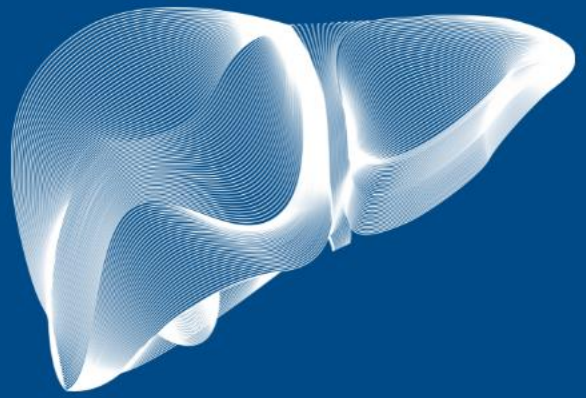


EASL CONGRESS
7-10 May 2025
Amsterdam, the Netherlands

Treatment with resmetirom for up to two years led to improvement in liver stiffness, fibrosis biomarkers, fibrosis scores and portal hypertension in 122 patients with compensated MASH cirrhosis

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

1: Arizona Liver Health, Phoenix, US; 2: Madrigal Pharmaceuticals, West Conshohocken, US; 3: University of Arizona for Medical Sciences, Tucson, US; 4: Houston Research Institute, Houston, US; 5: Universitätsklinikum des Saarlandes, Homburg, Germany

Unmet Need in 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 the only FDA-approved therapy for MASH (as of 2024).

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

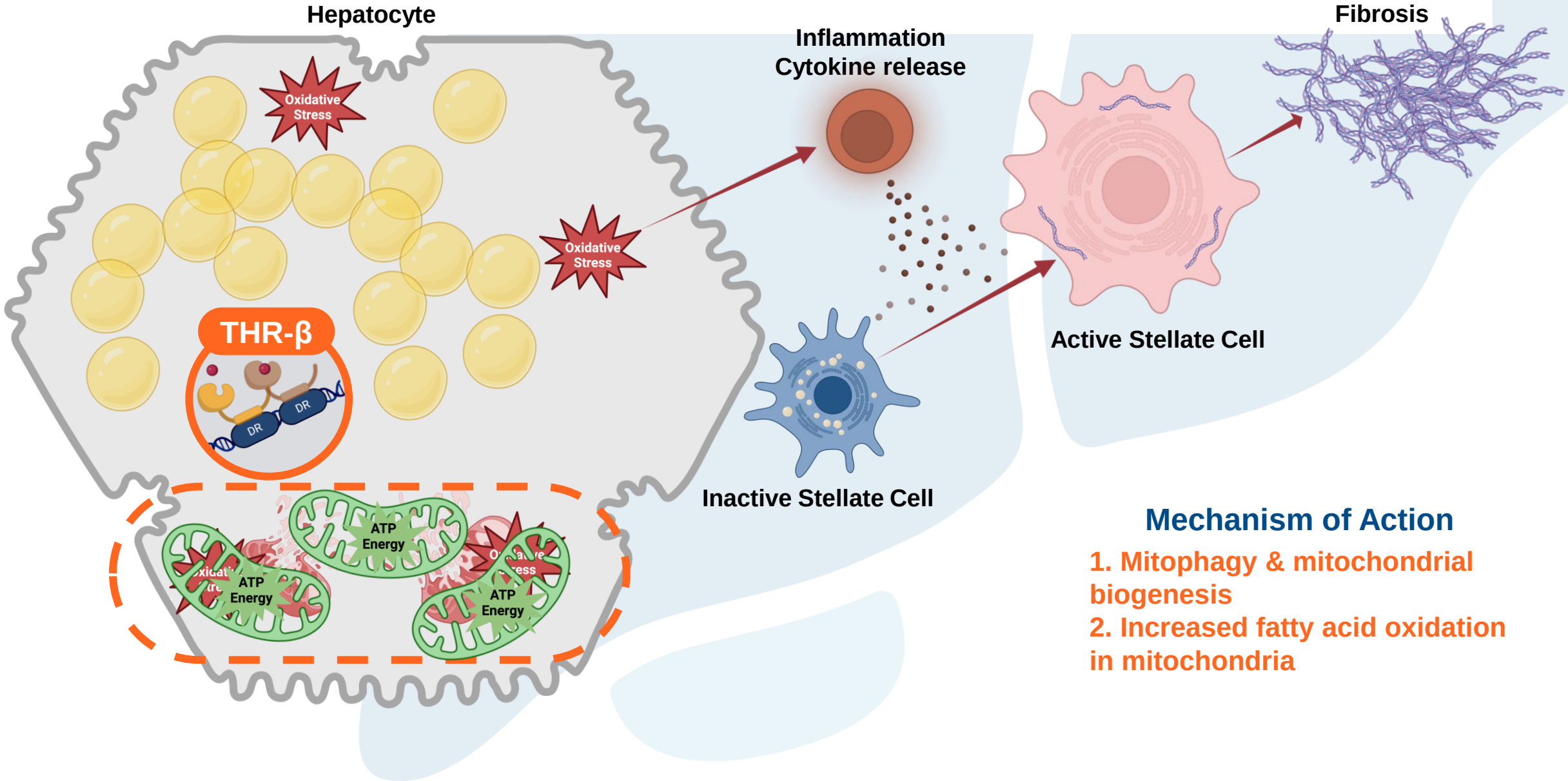
Cirrhosis (F4) is highly associated with clinical outcomes including hepatic decompensation events, liver failure, liver transplant and mortality

