Two-year Time Course of Biomarker and Imaging Responses in Patients with Well-Compensated MASH Cirrhosis Treated With Resmetirom

N. Alkhouri,[1] R. Taub,[2] X. Lu,[2]
M. Charlton,[2] J. Schattenberg[3]
A. Kohli,[4] S. Moussa,[5] M. Noureddin[6]

[1]Summit Clinical Research, San Antonio, TX; [2]Madrigal Pharmaceuticals, West Conshohocken, PA; [3]Universitätsklinikum des Saarlandes, Homburg, Germany; [4]Arizona Liver Health, Chandler, AZ; [5]University of Arizona for Medical Sciences, Tucson, AZ; [6]Houston Research Institute, Houston, TX

Madrigal

My Disclosures

- Speaking and teaching roles with Madrigal, Novo Nordisk, Echosens, Ipsen, and Intercept
- Consulting roles with Novo Nordisk, Perspectum, Cima, Fibronostics, Madrigal, Boehringer Ingelheim, Ipsen, Gilead, Perspectum, Cima, and 89bio.
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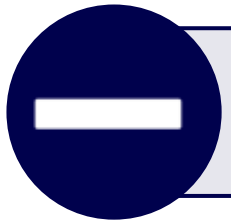
- Advisory roles with Cima and 89bio.

Unmet Need in Patients with MASH Cirrhosis

High Risk of 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).



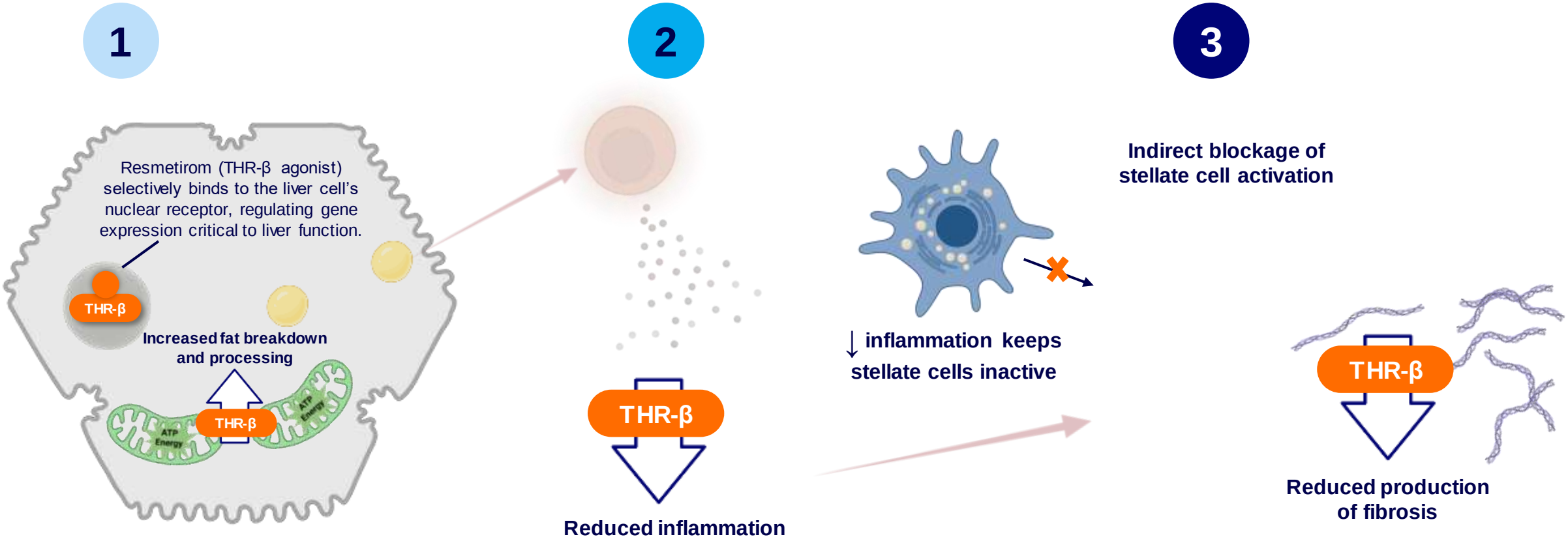
No approved therapies for patients with compensated cirrhosis due to MASH.

Cirrhosis (F4) is highly associated with clinical outcomes including hepatic decompensation events, liver failure, liver transplant and mortality

MASH: metabolic dysfunction-associated steatohepatitis.

Harrison SA et al. N Engl J Med. 2024 Feb 8;390(6):497-509; Sanyal AJ et al. N Engl J Med. 2021 Oct 21;385(17):1559-1569.

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

[a]Kendall TJ, Jimenez-Ramos M, Turner F, et al. An integrated gene-to-outcome multimodal database for metabolic dysfunction-associated steatotic liver disease. Nat Med. 2023;29:2939-2953.

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

Inclusion Criteria

- ≥3 metabolic risk factors
- Well-compensated MASH cirrhosis (Child Pugh A):
  - F4 fibrosis[a] on biopsy OR
  - Clinical assessment
- **Allowed platelet count ≥70,000**
- No history of decompensation

