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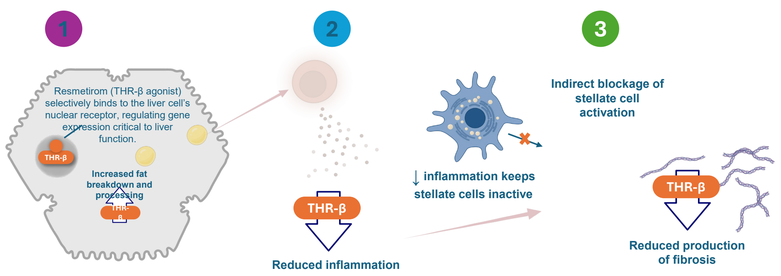
INTRODUCTION

Unmet Need in Patients with MASH Cirrhosis

High risk of negative outcomes, no approved disease modifying therapies

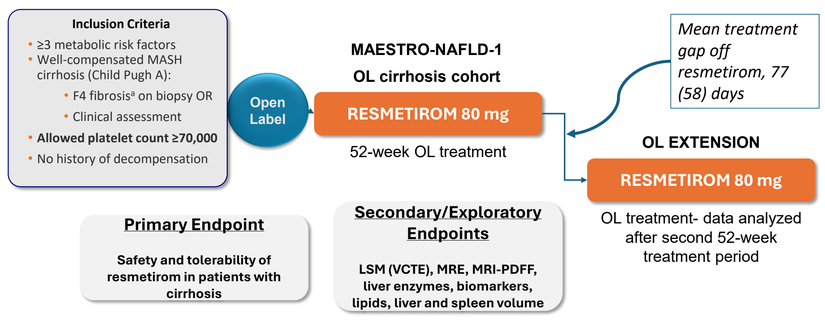
- Resmetirom, an oral, once-daily, liver-directed thyroid hormone receptor β (THR-β) agonist, is FDA-approved for treatment of MASH with liver fibrosis (as of 2024).
- No approved therapies for patients with compensated cirrhosis due to MASH.
- Cirrhosis (F4) is highly associated with clinical outcomes including hepatic decompensation events, liver failure, liver transplant and mortality.

Resmetirom, a THR-β Agonist, Works Directly in the Liver to Improve Critical Hepatic Processes and Reduce Fibrosis

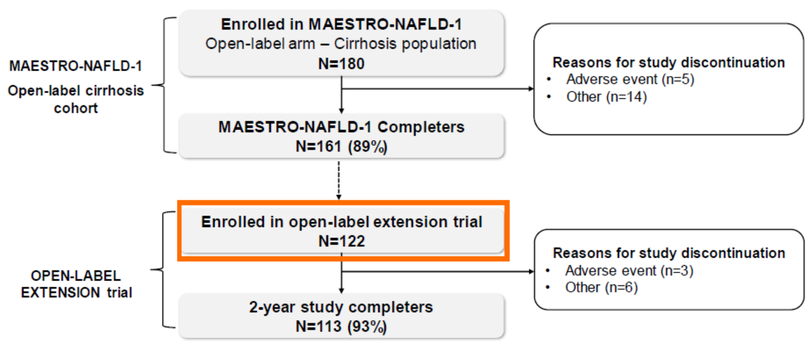


- Increase in clearance of defective mitochondria (mitophagy) and synthesis of healthy mitochondria (mitochondrial biogenesis)
- Liver THR-β Activity identified as a "Master Regulator"[a] in protecting from progression to decompensated MASH Cirrhosis

Open-Label (OL) 52 Week Cirrhosis Arm of MAESTRO-NAFLD-1 Followed by a 52 Week Extension Trial



Open-Label (OL) 52-Week Cirrhosis Arm of MAESTRO-NAFLD-1 Followed by a 52 Week Extension Trial



