# Reduction in Fibrosis and Steatohepatitis Imaging and Biomarkers in a 52-week Resmetirom NASH Trial

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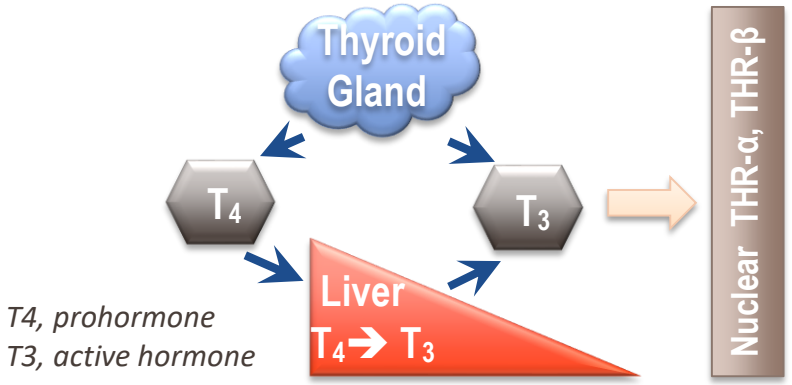
# Resmetirom: Target and Phase 2 Results in the Treatment of NASH




*Thyroid Hormone Pathway*

*Resmetirom: 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*

- Resmetirom, is a once a day, oral liver-directed thyroid hormone receptor-$\beta$ agonist that acts in the liver to improve histopathologic features of NASH
- In Phase 2, the primary endpoint was achieved: Liver fat reduction assessed by MRI-PDFF at Weeks 12, 36
- Reduction in PDFF of was associated with resolution of NASH and fibrosis improvement on biopsy
- Additional endpoints achieved: reduction in liver enzymes and fibrosis biomarkers; improvements in CV profile: LDL-cholesterol and lipid lowering; reduction in liver stiffness (fibrosis stage) on serial FibroScan, an office-based test

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# 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<br><br>**Treatment of Nonalcoholic Steatohepatitis (NASH)** | **Phase 2 MGL-3196-05** NCT02912260 | Completed | | | | ■ MRI-PDFF, liver biopsy: endpoints achieved[1]<br>• 36 week with 36 week open-label extension |
| | **Phase 3 MAESTRO-NASH** NCT03900429 | Recruiting → | | | | ■ Treatment of NASH with Fibrosis Stage 2-3<br>• Serial liver biopsy<br>• 52 week Phase 3; 54 month outcomes |
| | **Phase 3 MAESTRO-NAFLD-1** (presumed NASH) NCT04197479 | Ongoing → | | | | ■ Treatment of NASH<br>• *Safety, Lipids and NASH biomarker and imaging study*<br>• *52 week*<br>• *Enrollment of double-blind arms completed*<br>• *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*

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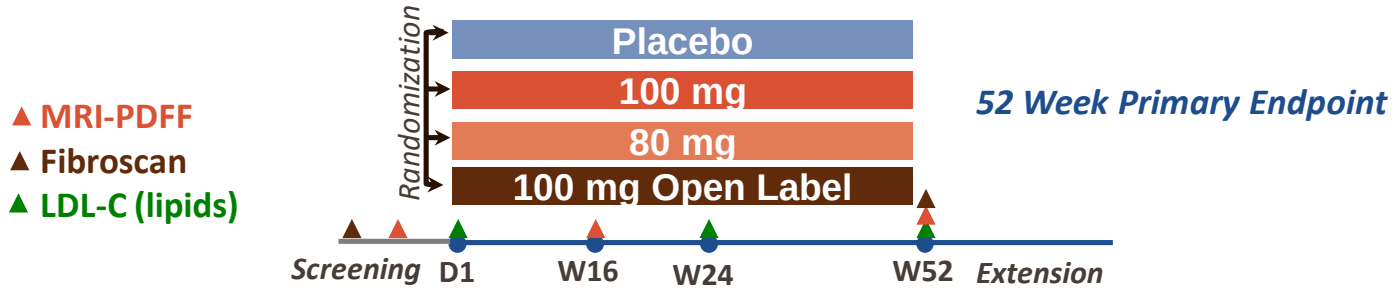
# Phase 3 MAESTRO-NAFLD-1 (presumed NASH) Study Design: Randomized, Double-Blind, PBO Controlled with 100 mg Open Label Arm




**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 (VCTE) kPa≥ 5.5, 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

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

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# MAESTRO-NAFLD-1 Non-cirrhotic NASH Open Label Active 100 mg Treatment Arm