MAESTRO-NAFLD-1

OL cirrhosis cohort

Open Label → **RESMETIROM 80 mg**

52-week OL treatment

Mean treatment gap off resmetirom, 77 (58) days

OL EXTENSION

RESMETIROM 80 mg

OL treatment- data analyzed after second 52-week treatment period

Primary Endpoint

Safety and tolerability of resmetirom in patients with cirrhosis

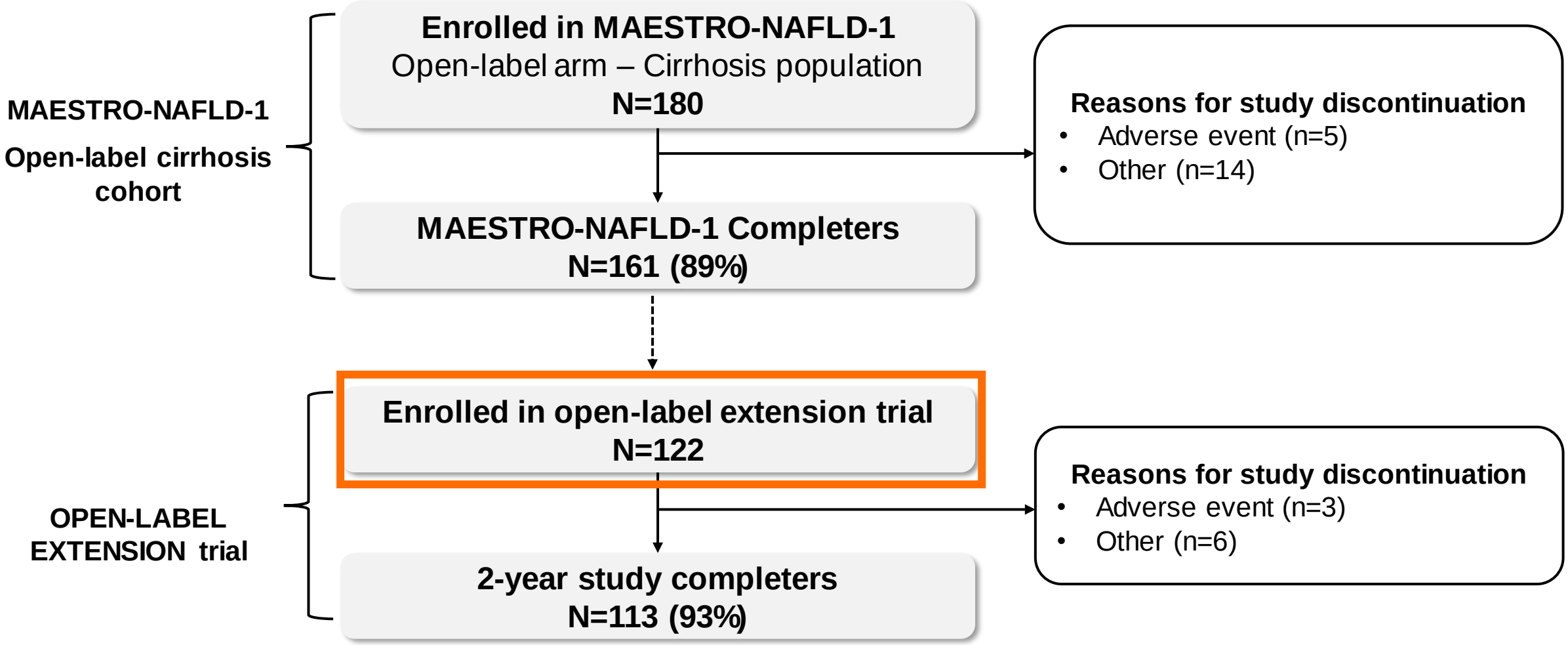
Secondary/Exploratory Endpoints

LSM (VCTE), MRE, MRI-PDFF, liver enzymes, biomarkers, lipids, liver and spleen volume

LSM, liver stiffness measurement; MASLD, metabolic dysfunction–associated steatotic liver disease; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction; OL, open-label; OLE, open-label extension; Liver biopsy was obtained 66% of patients; for patients with clinical progression from F3 on biopsy to F4; clinical assessment used imaging, biomarker and clinical identification consistent with F4.

[a]MAESTRO-NAFLD-1 included three OL arms in patients with a) noncirrhotic NASH; b) well-compensated NASH cirrhosis; and c) moderate renal impairment. Harrison SA, et al. Nat Med. 2023;390(6):497-509. CAP, controlled attenuation parameter; VCTE, vibration-controlled transient elastography.

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



[a]MAESTRO-NAFLD-1 included three OL arms in patients with a) noncirrhotic NASH; b) well-compensated NASH cirrhosis; and c) moderate renal impairment.
Harrison SA, et al. *Nat Med*. 2023;390(6):497-509.

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)

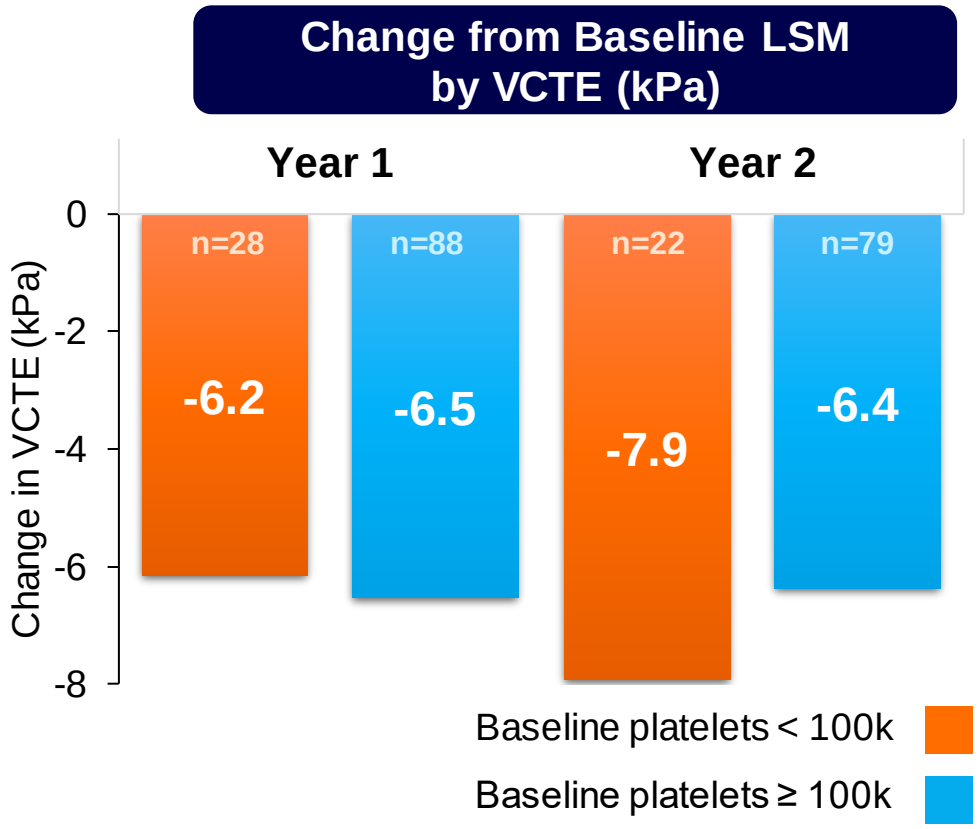
	BL Platelets < 100 (N=30)	BL Platelets ≥ 100 (N=92)
ALT, U/L	30 (26, 38)	38 (28, 53)
AST, U/L	35 (26, 39)	38 (24, 49)
Platelets, 10^9/L	89 (77, 91)	156 (128, 208)
Albumin, g/dL	4.2 (3.8, 4.3)	4.3 (4.0, 4.4)
FIB-4	3.9 (3.3, 5.8)	2.0 (1.5, 3.0)
ELF Score	11.1 (10.7, 11.9)	10.5 (9.9, 11.4)

