH with significant liver fibrosis

[1]MRI-PDFF, magnetic resonance imaging proton density fat fraction; a highly accurate measurement to diagnose fatty liver disease

Harrison Lancet. 2019 Nov 30; 394(10213):2012-2024.
doi: 10.1016/S0140-6736(19)32517-6
Harrison et al, Hepatology Communications, 2021; doi.org/10.1002/hep4.1657

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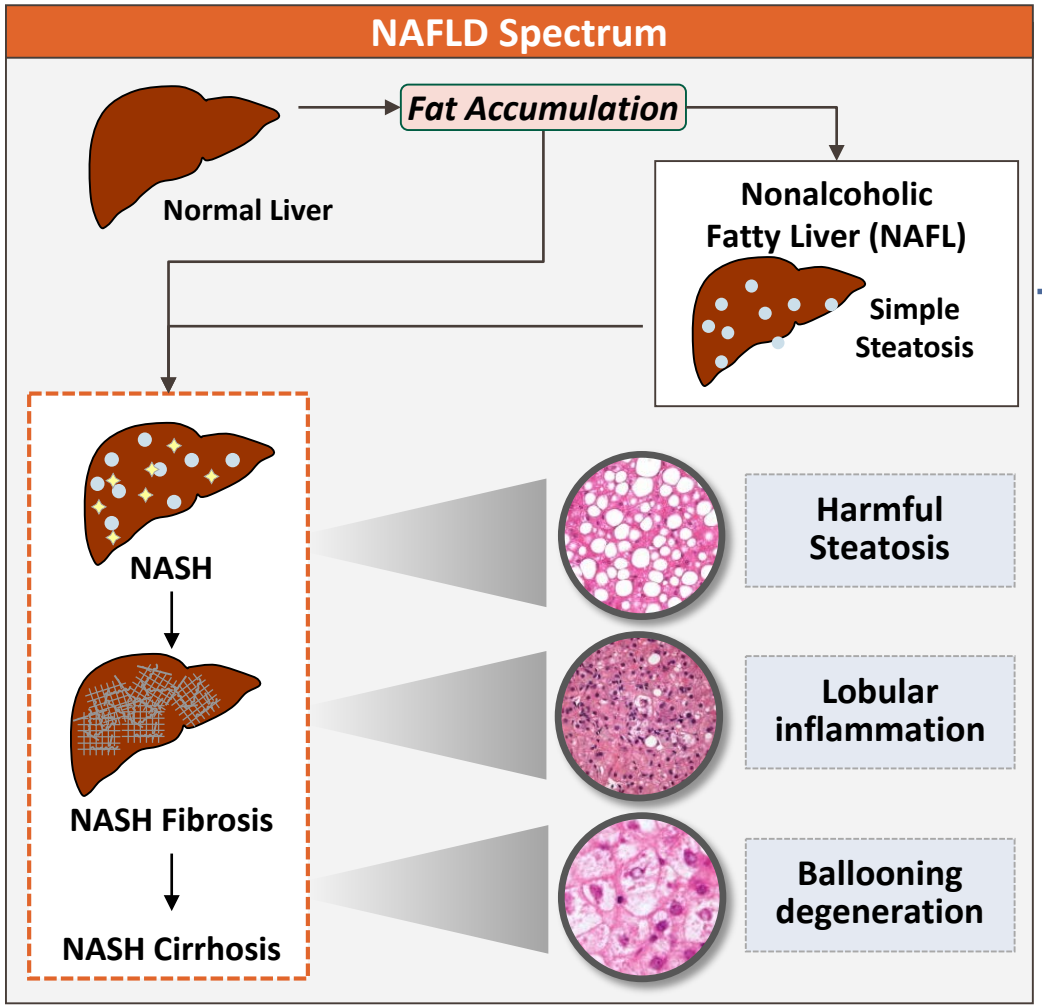
Non-Alcoholic Fatty Liver Disease (NAFLD) Ranges from Simple Steatosis (NAFL) to NASH, a Progressive Form of Liver Disease



DISEASE

- NAFLD results from accumulation of excess fat within the liver (steatosis) unrelated to alcohol use
- Some patients with NAFLD have NASH (nonalcoholic steatohepatitis)

INCIDENCE

- 25 – 30% of all adults in Western countries have NAFLD
- NASH afflicts 3 – 12% of the U.S. population. In certain populations such as type 2 diabetics, fat in the liver is virtually always NASH.

OUTCOME

- NAFLD leads to an increased risk of morbidity and mortality from:
  - Cardiovascular disease (leading cause of death for NAFLD patients)
  - Liver-related events
- 11% of advanced NASH patients progress to cirrhosis over a 15 year period

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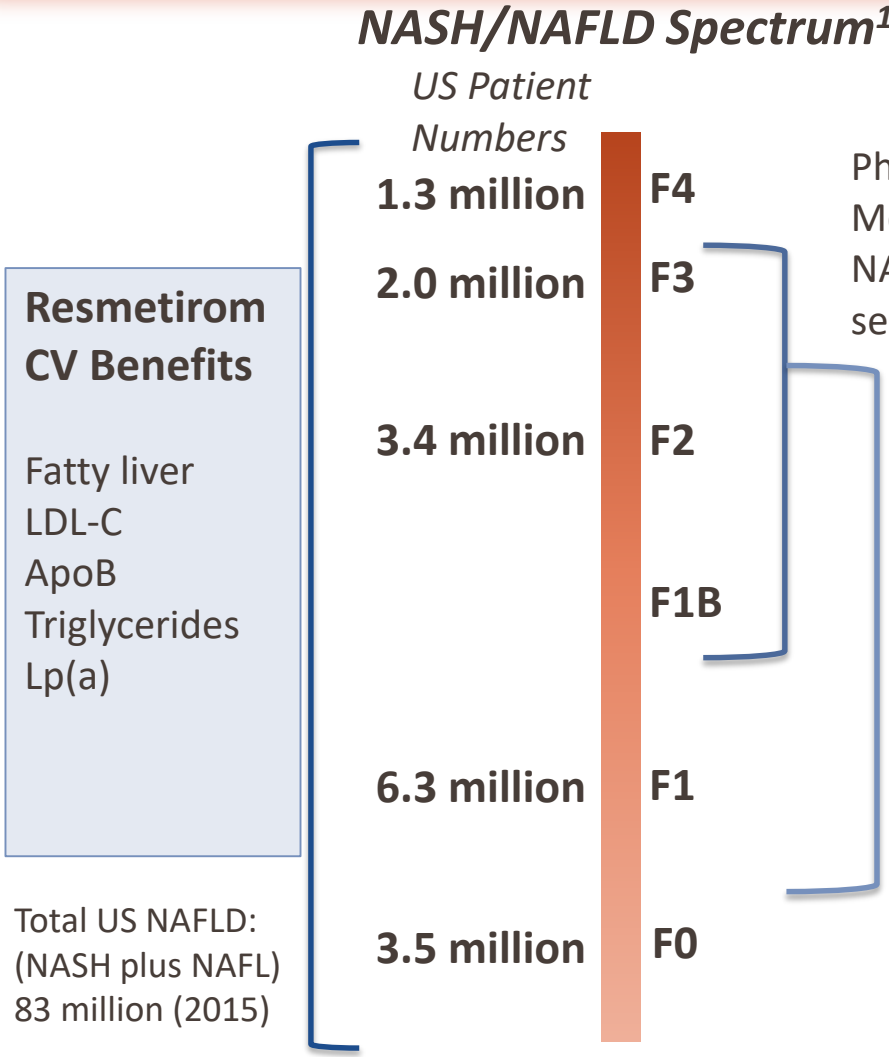
Resmetirom Development Path Across the Spectrum of NAFLD/NASH