- An exploratory evaluation of safety, imaging and biomarkers was conducted in >150 patients enrolled in the open label 100 mg daily resmetirom dose active treatment arm of MAESTRO-NAFLD-1
- At the time of this presentation 115 patients had completed Week 52 including laboratory tests, safety analyses, MRI-PDFF, MRE, and FibroScan (VCTE)

**MAESTRO-NAFLD-1 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

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# Baseline Characteristics, 100 mg Resmetirom Non-cirrhotic NASH Open Label Arm

| MAESTRO-NAFLD-1 Baseline | mean | SD |
|---|---|---|
| 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 (%) | 48 | (39%) |
| T2D, n (%) | 50 | (41%) |
| T2D Yrs since Dx 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) |
| ELF mean (SD) (ng/ml) | 9.3 | (0.89) |
| 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 Chol 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%
  - Comparatively, MAESTRO-NASH baseline FibroScan kPa mean is 13.0

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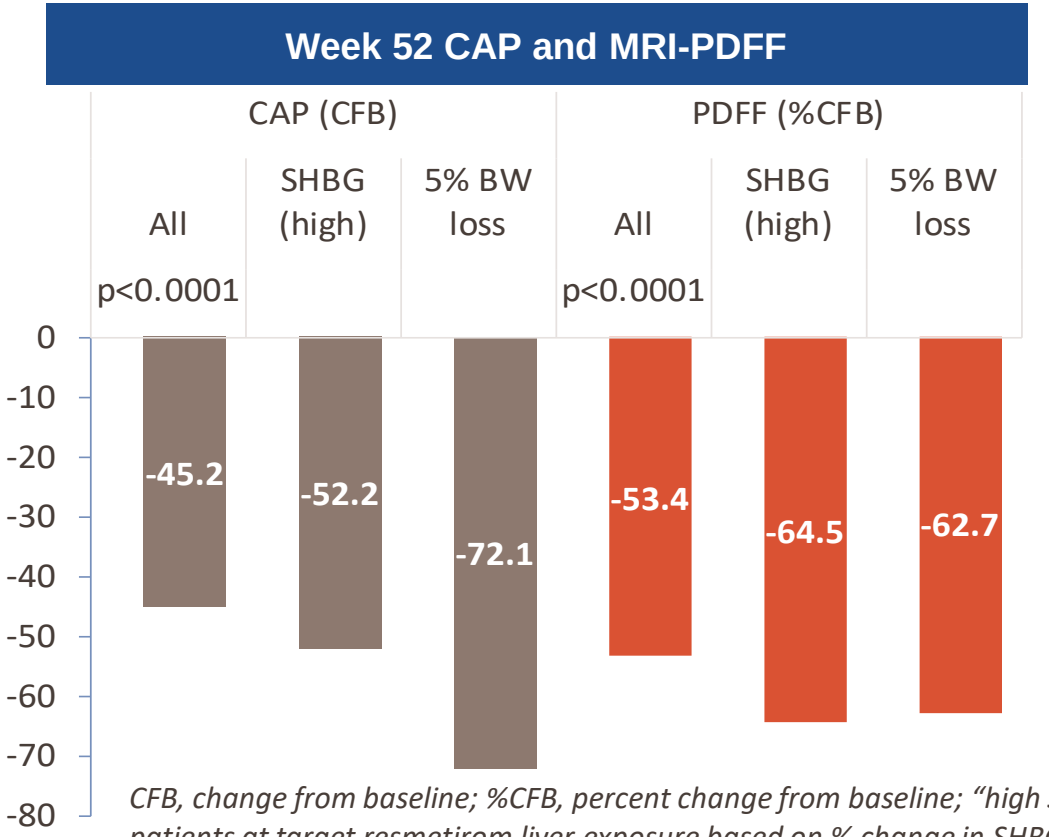
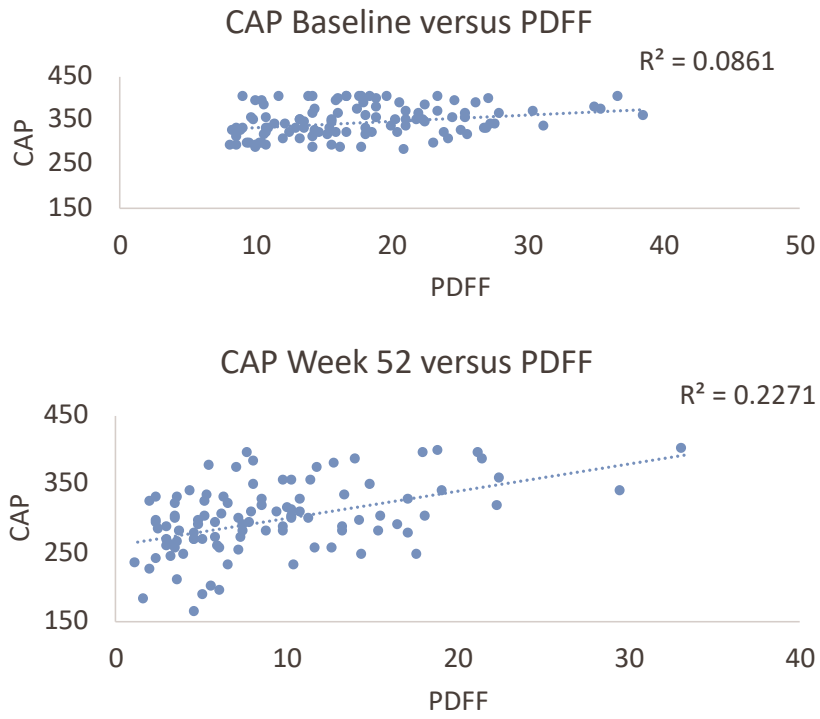
# Resmetirom-Mediated Reduction in Liver Fat as Assessed by MRI-PDFF and CAP