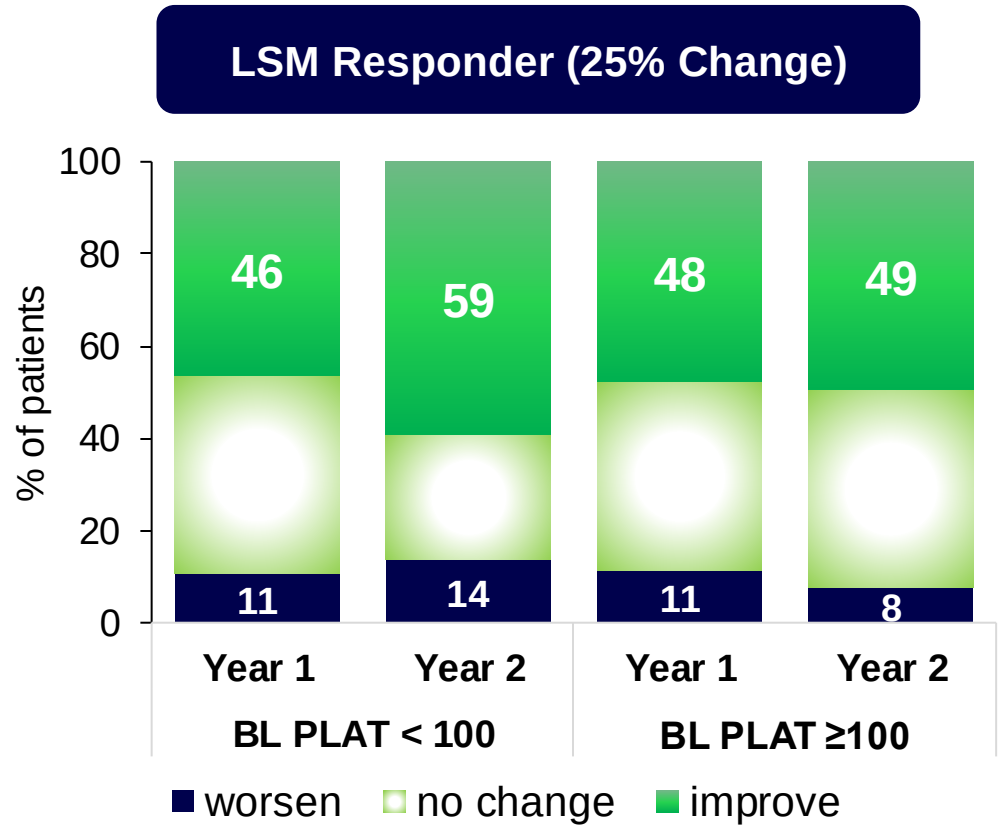
Major differences in subgroups:

- 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

Data are median (Q1, Q3) or n (%); BL, baseline. CAP, controlled attenuation parameter; VCTE, vibration-controlled transient elastography; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging proton density fat fraction.

Reduction in LSM by VCTE: Magnitude and Response

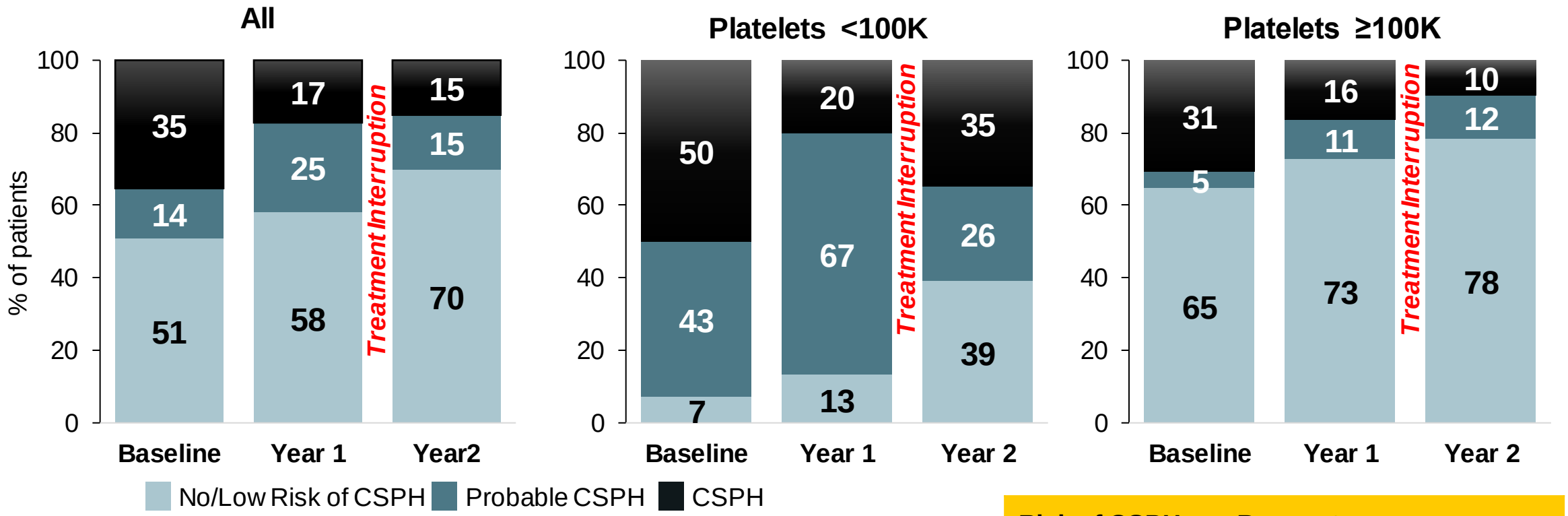




- Statistically significant improvements in VCTE at Year 1 and 2
- Clinically meaningful response ~50% improved, few worsening, independent of baseline platelets