RESULTS

Baseline Characteristics

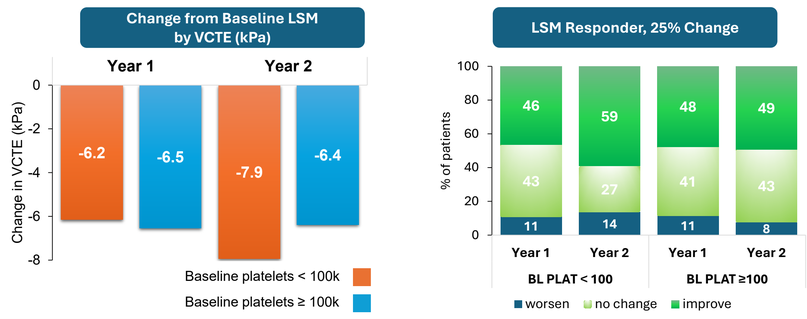
	BL Platelets < 100 (N=30)	BL Platelets ≥ 100 (N=92)
Age, years	61 (56, 66)	62 (57, 69)
Sex, Female	14 (46.7%)	54 (58.7%)
BMI, kg/m^2	35.1 (32.7, 38.9)	33.4 (30.4, 39.1)
Type 2 Diabetes	22 (73.3%)	63 (68.5%)
VCTE, kPa	26.4 (17.7, 39.6)	19.3 (16.1, 27.4)
CAP, dB/m	317.5 (291.5, 376.5)	331.0 (292.5, 368.5)
MRE, kPa	5.9 (4.9, 6.7)	5.1 (4.0, 5.9)
MRI-PDFF, %	6.7 (4.8, 8.6)	9.2 (6.6, 12.2)
Agile 3+	0.98 (0.97, 0.99)	0.95 (0.87, 0.98)
Agile 4	0.85 (0.80, 0.92)	0.56 (0.31, 0.72)
Liver Volume, mL	2035.3 (1773.1, 2468.0)	2295.0 (1920.5, 2687.1)
Spleen Volume, mL	906.5 (657.2, 1121.1)	424.7 (305.4, 633.8)

	BL Platelets < 100 (N=30)	BL Platelets ≥ 100 (N=92)
ALT, U/L	30 (26, 38)	38 (28, 53)
AST, U/L	35 (26, 39)	38 (24, 49)
Platelets, 10^9/L	89 (77, 91)	156 (128, 208)
Albumin, g/dL	4.2 (3.8, 4.3)	4.3 (4.0, 4.4)
FIB-4	3.9 (3.3, 5.8)	2.0 (1.5, 3.0)
ELF Score	11.1 (10.7, 11.9)	10.5 (9.9, 11.4)

Major differences in subgroups:

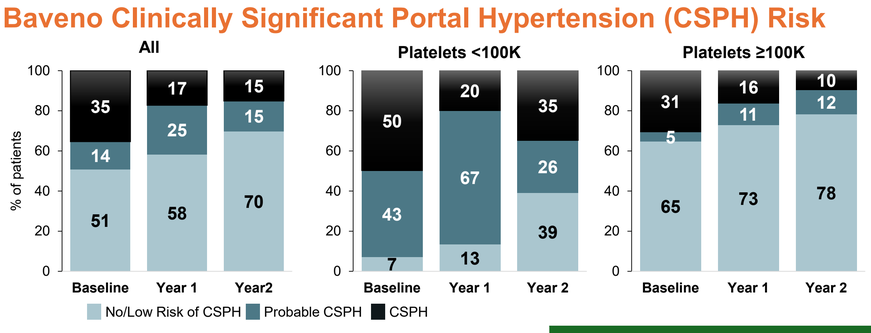
- Spleen volume, twice as high in low platelet group reflective of advanced portal hypertension
- Agile-4, MRE, VCTE, FIB-4, all higher in low platelet group

Reduction in LSM by VCTE: Magnitude and Response



- Statistically significant improvements in VCTE at Year 1 and 2
- Clinically meaningful response ~50% improved, few worsening, independent of baseline platelets

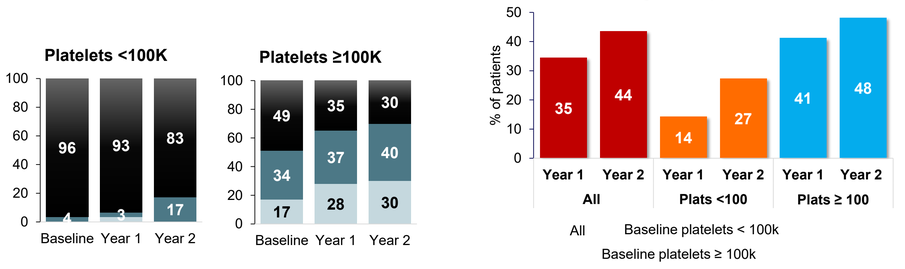
Baveno Clinically Significant Portal Hypertension (CSPH) Risk