*CFB, change from baseline; %CFB, percent change from baseline; "high SHBG", majority of patients at target resmetirom liver exposure based on % change in SHBG*




- Serial MRI-PDFF measurements and FibroScan with CAP, both measures of liver fat content in 115 patients at Week 52
- The correlation between baseline MRI-PDFF and CAP was weak; relative inability of CAP to accurately quantitate steatosis
- Resmetirom potently reduced both CAP and MRI-PDFF at Week 52

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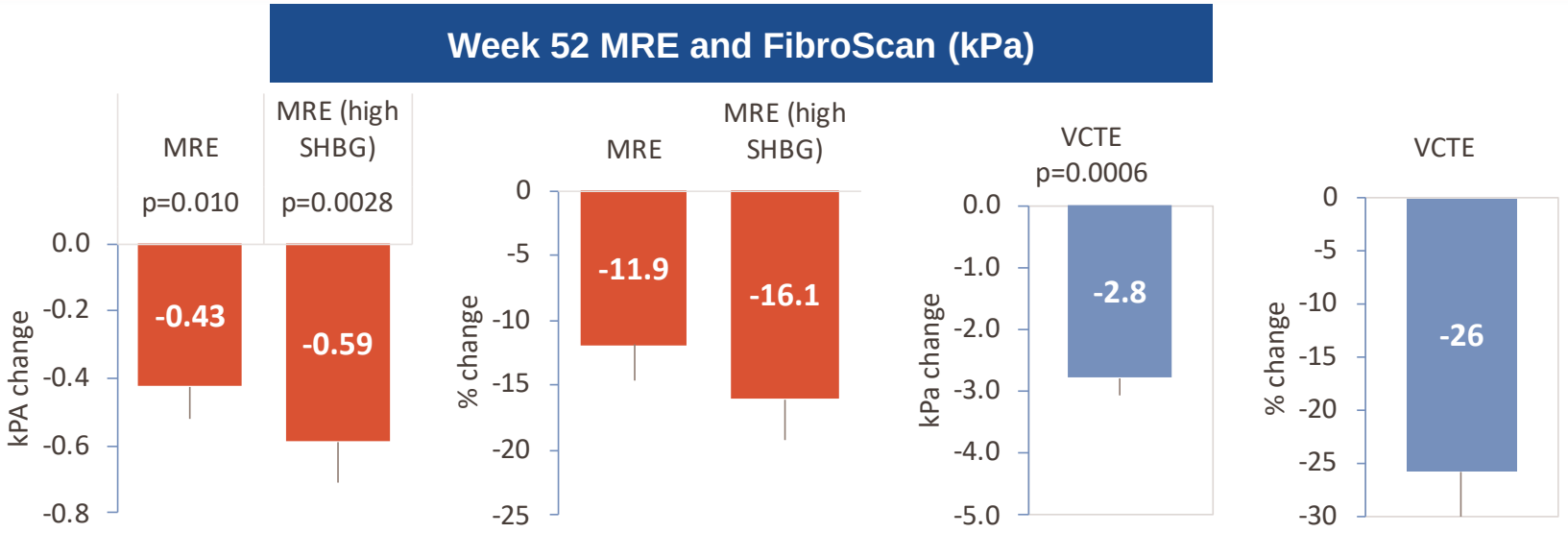
# Improvements in Fibrosis Imaging and Biomarkers at Week 52




| | Baseline | Week 52 | |
|---|---|---|---|
| | | Change | p-value |
| CK-18 (M30) | 637 | -300 | <0.0001 |
| ELF | 10.6 | -0.4 | 0.03 |
| Reverse T3 | 17.6 | -3.6 | <0.0001 |
| | | | |
| | Parameter | Baseline | Week 52 |
| FibroScan (kPa) | BL >=7.4 | 9.8 | 7.0 |
| MRE (kPa) | BL>=2.9 | 3.5 | 3.1 |