Based on observed data – Mean change from baseline (CFB); 95% CI: BL PLAT < 100K, Year 1, (-13.2, 0.9) kPa, Year 2, (-15.3, -0.5) kPa; BL PLAT ≥ 100K, Year 1, (-9.4, -3.7) kPa, Year 2, (-9.2, -3.6) kPa
LSM, liver stiffness measure; VCTE, vibration controlled transient elastography (FibroScan)

Baveno Clinically Significant Portal Hypertension (CSPH) Risk

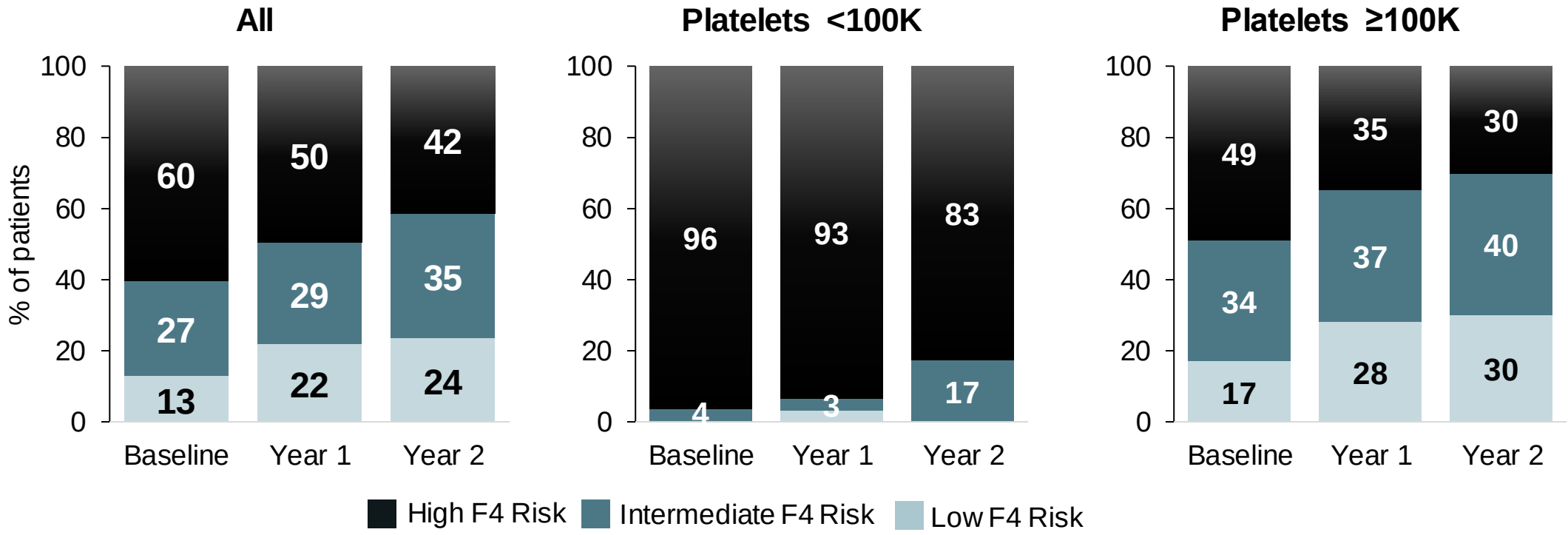


- >90% of patient with platelets <100k have CSPH/probable CSPH
- Resmetirom treatment shifted 2/3 of patients with CSPH to lower Baveno CSPH risk score

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

[a]J Hepatol. 2021 Dec 30;76(4):959–974. doi: 10.1016/j.jhep.2021.12.022

Agile-4 Cirrhosis Risk



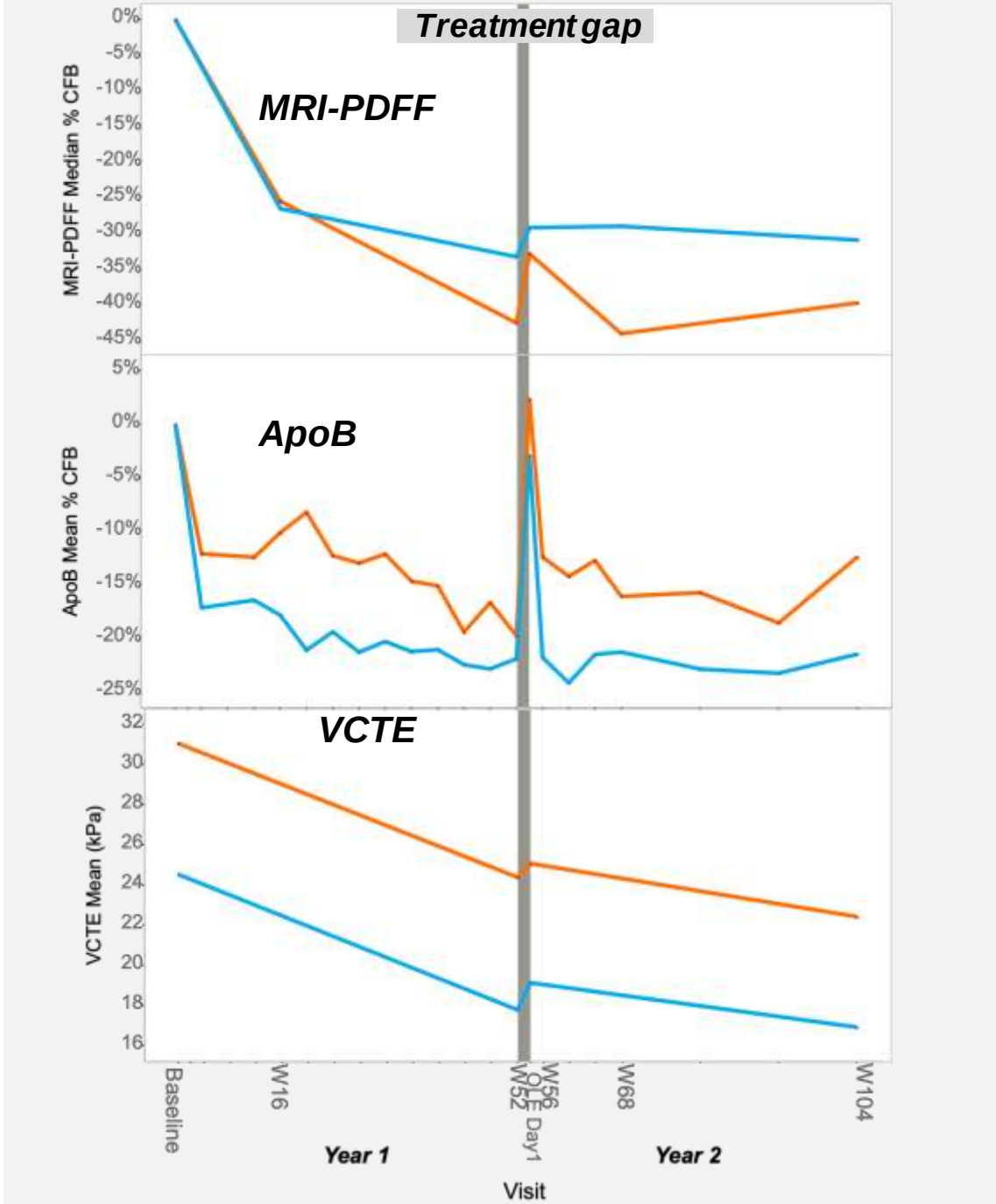
- Agile-4 predicts the likelihood of having F4 stage fibrosis (cirrhosis)
  - Sensitivity and specificity of predicting cirrhosis and ruling out cirrhosis, 0.93 and 0.90[a,b]: parameters include VCTE, platelets, AST/ALT ratio, sex, diabetes status
- Resmetirom shifts patients to a lower Agile-4 Score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