- >90% of patient with platelets <100k have CSPH/probable CSPH
- Resmetirom treatment shifts 2/3 of patients with CSPH to lower Baveno CSPH risk score

Risk of CSPH	Baveno[a]
CSPH	VCTE ≥ 25
Probable CSPH	20 ≤ VCTE < 25 & PLT < 150 **or** 15 ≤ VCTE < 20 & PLT < 110
No/Low CSPH	Not meeting above criteria

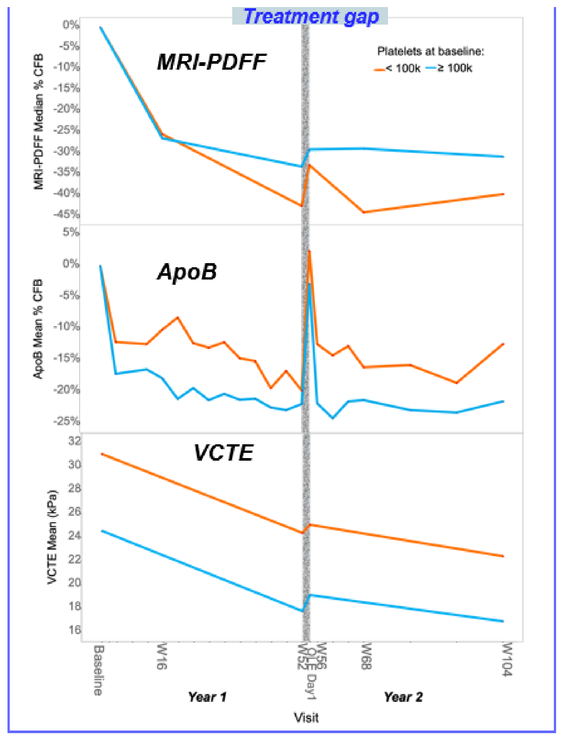
AGILE-4 Cirrhosis Risk



- Agile-4 predicts the likelihood of having F4 stage fibrosis (cirrhosis)
  - Sensitivity and specificity of predicting cirrhosis and ruling out cirrhosis, 0.93 and 0.90: parameters include VCTE, platelets, AST/ALT ratio, sex, diabetes status
- Resmetirom shifts patients to a lower Agile-4 Score and lower risk of cirrhosis

Agile 4 Risk Groups	
High F4 Risk	Agile 4 > 0.57
Intermediate F4 Risk	0.25 ≤ Agile 4 ≤ 0.57
Low F4 Risk	Agile 4 < 0.25

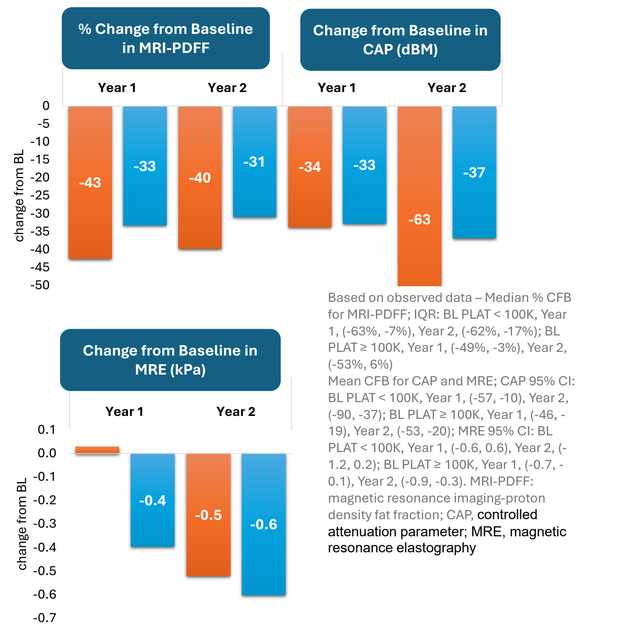
Impact of Resmetirom Treatment Interruption