- Reductions in kPa on FibroScan and MRE were observed
  - Approximately 50% of patients had a 15% reduction in MRE (kPa) and/or 25% reduction in FibroScan (VCTE) kPa
  - Worsening of fibroscan kPa (25% increase) and MRE kPa (15% increase) are associated with disease progression[1]
- Serum fibrosis/inflammation biomarkers showed reductions over the time-course of the study and at Week 52
- Change from baseline in non-invasive fibrosis imaging and biomarkers may reflect change in inflammation and/or fibrosis on liver biopsy at Week 52

CK-18, cytokeratin 18; ; ELF, Enhanced liver fibrosis (>=10 BL);; Reverse T3, reverse triiodothyronine, kPa, kilopascal; VCTE, vibration-controlled transient elastography; MRE, magnetic resonance elastography; BL, baseline

[1] Hepatology, VOL . 71, NO. 3, 2020; Hepatology, VOL . 73, NO. 2, 2021



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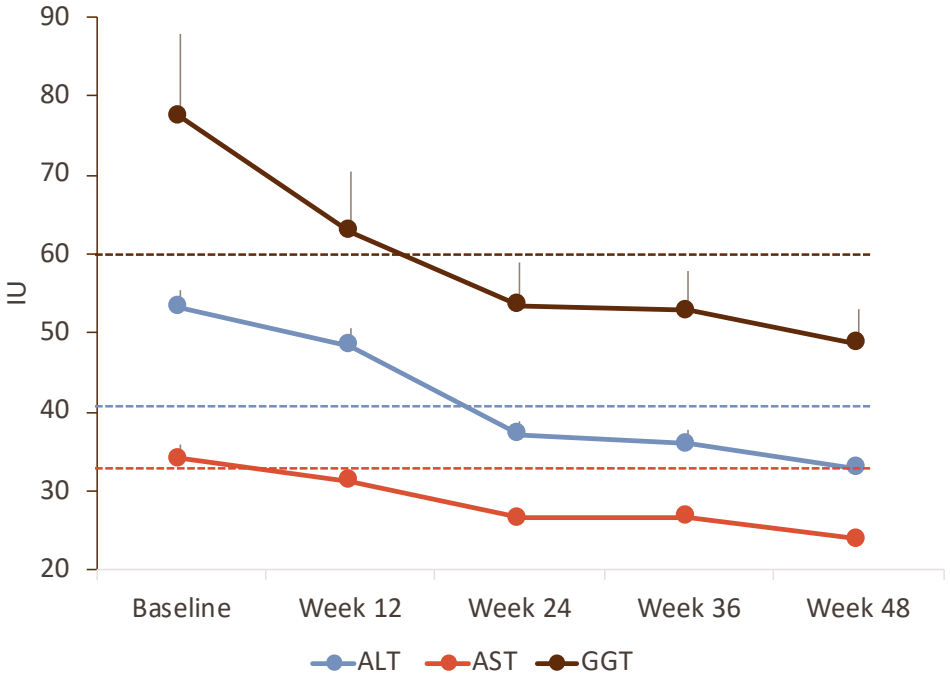
# Resmetirom-Mediated Reductions in Liver Enzymes