[a]Diabetes Obes Metab 2024 Dec 20;27(3):1406–1414. doi: 10.1111/dom.16142; [b]Sanyal AJ, Foucquier J, Younossi ZM, et al. J Hepatol. 2023;78:247-259. Enhanced diagnosis of advanced fibrosis and cirrhosis in individuals with NAFLD using FibroScan-based agile scores.

Impact of Resmetirom Treatment Interruption

- 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



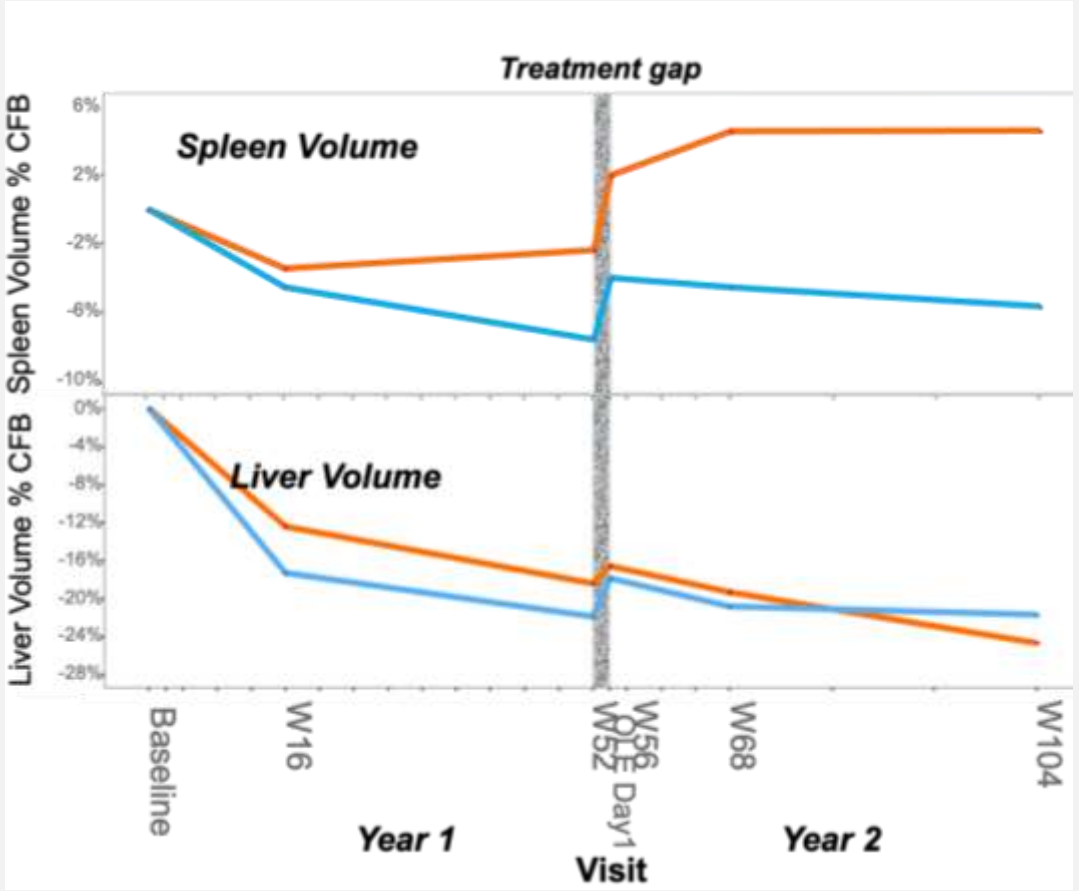
Baseline platelets < 100k

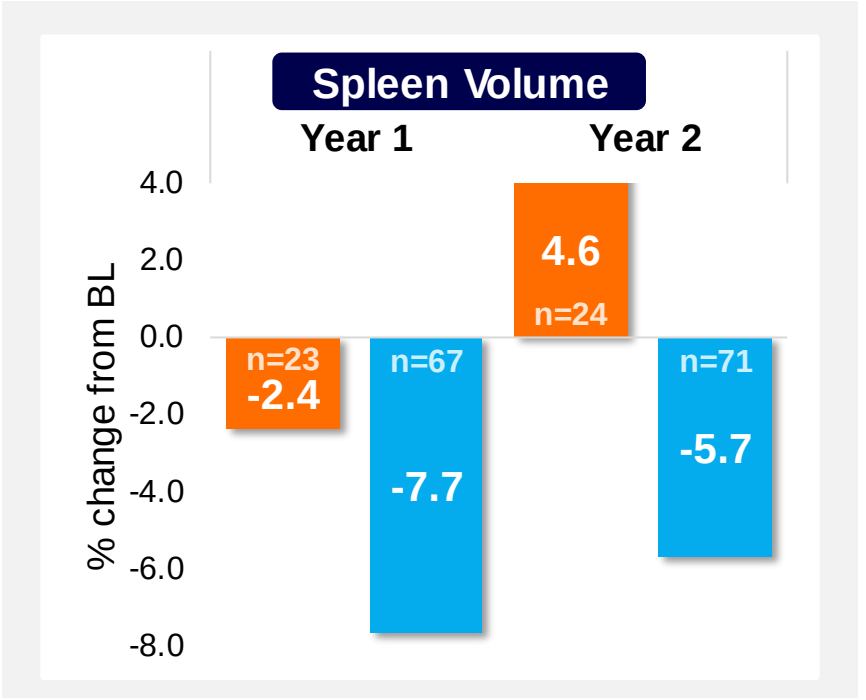
Baseline platelets ≥ 100k