Phase 3 MAESTRO-NASH study: F2/F3 NASH with Metabolic Syndrome
NASH Resolution (primary), LDL-C, fibrosis (key secondary); Phase 4 (post-approval): cirrhosis and MACE

Phase 3 MAESTRO-NAFLD-1 study:
F1-F3 NASH with Metabolic Syndrome diagnosed non-invasively (no liver biopsy requirement)
100 mg Open label arm; cirrhosis arm
Endpoints; Safety, LDL-C, lipids, MRI-PDFF, PRO-C3

Data show that NASH with fibrosis is associated with highest CV risk[2]

[1] Estes et al; *Hepatology*, Vol. 67, No. 1, 2018 [2] Henson Aliment Pharmacol Ther. 2020;51(7):728-736; Clinical Gastroenterology and Hepatology 2020;18:2324–2331

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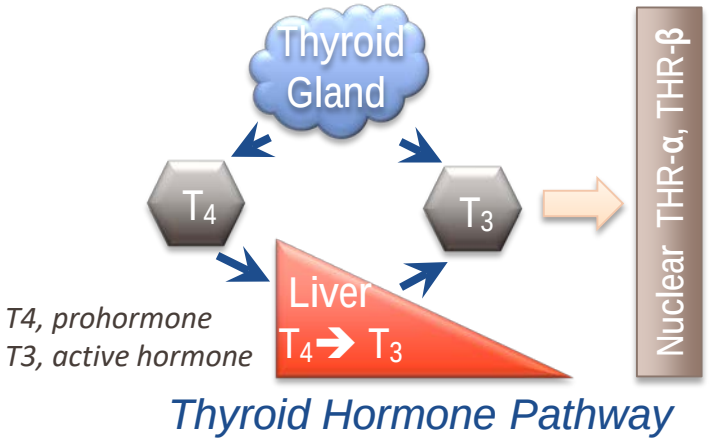
Mechanism of Action: The Importance of Liver THR-β in NASH



Thyroid Hormone Pathway

In humans, thyroid hormone receptor-β (THR-β) agonism:

- ↓ Lowers LDL-cholesterol
- ↓ Lowers triglycerides
- ↓ Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

Resmetirom (MGL-3196)

- THR-β selective liver targeted molecule, once a day oral, with proven safety and efficacy in more than 500 subjects and patients treated
  - No exposure outside the liver or activity at the systemic THR-α receptor
- Pleiotropic effects in the liver with potential for addressing the underlying metabolic syndrome and hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly and indirectly)
  - Reduction of liver fat through breakdown of fatty acids, normalization of mitochondrial and liver function

Sinha and Yen Cell Biosci (2016) 6:46 DOI 10.1186/s13578-016-0113-7;
Autophagy, 11:8, 1341-1357, DOI: 10.1080/15548627.2015.1061849

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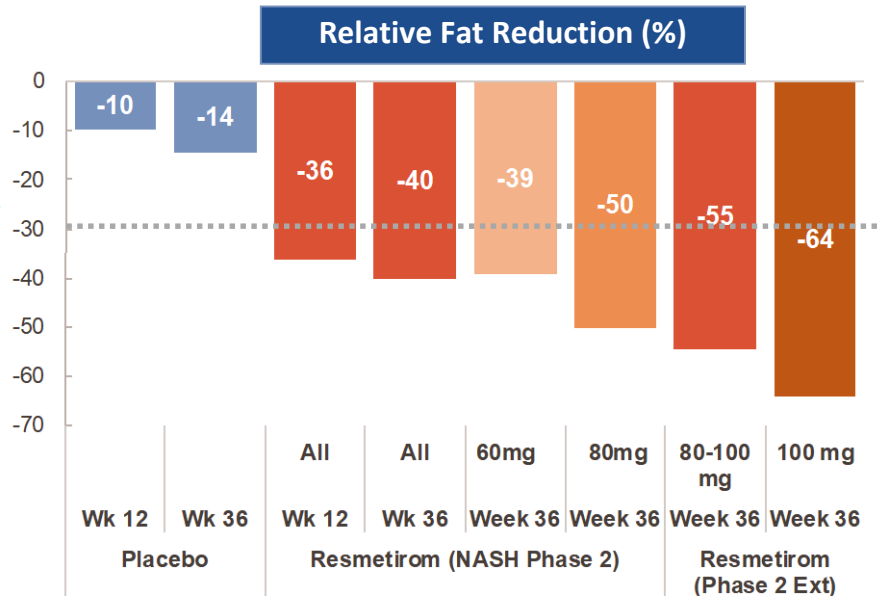
Results from Phase 2 Study