Baseline platelets < 100k Baseline platelets ≥ 100k

- Resmetirom treatment was interrupted for approximately 77 days between Year 1 and Year 2
- MRI-PDFF, Apolipoprotein B (ApoB), VCTE (liver stiffness) decreased during Year 1 of resmetirom treatment and increased during the treatment gap between Year 1 and 2
- Addition of resmetirom at Year 2 led to restoration of resmetirom treatment effect that was observed at the end of Year 1
- Results for these 3 biomarker measures were generally independent of baseline platelet count

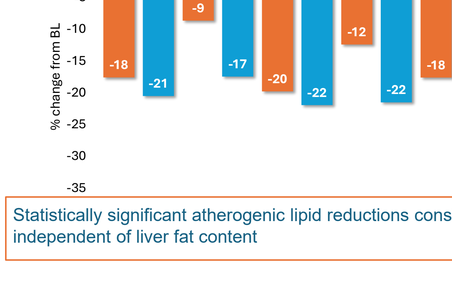
Improvement in Imaging Measures Independent of Baseline Platelets

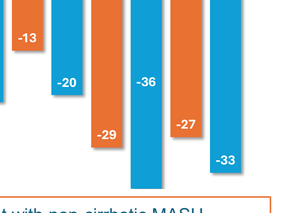


Based on observed data – Median % CFB for MRI-PDFF; IQR: BL PLAT < 100K, Year 1, (-63%, -7%), Year 2, (-62%, -17%); BL PLAT ≥ 100K, Year 1, (-49%, -3%), Year 2, (-53%, 6%)
Mean CFB for CAP and MRE; CAP 95% CI: BL PLAT < 100K, Year 1, (-57, -10), Year 2, (-90, -37); BL PLAT ≥ 100K, Year 1, (-46, -19), Year 2, (-53, -20); MRE 95% CI: BL PLAT < 100K, Year 1, (-0.6, 0.6), Year 2, (-1.2, 0.2); BL PLAT ≥ 100K, Year 1, (-0.7, -0.1), Year 2, (-0.9, -0.3). MRI-PDFF: magnetic resonance imaging-proton density fat fraction; CAP, controlled attenuation parameter; MRE, magnetic resonance elastography

Statistically significant improvements in MRI-PDFF, CAP and MRE at 2 Years

Spleen Volume Improvements

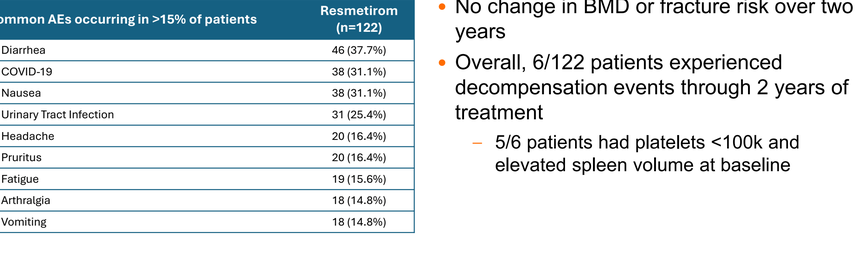




[a]95% confidence intervals, spleen volume (platelets ≥100k): Year 1, (-10.6, -4.7); Year 2, (-9.5, -1.9).

- In Year 1, both platelet groups showed a decline in spleen and liver volume
  - The decrease in liver volume was independent of liver fat content
- The gap in resmetirom treatment led to a rapid increase in spleen volume (independent of gap length), more notable in group with baseline platelets <100K
- Year 2 of treatment stabilized spleen volume in patients with platelets <100K and significantly[a] decreased spleen volume in patients with platelets ≥100K, correlated with an increase in platelet count (correlation coefficient= -0.53)

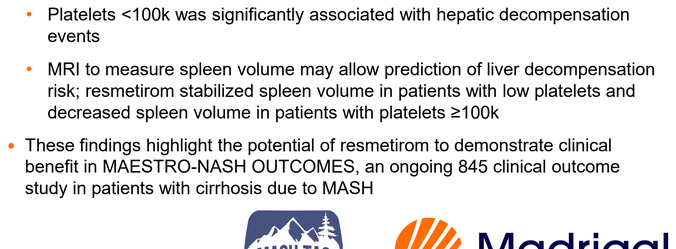
Improvements in ALT, AST, and GGT



- Statistically significant liver enzyme reductions especially in group with baseline platelets ≥100k
- No change in MELD