MRI-PDFF: magnetic resonance imaging-proton density fat fraction; ApoB, apolipoprotein B; VCTE, vibration controlled transient elastography

Spleen Volume Improvement

Baseline platelets < 100k
Baseline platelets ≥ 100k

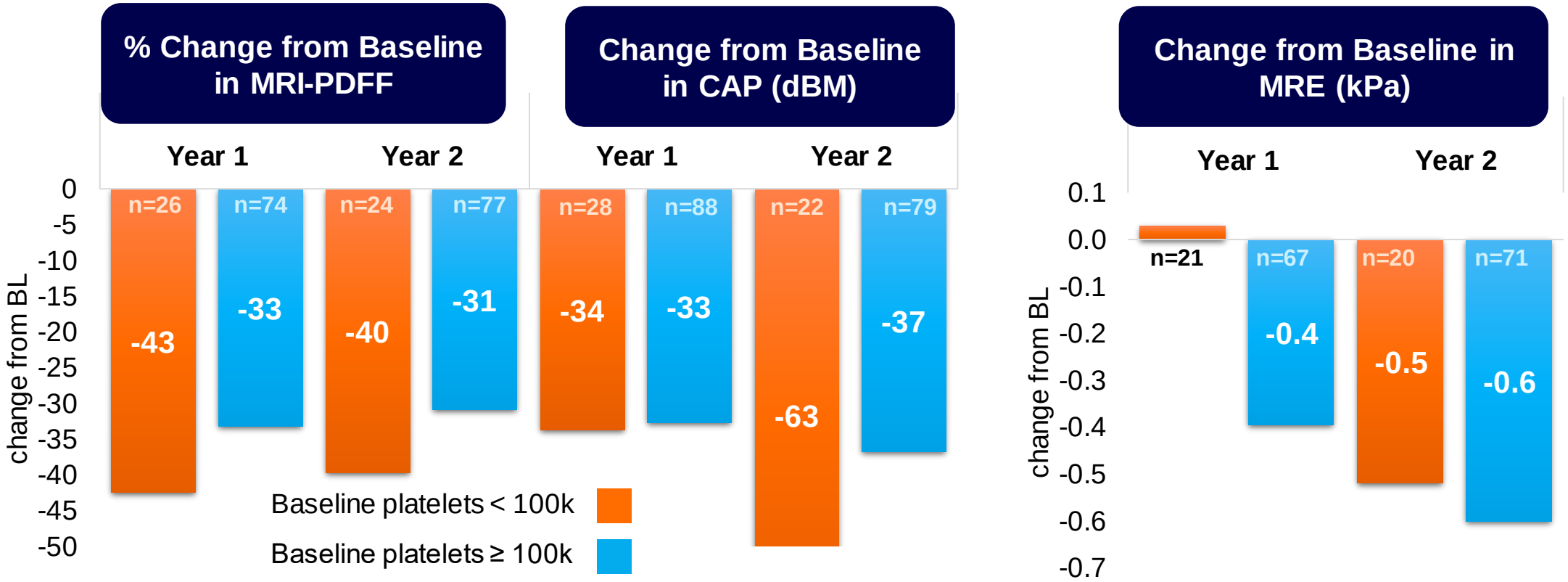




- In Year 1, both platelet groups showed a decline in spleen and liver volume
- The gap in resmetirom treatment led to a rapid increase in spleen volume, more notable in group with baseline platelets <100K
- Year 2 of treatment stabilized spleen volume in patients with platelets <100K
- Spleen volume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