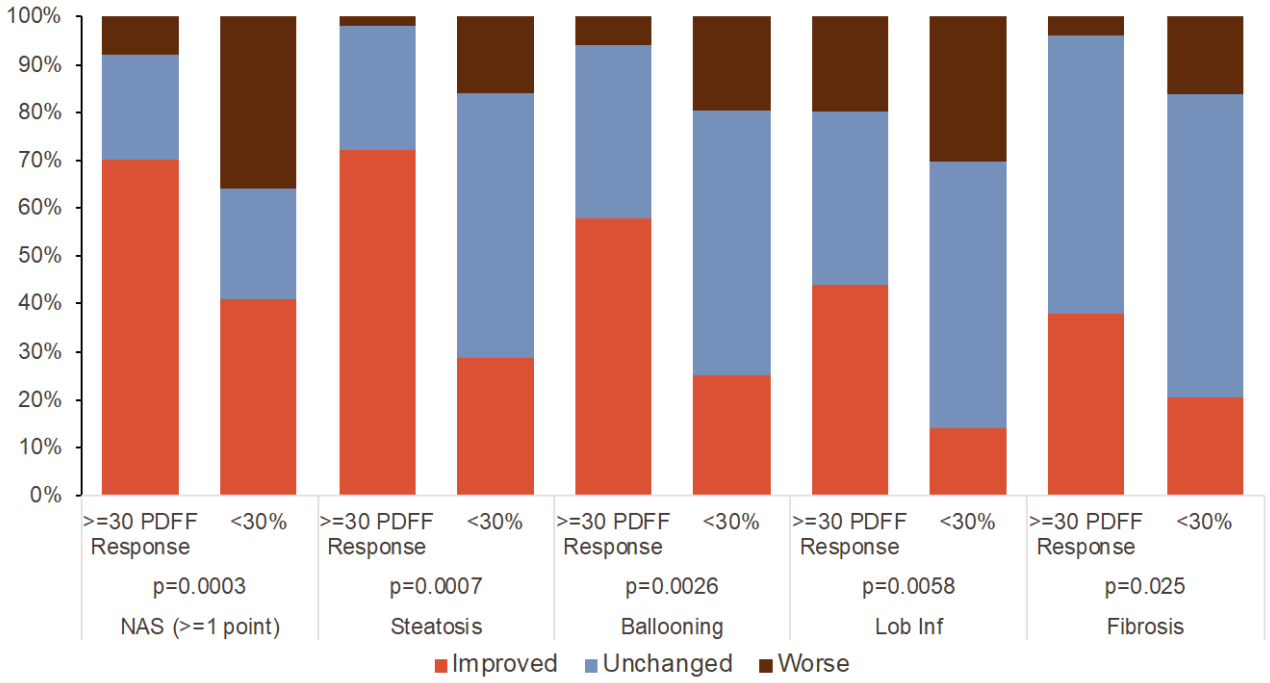
- Primary endpoint achieved, relative reduction in hepatic fat on MRI-PDFF at Week 12
  - Dose dependent 50% reduction of hepatic fat at 80 mg dose and >50% at 100 mg dose in the open label extension (Ext)
- Key secondary and exploratory endpoints achieved
  - Statistically significant reduction and resolution of NASH as compared with placebo
  - Statistically significant reduction in fibrosis biomarkers
  - Statistically significant reduction in liver enzymes
  - Statistically significant reduction in LDL-cholesterol, apolipoprotein B, triglycerides and lipoprotein(a)
- Safety
  - No change in Grade 2 or higher AEs
  - No safety signals related to mechanism of action

Resmetirom responders with ≥ 30% PDFF reduction had higher rates of NASH resolution (37%) on Week 36 liver biopsy compared to non-responders (4%) — hypothesis generating

Harrison et al Lancet. 2019 Nov 30;394(10213):2012-2024. doi: 10.1016/S0140-6736(19)32517-6
Harrison et al, Hepatology Communications, 2021; doi.org/10.1002/hep4.1657

Relationship of PDFF Reduction to Liver Biopsy Component Response in Resmetirom's Phase 2

- All patients in the study with serial evaluable liver biopsies (baseline and week 36) and PDFFs (baseline and week 12) were included in the analysis
- Statistically significant differences in NASH component response were observed between Week 12 PDFF responders(≥30% fat reduction) and non-responders
- Improvement and less worsening of all component responses (ballooning, inflammation, steatosis and fibrosis) were observed in PDFF responders



NAS, NAFLD activity score, comprised of ballooning, steatosis and inflammation

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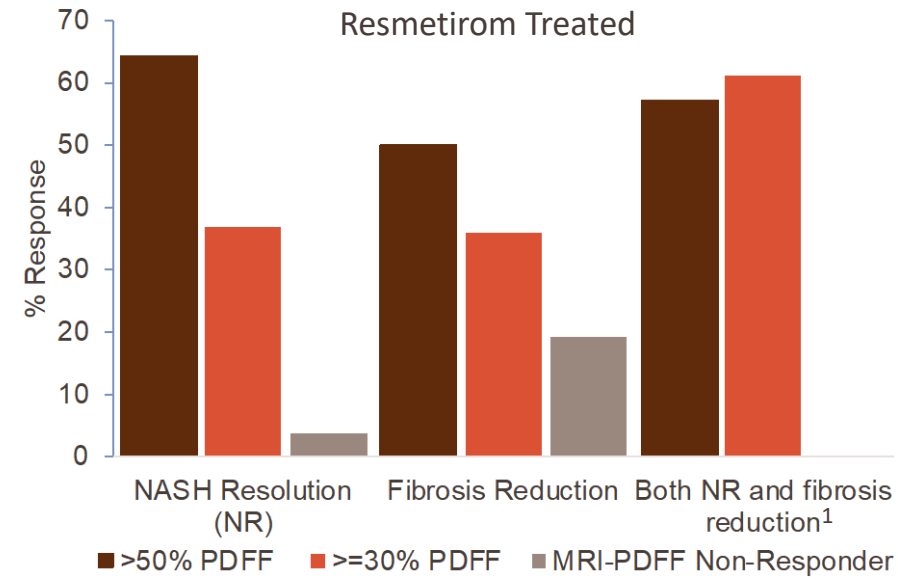
Association of PDFF Response with NASH Resolution and Fibrosis Reduction - Resmetirom

- Percentages of patients with NASH resolution increased with greater PDFF reduction (agreement between two independent pathologist central biopsy readers)
- In resmetirom-treated patients with ≥ 50% fat reduction at Week 12, 64% had NASH resolution with a component response driven primarily by ballooning and inflammation
- PDFF reduction ≥ 30 and ≥ 50% at Week 12 was also associated with
  - Fibrosis reduction on subsequent liver biopsy
  - Achievement of both endpoints: NASH resolution and ≥ 1 point fibrosis reduction