[a] Reported as median CFB in <100k platelet group, based on small ns; year 1, n=17; Year 2, n=16. Based on observed data – Mean % CFB, for AST and ALT in patients with baseline ALT>=30 IU; ALT 95% CI: BL PLAT < 100K, Year 1, (-22%, 16%), Year 2, (-15%, 27%); BL PLAT ≥ 100K, Year 1, (-29%, -10%), Year 2, (-33%, -17%); AST 95% CI: BL PLAT < 100K, Year 1, (-9%, 24%), Year 2, (3%, 59%); BL PLAT ≥ 100K, Year 1, (-28%, -7%), Year 2, (-27%, -10%); GGT 95% CI: BL PLAT < 100K, Year 1, (-33%, -18%), Year 2, (-39%, -4%); BL PLAT ≥ 100K, Year 1, (-32%, -18%), Year 2, (-38%, -22%).
ALT: alanine aminotransferase; AST: Aspartate Aminotransferase; GGT: gamma-glutamyl transferase; CFB, change from baseline

Reductions in Fibrosis and Liver Injury Biomarkers



Statistically significant changes in in liver injury/fibrosis markers

Based on observed data – Mean CFB for CK-18; 95% CI: BL PLAT < 100K, Year 1, (-196,20), Year 2, (-309,-102); BL PLAT ≥ 100K, Year 1, (-252,-35), Year 2, (-452,-260); Mean % CFB for PRO-C3 and Adiponectin; PRO-C3 95% CI: BL PLAT < 100K, Year 2, (-57%, -9%); BL PLAT ≥ 100K, Year 2, (-49%, -35%); Adiponectin 95% CI: BL PLAT < 100K, Year 1, (15%, 65%), Year 2, (25%, 100%); BL PLAT ≥ 100K, Year 1, (13%, 32%), Year 2, (24%, 48%)

Sustained Reductions in Atherogenic Lipids

Statistically significant atherogenic lipid reductions consistent with non-cirrhotic MASH, independent of liver fat content

Safety Summary

Summary AEs	Resmetirom (n=122)
Any TEAE	120 (98.4%)
Any SAE	27 (22.1%)
TEAE leading to Trial Discontinuation	3 (2.5%)
Death	2 (1.6%)
Common AEs occurring in >15% of patients	**Resmetirom (n=122)**
Diarrhea	46 (37.7%)
COVID-19	38 (31.1%)
Nausea	38 (31.1%)
Urinary Tract Infection	31 (25.4%)
Headache	20 (16.4%)
Pruritus	20 (16.4%)
Fatigue	19 (15.6%)
Arthralgia	18 (14.8%)
Vomiting	18 (14.8%)

- Safety data were consistent with previous studies
- Resmetirom was well-tolerated in this high-risk population, low discontinuation rate
  - All SAEs were unrelated to study drug
- No change in BMD or fracture risk over two years
- Overall, 6/122 patients experienced decompensation events through 2 years of treatment
  - 5/6 patients had platelets <100k and elevated spleen volume at baseline

SUMMARY

- Resmetirom treatment for 2 years led to statistically significant improvement in multiple imaging and biomarker parameters
- Temporary interruption of resmetirom treatment between year 1 and 2 led to temporary attenuation of beneficial effects that generally reversed with treatment restoration
- Patients with platelets <100k at baseline, representing 25% of the enrolled population, had greatly enlarged spleens at baseline that increased in volume when resmetirom treatment was interrupted
  - Platelets <100k was significantly associated with hepatic decompensation events
  - MRI to measure spleen volume may allow prediction of liver decompensation risk; resmetirom stabilized spleen volume in patients with low platelets and decreased spleen volume in patients with platelets ≥100k
- These findings highlight the potential of resmetirom to demonstrate clinical benefit in MAESTRO-NASH OUTCOMES, an ongoing 845 clinical outcome study in patients with cirrhosis due to MASH