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

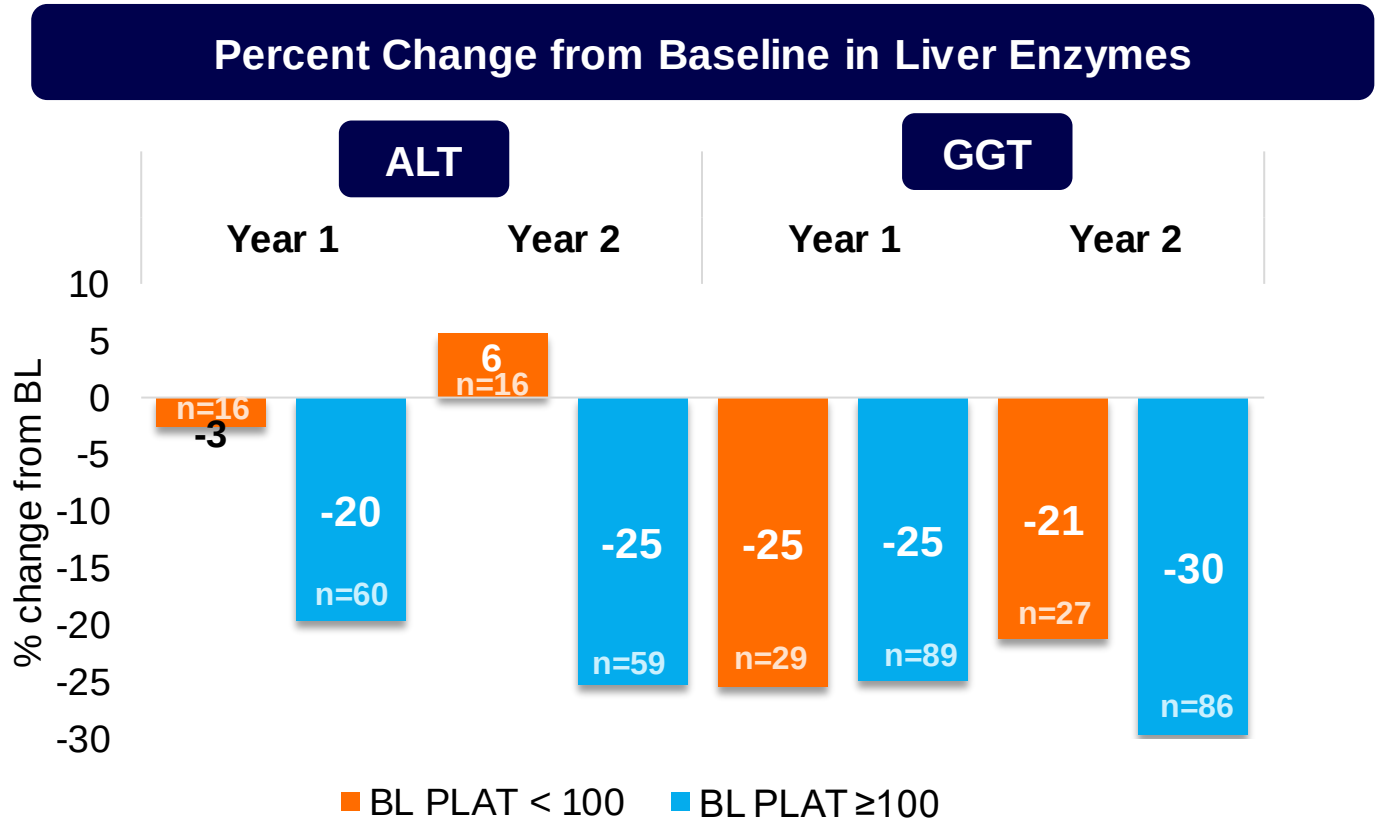
Improvement in Imaging Measures Independent of Baseline Platelets



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

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

Improvements in ALT and GGT



Baseline platelets < 100k

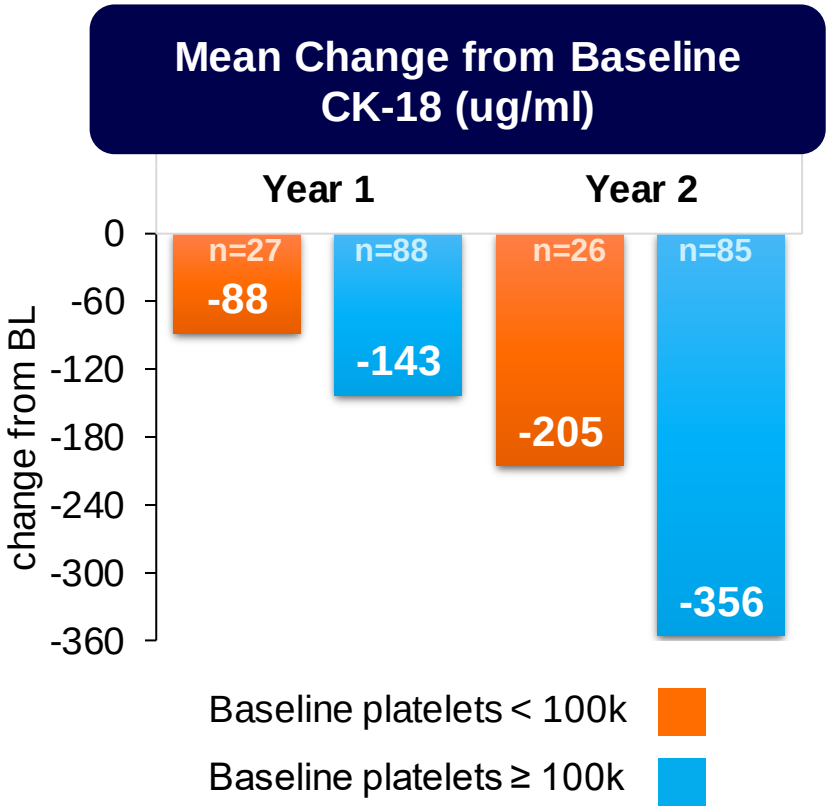
Baseline platelets ≥ 100k

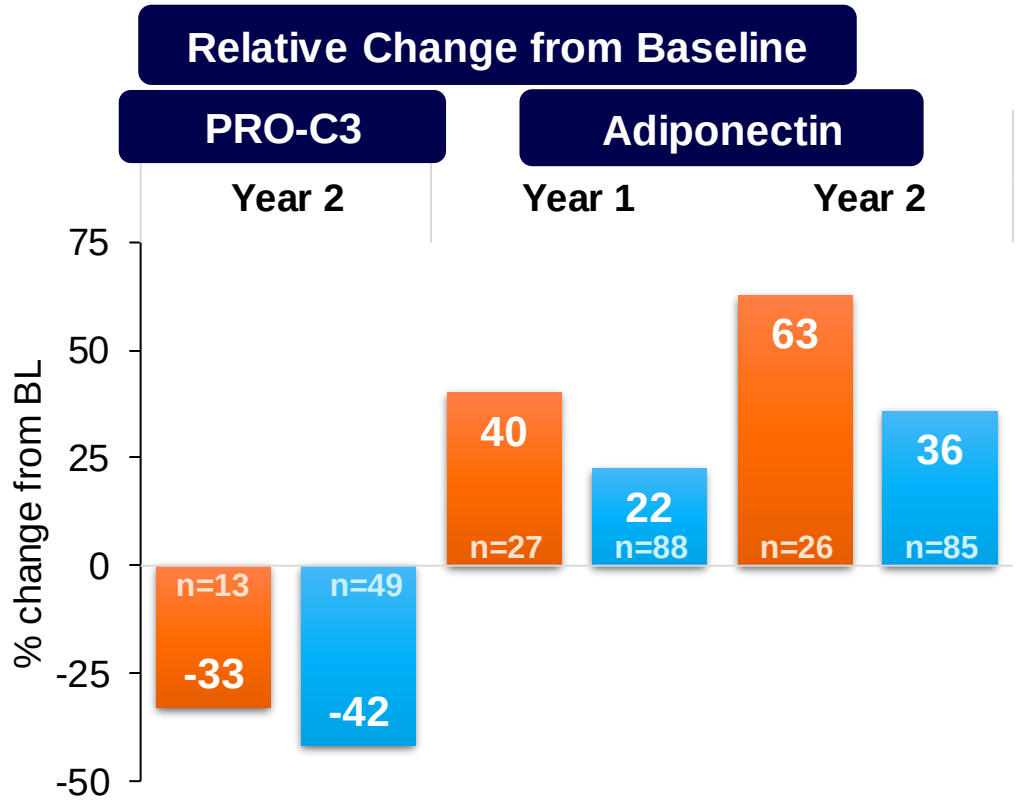
Mean % CFB, for ALT in patients with baseline ALT≥30 IU