Non Responder: <30% fat reduction on Week 12 MRI-PDFF

Loomba et al AS077 ILC 2021, Oral Presentation

[1] %fibrosis reduction in biopsies with NR

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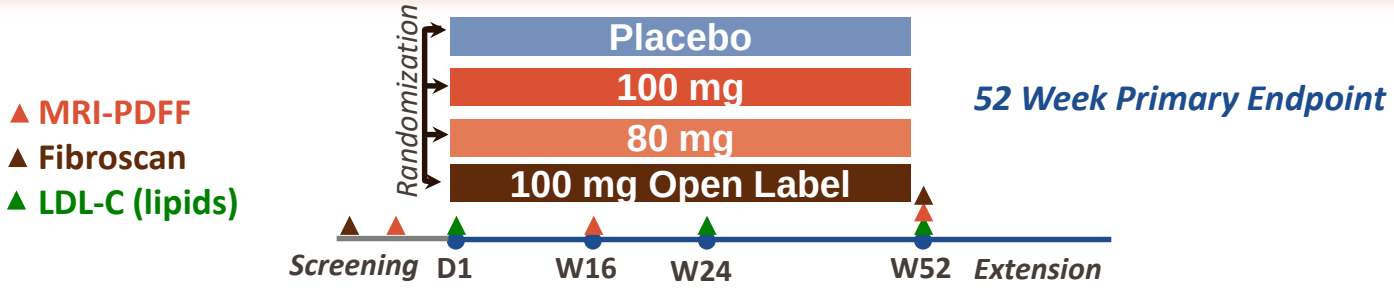
Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled



Comparator/Arms

- 1:1:1:1 resmetirom 80, 100 mg , placebo, open label 100 mg
- ~1200 NASH patients enrolled in the USA (~65 sites)

Inclusion/Exclusion

- Requires 3 metabolic risk factors (Metabolic Syndrome)
- Fibroscan kPa≥ F1, CAP≥280, except where eligible for MAESTRO-NASH; includes MAESTRO-NASH patients who screen fail at the biopsy stage
- ≥8% liver fat on MRI-PDFF
- Open label arm, >100 patients
  - NASH patients on 100 mg resmetirom to assess non-invasive measure of safety and efficacy
  - Open-label treatment of special safety population, e.g. compensated cirrhosis

Endpoints

- 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 efficacy objectives: percent change from baseline in LDL-C; percent change from baseline in ApoB; percent change from baseline in hepatic fat fraction by MRI-PDFF; percent change from baseline in triglycerides; change in PRO-C3

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

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MAESTRO-NAFLD-1 Phase 3 Open Label Arm-100 mg dose

	All	SHBG (high)
MRI-PDFF (%)		
Baseline (%)	17.6	17.9
Relative % Change	-53%	-62%
p-value	<0.0001	<0.0001
MRE (kPa)		
Baseline (≥2.9)	3.5	3.5
Absolute Change	-0.34	-0.46
p-value	0.003	0.003

LSM	Fibrosis stage
<2.5kPa	Normal
2.5 to 2.93 kPa	Normal or inflammation
2.93 to 3.5 kPa	Stage 1–2 fibrosis
3.5 to 4.0 kPa	Stage 2–3 fibrosis
4.0 to 5.0 kPa	Stage 3–4 fibrosis
>5.0 kPa	Stage 4 fibrosis

Average MRE by fibrosis stage[2]

Harrison et al #1707 AASLD 2020

Week 16 MRI-PDFF (%) and MRE (kPa) Changes from Baseline

- MRI-PDFF reduction of 53% fat fraction overall, and MRE (-0.34) were observed at Week 16
- MRE, unlike other elastography techniques, provides a stiffness map (elastogram)
  - The volume of liver parenchyma assessed with a single slice of MRE is about 250 cm3[1]

[1]Top Magn Reson Imaging. 2018 October ; 27(5): 319–333. doi:10.1097
[2]Abdom Radiol (NY). 2018 July ; 43(7): 1590–1611. doi:10.1007/s00261-017-1383-

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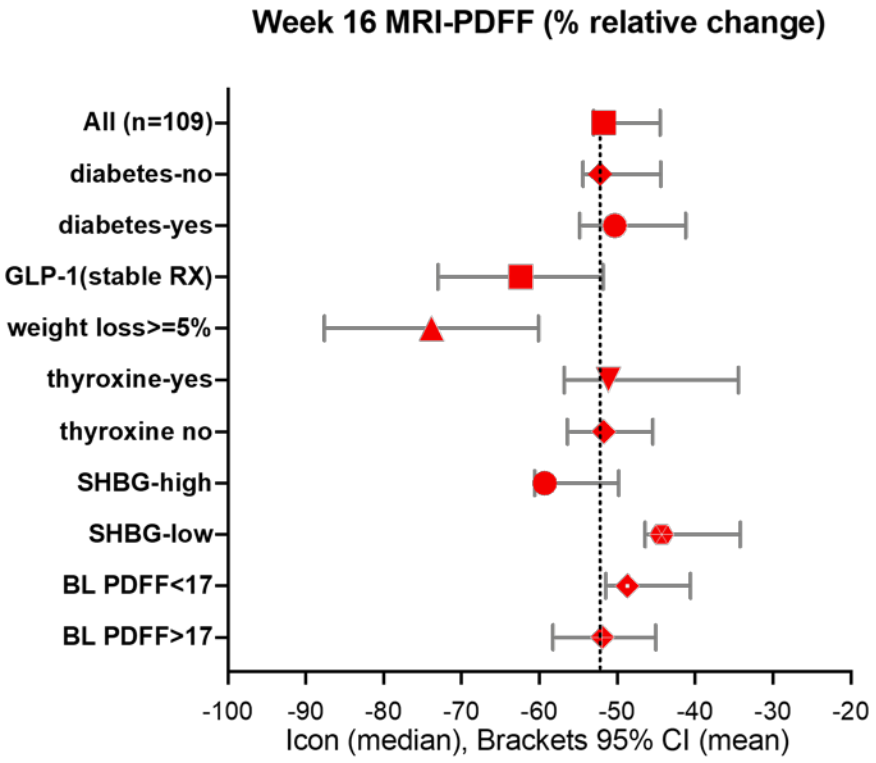
MAESTRO-NAFLD-1 Phase 3 Open Label Arm-100 mg dose