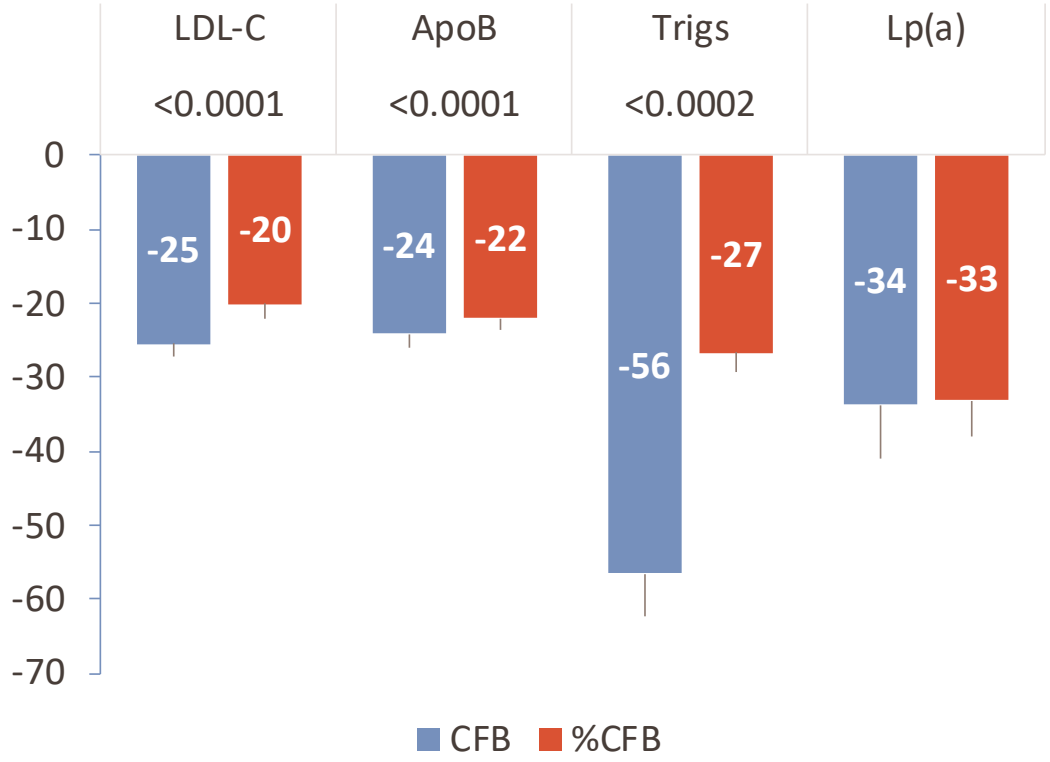

| Week 48 | CFB | %CFB | p-value |
|---|---|---|---|
| ALT | -20.36 | -33.04 | <0.0001 |
| AST | -10.19 | -21.50 | 0.0003 |
| GGT | -28.52 | -19.83 | 0.015 |

- Liver enzymes are minimally elevated in most NASH patients
- Patients with mild to moderate ALT or GGT elevations at baseline reduced their liver enzymes on resmetirom treatment during the study

*Upper limit of normal range, dotted line; Population was patients with baseline ALT>30 IU for ALT and AST; GGT>=30 for GGT*

# Safety Summary and CV Effects

- Resmetirom at 100 mg per day was well-tolerated
  - 95% completion rate; 1 withdrawal for AE
  - GI AEs, generally mild AE, increased stool frequency in ~10% over historic placebo rates, not leading to study discontinuation, observed at the beginning of therapy
  - 6.8% with COVID AE; COVID, most common SAE; no other SAE more than 1 occurrence, none related, total non-COVID SAEs 3.4%
  - All other AEs <5%
  - No central thyroid axis changes or adverse effects on vital signs
- Resmetirom reduced markers of cardiovascular risk
  - CV disease is increased in NASH patients
  - Reduced LDL-C, ApoB, triglycerides and lipoprotein (a), key secondary endpoints in MAESTRO studies
  - Small decrease in BP may reflect metabolic syndrome improvement




| | CFB | SE | P-value |
|---|---|---|---|
| Blood pressure (mm Hg) | | | |
| Systolic | -5.3 | 1.4 | 0.0093 |
| Diastolic | -3.7 | 0.89 | 0.0033 |
| Body weight (kg)[1] | -1.5 | 0.50 | NS |

*CFB, change from baseline [1]21% lost >=5% BW; 9% increased BW>=5%*

# Conclusions: MAESTRO-NASH-NAFLD-1 100mg Open Label

- In this 52 week Phase 3 open label study of resmetirom, a once-a-day oral medication, noninvasively identified NASH patients treated with 100 mg per day of resmetirom for up to 52 weeks demonstrated rapid and sustained reduction in
  1. Hepatic fat
  2. Fibrosis as assessed by ELF, MRE and FibroScan
  3. Liver cell injury and inflammatory biomarkers
  4. LDL and atherogenic lipids

- Resmetirom is well-tolerated at 100 mg per day

- Limitations of the study include relatively early patient population, absence of a placebo control group

- This study highlights the potential use of non-invasive tests to diagnose NASH and monitor individual NASH patient response to resmetirom treatment

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