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

Based on observed data – Mean % CFB, for 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%); 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; GGT: gamma-glutamyl transferase; CFB, change from baseline

Reductions in Fibrosis and Liver Injury Biomarkers

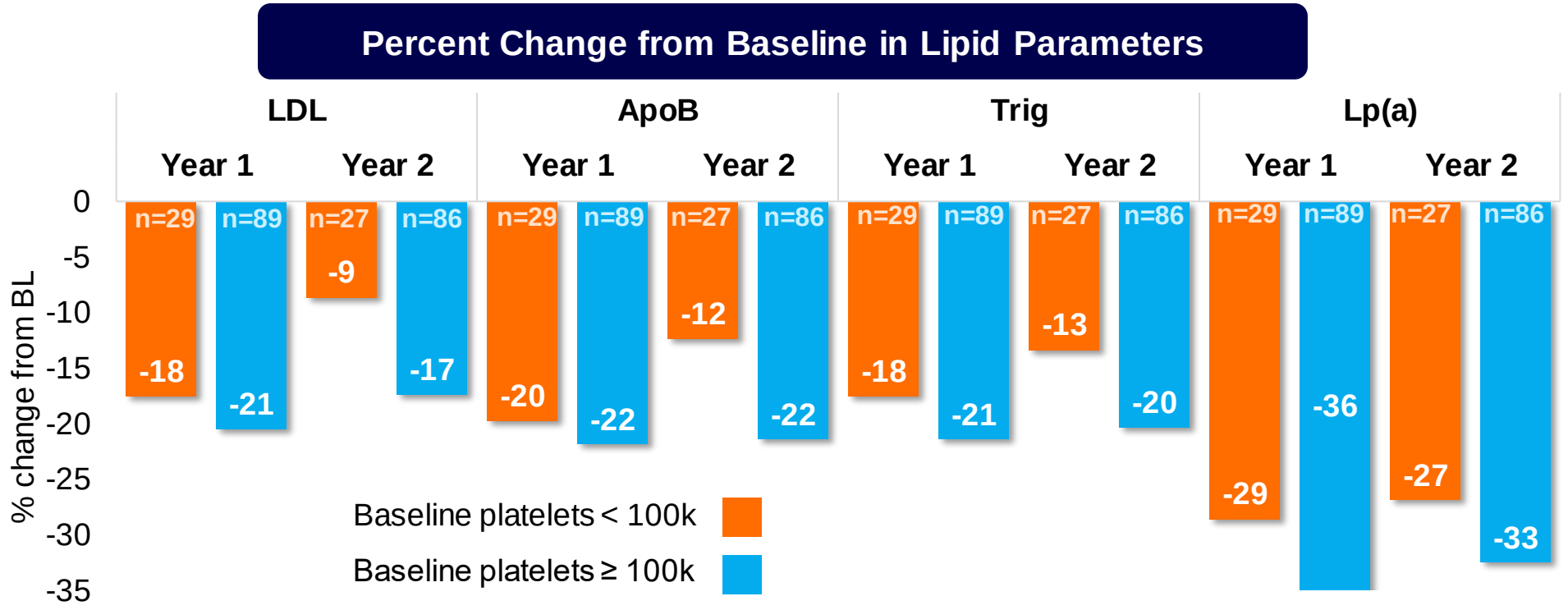




Statistically significant changes in in liver injury/fibrosis markers

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 and Lipoproteins



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

Based on observed data – Mean % CFB; LDL 95% CI: BL PLAT < 100K, Year 1, (-25%, -11%), Year 2, (-21%, 3%); BL PLAT ≥ 100K, Year 1, (-26%, -15%), Year 2, (-24%, -11%); ApoB 95% CI: BL PLAT < 100K, Year 1, (-26%, -13%), Year 2, (-20%, -5%); BL PLAT ≥ 100K, Year 1, (-26%, -18%), Year 2, (-26%, -17%); Trig 95% CI: BL PLAT < 100K, Year 1, (-33%, -2%), Year 2, (-40%, 13%); BL PLAT ≥ 100K, Year 1, (-27%, -16%), Year 2, (-28%, -13%); Lp(a) 95% CI: BL PLAT < 100K, Year 1, (-38%, -19%), Year 2, (-41%, -13%); BL PLAT ≥ 100K, Year 1, (-43%, -30%), Year 2, (-42%, -23%).
LDL: low-density lipoprotein cholesterol; ApoB: Apolipoprotein B; Trig, Triglycerides; Lp(a), lipoprotein(a).

Safety Summary (2 years of Resmetirom treatment)

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%)

Data are n (%); 2 deaths are COVID and metastatic cancer. TEAE, treatment emergent adverse event; SAE, serious adverse event; BMD, bone marrow density

- 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, 25% of the enrolled population, had more hepatic decompensation events after two years of treatment
- 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

MASH, metabolic dysfunction–associated steatohepatitis; NASH, nonalcoholic steatohepatitis.