Week 16 MRI-PDFF Relative % Change from Baseline)



Resmetirom is effective across multiple subgroups and in combination with other diabetes therapies

- PDFF reduction of ≥60% was observed in subgroups: stable GLP-1 (no weight loss), ≥5% weight loss, or high SHBG response (reflects resmetirom liver levels)
- Well-tolerated, no safety signals

Harrison et al #1707 AASLD 2020

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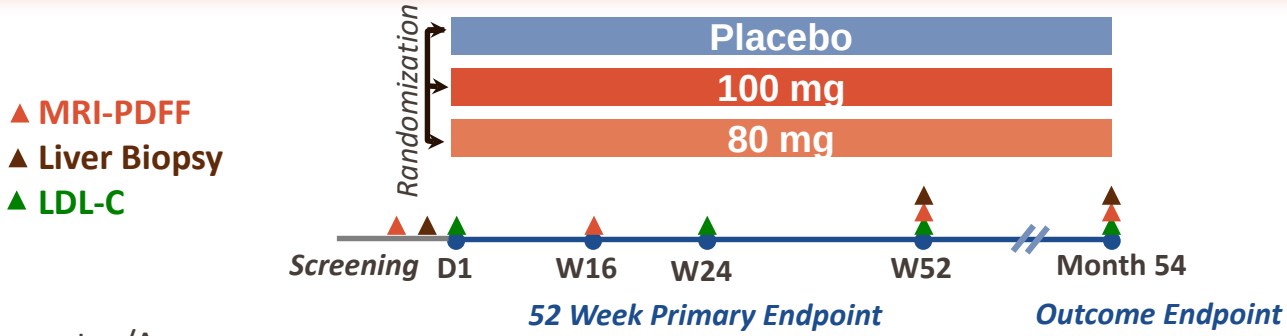
Phase 3 MAESTRO-NASH Study Design: Randomized, Double-Blind, PBO Controlled: Serial Liver Biopsy Study



Comparator/Arms

- 1:1:1 MGL-3196 80, 100 mg , placebo
- 900 F2/F3 patients enrolled in USA, Europe for primary Week 52 analysis, ~200 F1 patients
- Up to 2000 patients total enrollment for Phase 4 including first 900
- >150 centers, world-wide

Key Inclusion/Exclusion

- Requires 3 metabolic risk factors (Metabolic Syndrome); Fibroscan kPa consistent with F2-F3, CAP≥280
- NASH on liver biopsy: NAS≥4 with fibrosis stage 1A (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, the rest F2
- ≥8% liver fat on MRI-PDFF

Primary Endpoints

- Resolution of NASH at Week 52 with at least 2 point reduction in NAS
  - —Key secondary endpoints LDL-C lowering at Week 24, reduction in fibrosis stage Week 52 biopsy
- Composite liver-related outcome at 54 months [histologic evidence of cirrhosis on biopsy, MELD>=15, hepatic decompensation, liver transplant, all cause mortality]

https://clinicaltrials.gov, NCT03900429

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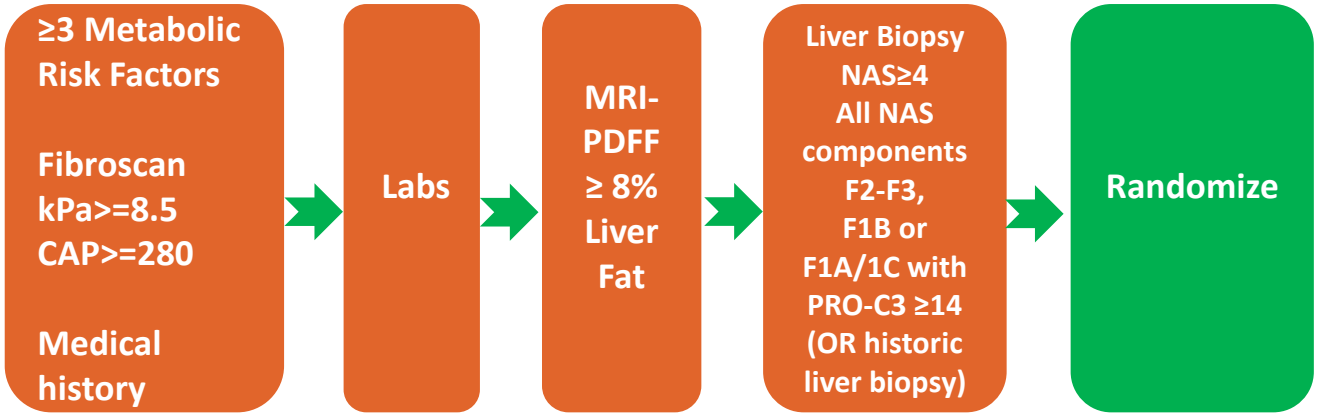
Phase 3 MAESTRO-NASH Screening Algorithm

RISK FACTORS for NASH

- Age >50
- BMI >30
- Elevated Liver enzymes (AST >20 U/L, AST/ALT ≥1)
- Type 2 Diabetes
- Hypertension
- Dyslipidemia
- Metabolic Syndrome
- Historical Fibroscan >8.5 kpa, CAP >=280 dB/M (Ideally 300)

Enrolling NASH fibrosis studies is particularly challenging because most patients at the time of screening do not have a definitive diagnosis of NAFLD (or NASH) and their fibrosis stage is unknown

MAESTRO-NASH 8 Week Screening Process



Using this screening paradigm, more than 80% of screened patients have had definitive NASH with significant fibrosis on liver biopsy

Harrison et al #1657 AASLD 2020

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Strong Positioning in NASH Landscape

Target class›	Stage	NASH res	Fibrosis	Liver Fat	Insulin Sensitivity	LDL	TGs	CV risk	SC or oral	Side Effects[2]
FXR	**Ph 3**	✓	✓[1]	✓	—	↑↑	↓	↑LDL-C	oral	Pruritus, ↑LDL-C
GLPs (GLP/GIP; GLP/Glucagon)	Ph 2	✓	X	✓	✓	—	✓	✓	**SC**	Nausea, vomiting; (requires titration; low adherence)
FGF-19 or FGF-21	Ph 2	✓	✓	✓	— or ✓	↑↑ or ✓	↓	?	**SC**	Nausea, vomiting, diarrhea, abdominal pain
PPARαδ	Ph 2	✓	X	—	✓	↓	↓	PPAR	oral	Well-tolerated
PPARɣ (pioglitazone)	Ph 2	✓	✓	✓	✓	↓	↓	PPAR	oral	CHF, ↓ bone, weight gain
Anti-steatotic (ACC; DGAT)	Ph 2	✓	X	✓	—	—	— or ↑↑	?	oral	Multiple mechanisms
Anti-fibrotic	Ph 0	—	?	—	—	—	—	?	?	Unknown
Resmetirom (THR-β)	**Ph 3**	✓	✓	✓	— ✓	↓	↓	**CV Benefit**	**oral**	Well-tolerated

- Once a day oral medication, pleiotropic and cardio-beneficial actions position resmetirom as potential best-in-class, first-to-market NASH therapeutic
- Differentiated from other NASH agents
- Can be used in combination with existing diabetic an lipid medications AND/OR add-on anti-fibrotic, anti-steatotic and/or anti-inflammatory NASH agents

[1]Based on Phase 3 data for obeticholic acid; unknown or not observed for other FXR agonists
[2]Adverse events (AEs) leading to increase in discontinuation rate and/or increase in at least Grade 2 (moderate) AEs

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Non-cirrhotic NASH with Liver Fibrosis is a Large, Underserved Market

>10M
Estimated Prevalence in the U.S.[1]

~11%
Current diagnosis rate estimate[2]

20-25%
Current off-label Rx treatment rate reported by Physicians[3]

NASH patients already identified could be immediate candidates for FDA approved drugs

- Prevalence expected to nearly double over this decade[1]
- Diagnosis and treatment rates may increase substantially over time to levels seen in T2D/Dyslipidemia (60-80%) as NASH specific drugs enter market
- Similar market dynamics in EU-5 & Japan[1,4]

Sources:
1: Estes et al. (2018)
2: Edison Group, Cowen, Kepler Chevreux, Morningstar
3: Madrigal US primary market research, Heps/GIs/Endos (n=127), Q4 2020
4: Madrigal EU-5/Japan primary market research, Heps/GIs/Endos (n = 336), Q1 2021

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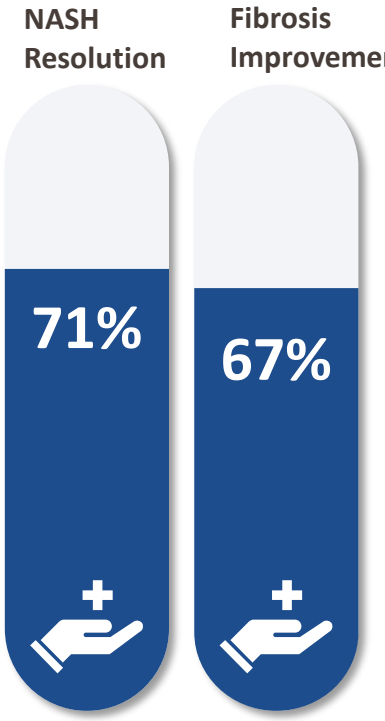
U.S. Commercial Opportunity is Primed for a Fit-for-purpose NASH Drug

Physicians reported **"Extremely High"** unmet need for FDA approved drugs to treat non-cirrhotic NASH with liver fibrosis



Physicians rated resolving NASH as **"Extremely High"** Unmet Medical Need similar to Fibrosis Improvement

Physicians reported that a drug that can resolve NASH, improve fibrosis, reduce LDL, and has a favorable safety profile with QD oral dosing would have **"Extremely High"** Clinical Utility

Source: Madrigal US primary market research, Heps/GIs/Endos (n=127), Q4 2020

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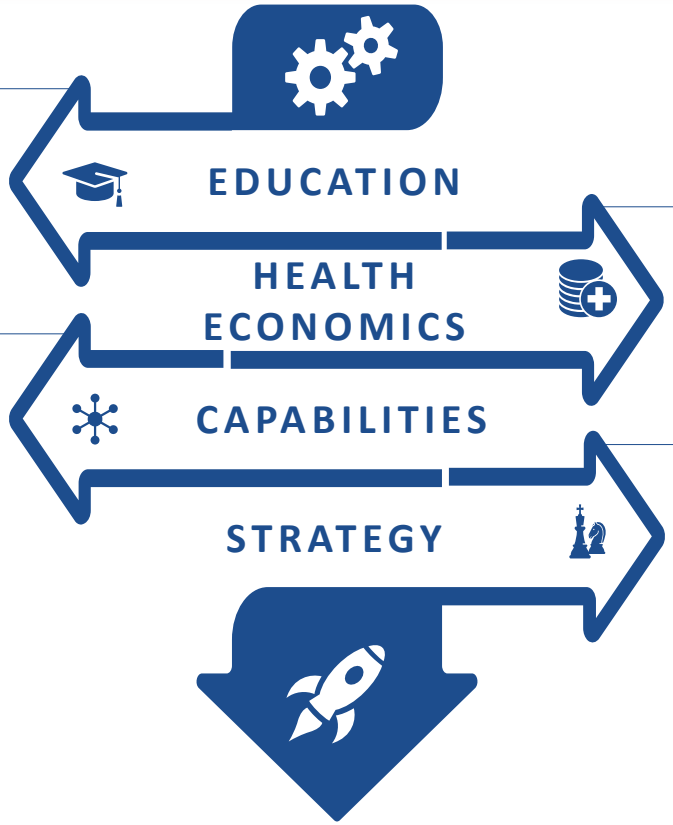
Launch Preparation Is Underway

- Medical Science Liaison team deployed for physician education
- Payer engagements targeted to start H2-2021

- Building infrastructure and organization in the U.S. with initial focus on Medical Affairs, Market Access, Data/Analytics, Marketing
- Seek to commercialize ex-US through strategic partners



- Select Health Economics and Outcomes Research studies to initiate in 2021

- Clear product positioning and messaging
- Market access for labelled- patient population
- Support physicians in identification of priority patients via non-invasive techniques

Madrigal believes that U.S. Launch of Resmetirom with 15-20K Hepatologists/Gastroenterologists & Endocrinologists will occur in 2023

POTENTIAL FIRST TO MARKET

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Expectations for Development Timing and Data

2019 | **2020** | **2021**

Completed Milestones:

- ✓ Completion of 36 Week Phase 2 NASH Extension Study
- ✓ Initiation of Phase 3 Study MAESTRO-NASH
- ✓ Initiation of Phase 3 Study MAESTRO-NAFLD-1
- ✓ Phase 2 NASH publication, Lancet

- ✓ Completion of enrollment of MAESTRO-NAFLD-1
- ✓ Data from open label arm MAESTRO-NAFLD-1
- ✓ Ongoing milestones from MAESTRO-NASH

- ✓ Publication of Extension study in Hepatology
- ✓ Data from open label arm MAESTRO-NAFLD-1

- Meeting presentations of open-label patients; publications
- Completed enrollment of Phase 3 population for accelerated approval, MAESTRO-NASH
- Year-end topline data from blinded arms MAESTRO-NAFLD-1

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Back-up Slides

AASLD 2020 #1707, TREATMENT WITH RESMETIROM IN PHASE 3 MAESTRO-NAFLD-1 NASH STUDY OPEN LABEL ARM: EFFECTS ON BIOMARKERS AND IMAGING

- An exploratory evaluation of safety, imaging and biomarkers was conducted in patients enrolled in the open label 100 mg active treatment arm of MAESTRO-NAFLD-1

- Typically ~20% of the overall NASH population are on thyroxine for the treatment of hypothyroidism. Thyroxine has equal activity at the thyroid receptor alpha and beta receptors
  - In order to assess the effects of resmetirom in NASH patients on thyroxine, a subgroup of the open label arm included patients on stable thyroxine (patients on thyroxine are also enrolled in the double-blind arms)
  - More females were on thyroxine as a percentage of enrolled open label patients (49.4% versus 19.4% male)

- Data analysis
  - Group included open label patients that had completed at least 16 weeks of dosing
  - MRI-PDFFs and MREs were assessed in patients who had both baseline and Week 16 MRI-PDFFs and MREs

Harrison et al #1707 AASLD 2020

Baseline Characteristics

Parameter	
Mean age, years (SD)	55.7(11.3)
Male, n (%)	36(29%)
Female, n (%)	87(71%)
Hispanic/Latino, n (%)	32(26%)
Mean Body weight (SD) (kg)	99.3(19.8)
BMI mean (SD) (kg/m2)	36.2(6.2)
Hypertension, n (%)	79(64%)
Hypothyroid#, n (%)	50(41%)
T2D, n (%)	50(41%)
T2D Yrs since diagnosis mean (SD)	10.1(7.5)
ASCVD score mean (SD)	11.1%(11.7%)
Fibroscan TE mean (SD) (kPa)	7.4(2.9)
Fibroscan CAP mean (SD)	341(35.0)
MRI-PDFF mean (SD) (%FF)	18.0%(6.9%)
MRE mean (SD) (kPa)	2.67(0.73)
PRO-C3 mean (SD) (ng/ml)	12.8(5.6)
HbA1c mean (SD) (%)	6.3(1.0)
HOMA-IR mean (SD)	8.9(8.9)
Statin use (n, %)	56(46%)
GLP-1s (n, %)	15(12.2%)
SGLT2s (n, %)	16(13.0%)

Other lab parameters, mean (SD)	
MELD	7.0(1.6)
NAFLD fibrosis score	-1.2(1.3)
Fib-4	0.99(0.50)
Total Cholesterol mean (SD) (mg/dL)	190.2(49.2)
TG mean (SD) (mg/dL)	186.9(85.5)
Lp(a) mean (SD) (nmol/L)	46.1(64.3)
ApoB mean (SD) (mg/dL)	102.9(29.6)
LDL-C mean (SD) (mg/dL)	117.7(42.5)
HDL-C mean (SD) (mg/dL)	44.2(11.9)
ALT (IU/L)	36.6(23.7)
AST (IU/L)	25.5(12.4)
GGT (IU/L)	44.1(46.5)
CK (IU/L)	121.2(111.6)
ALP (IU/L)	83.6(26.5)
Total bilirubin (mg/dL)	0.55(0.21)
Direct bilirubin (mg/dL)	0.10(0.04)
Platelet count	263(67)
Albumin (g/dL)	4.3(0.3)
INR	1.1(0.3)
CDT (%)	1.62(0.23)

- Demographics include
  - Mean age 55.7,
  - female 71%,
  - BMI 36.2,
  - diabetes 41%,
  - hypertension 64%,
  - dyslipidemia >70%,
  - hypothyroid 41%
  - mean ASCVD score 11.1%
- Fibroscan (kPa 7.4) and mean MRI-PDFF 18% are consistent with, on average, F2-stage NASH
  - Comparatively, MAESTRO-NASH fibroscan mean is consistent with F3

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Inflammatory and Fibrosis Biomarker Responses

Biomarker*	Baseline	SD	Post-Baseline*	SD	CFB	P value
ALT (BL >34 U/L)	58.3	47.4	38.9	16.1	-17.7	<0.0001
AST (BL >26 U/L)	39.3	12.2	31.8	11.3	-6.9	0.0060
GGT (BL >30 U/L)	70.2	58.3	54.6	47.8	-16.2	0.0015
Adiponectin (ug/mL)	5.0	3.5	5.9	1.6	0.9	<0.0001
Reverse T3 (ng/dL)	17.7	5.4	12.4	4.8	-5.3	<0.0001
PRO-C3 (BL ≥14) (ng/L)	19.2	4.9	16.0	3.5	-3.4	0.019
hsCRP (mg/L)	4.9	(1.9-8.4)	3.3	(1.5-6.2)	-1.1	0.027

- At weeks 12-24, decreases from baseline in ALT, AST, GGT occurred to the normal range in most patients; statistically significant reductions in inflammatory and fibrosis biomarkers PRO-C3, hsCRP and reverse T3 were observed
- Liver enzyme and biomarker responses were consistent with Phase 2 data

*Biomarkers were assessed at Weeks 12 or 24; LE at Week 20; median is shown for hsCRP

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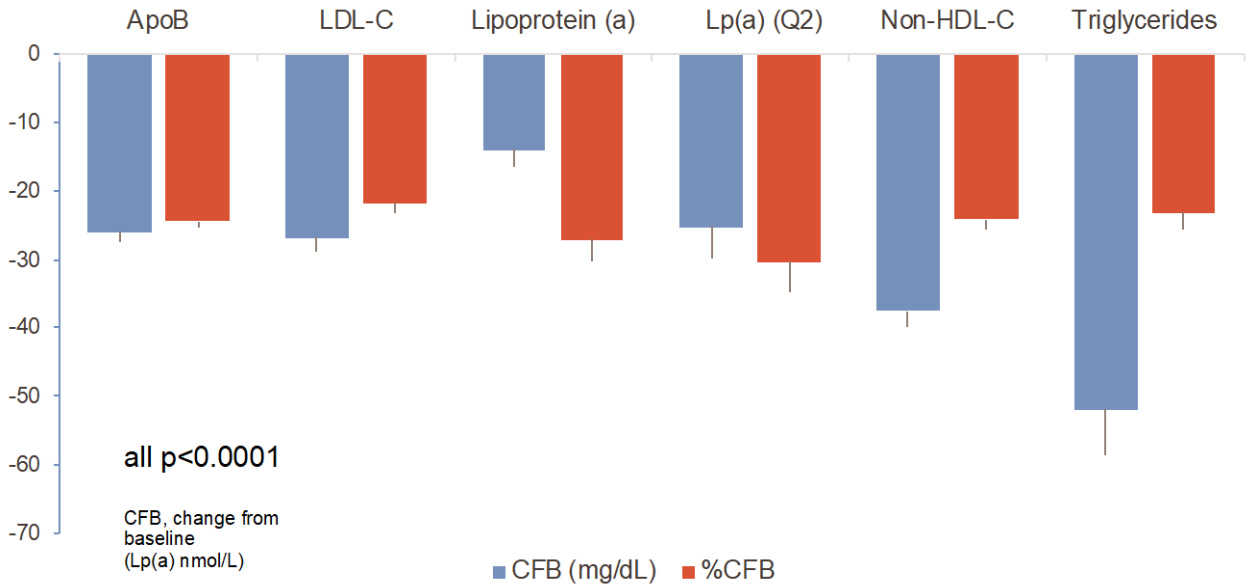
Reduction in Lipids and Lipoproteins



- LDL-C, apolipoprotein-B (-24%), triglycerides (23%), and lipoprotein(a) (-27%)) were statistically significantly reduced ($p<0.0001$) compared to baseline
- The magnitude of atherogenic lipid and lipoprotein reductions was similar to reductions observed in Phase 2
- Lipid baselines and reductions with resmetirom were comparable in patients on thyroxine or not on thyroxine (not shown)

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Madrigal Pharmaceuticals

Safety

AEs	N=123
Patients with treatment-emergent adverse Events, n (%)	75 (61)
Severe	0 (0)
Moderate	36 (29)
Mild	61 (50)
Patients with SAEs	1 (0.7)
Patients with drug-related SAEs	0 (0)

Vital signs	BL	SD	CFB	p-value
Blood pressure, systolic (mm Hg)	127.7	16.4	-3.8	0.0003
Blood pressure, diastolic (mm Hg)	80.4	10.3	-2.9	0.0022
Heart rate (bpm)	72.5	11.9	-2.8	0.015

- Resmetirom was well-tolerated with loose stools lasting <2 weeks in 6.5%
- No other AEs above historic placebo rates
- No changes in thyroid axis, thyroid pathway effects, irrespective of thyroxine treatment, or safety flags were observed

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Biopsy Success Rate in MAESTRO-NASH

Qualifying Liver Biopsies with NAS≥4, all components, F1-F3	%	Total
Fibrosis stage F2-F3	60.3%	
Fibrosis stage F1B or F1A/C with PRO-C3>14 ng/mL	10.3%	
Total Qualifying Biopsies		**70.6%**
Non-qualifying Biopsies with NASH, F1-F4		
NAS, >=3 (<4) with F2-F3 fibrosis	3.2%	
F1 NAS=3, all components	1.8%	
F4 NASH cirrhosis	2.2%	
NAS≥4 F1A/C with PRO-C3<14 ng/mL	3.2%	
Total non-qualifying biopsies with NASH		**10.5%**
Total biopsies with NASH		**81.1%**
Total biopsies without definite NASH or with F0 NASH		18.8%

NAS: NAFLD Activity Score

- ~70% of biopsies met eligibility requirements
- ~80% had NASH, some with NASH cirrhosis, or advanced NASH (F2-F3) with NAS<4

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FDA: Recent Statements on Accelerated Approval of NASH drugs

Special Article published in Hepatology (Dec-2020)

> Hepatology. 2020 Dec 19. doi: 10.1002/hep.31687. Online ahead of print.

Nonalcoholic Steatohepatitis: Current Thinking from the Division of Hepatology and Nutrition at the Food and Drug Administration

Frank A Anania [1], Lara Dimick-Santos [1], Ruby Mehta [1], Joseph Toerner [1], Julie Beitz [1]

Affiliations + expand

PMID: 33340111 DOI: 10.1002/hep.31687

"The accelerated approval pathway for drugs intended to treat NASH with liver fibrosis is appropriate because of the seriousness of the condition. Accelerated approval relies on adequate and well-controlled clinical trials establishing that the drug affects a surrogate endpoint that is reasonably likely to predict clinical benefit. A post-marketing clinical outcomes trial to verify the drug's clinical benefit should be under way before the phase 3 trial data is submitted for review. The outcomes trial must also be adequate and well controlled and carried out with due diligence (2)."

FDA also held a public webinar (Jan-2021)

U.S. FOOD & DRUG ADMINISTRATION

Drug Development for
Nonalcoholic Steatohepatitis (NASH) with Fibrosis:
A Regulatory Perspective

Toru Matsubayashi, MD, MPH, DrPH
Division of Hepatology and Nutrition
Office of New Drugs
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US Food and Drug Administration
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Histology Based Surrogate Efficacy Endpoints to Support Accelerated Approval

- Resolution of steatohepatitis on overall histopathological reading AND no worsening of liver fibrosis on NASH CRN fibrosis score
  OR
- At least one stage improvement in liver fibrosis AND no worsening of steatohepatitis
  OR
- Both resolution of steatohepatitis and improvement in fibrosis

Liver Biopsies
- Fibrosis stage
- Inflammation
- Ballooning
- Steatosis
- Other histopathology endpoints

Source: Noncirrhotic Nonalcoholic Steatohepatitis Liver Fibrosis: Developing Drugs for Treatment—Guidance for Industry

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