MASH: metabolic dysfunction-associated steatohepatits

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

Mechanism of Action: Direct and Indirect Antifibrotic Effects

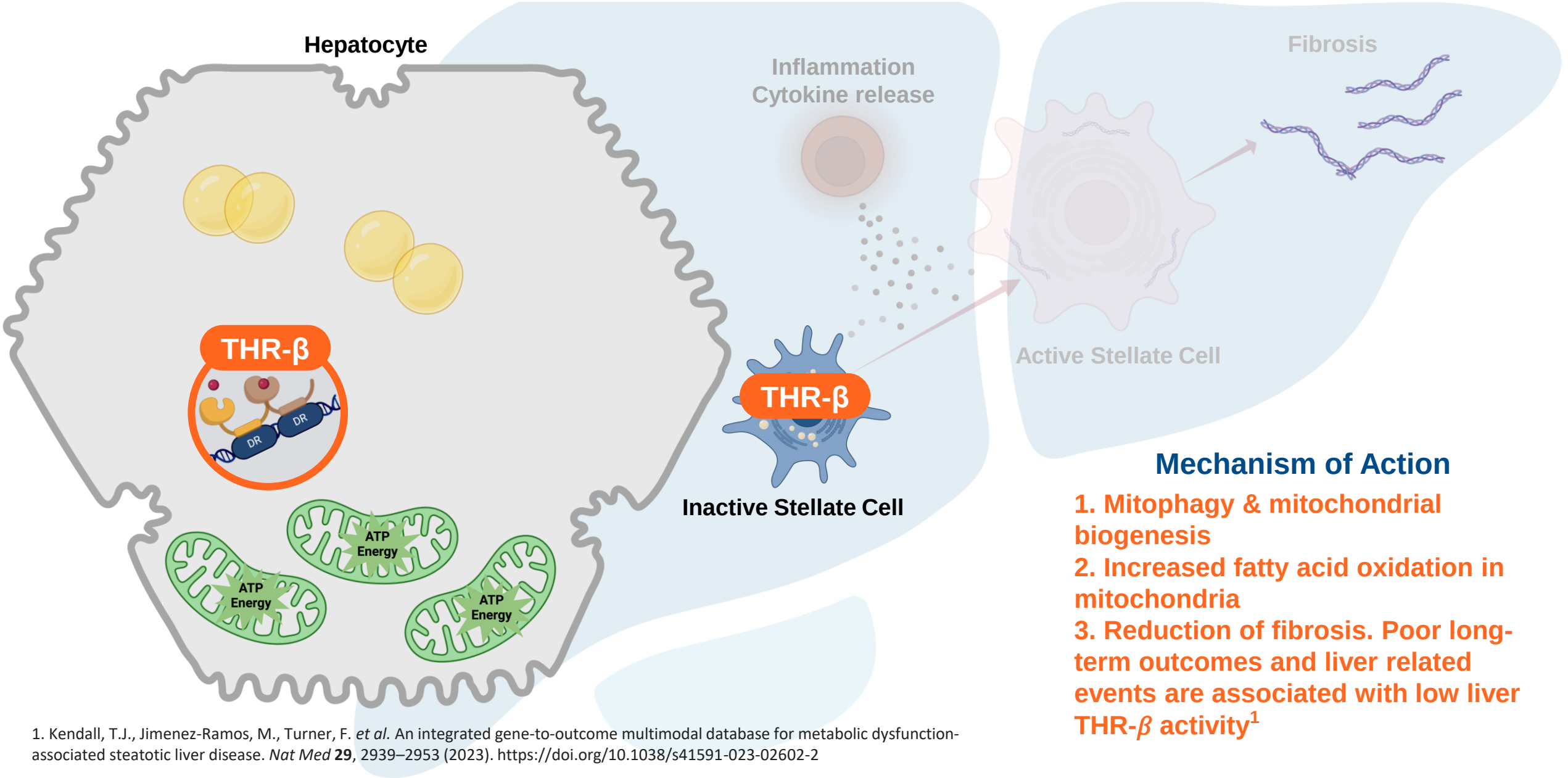


Mechanism of Action

1. Mitophagy & mitochondrial biogenesis
2. Increased fatty acid oxidation in mitochondria

Resmetirom

Mechanism of Action: Direct and Indirect Antifibrotic Effects



Mechanism of Action

1. Mitophagy & mitochondrial biogenesis
2. Increased fatty acid oxidation in mitochondria
3. Reduction of fibrosis. Poor long-term outcomes and liver related events are associated with low liver THR-β activity[1]

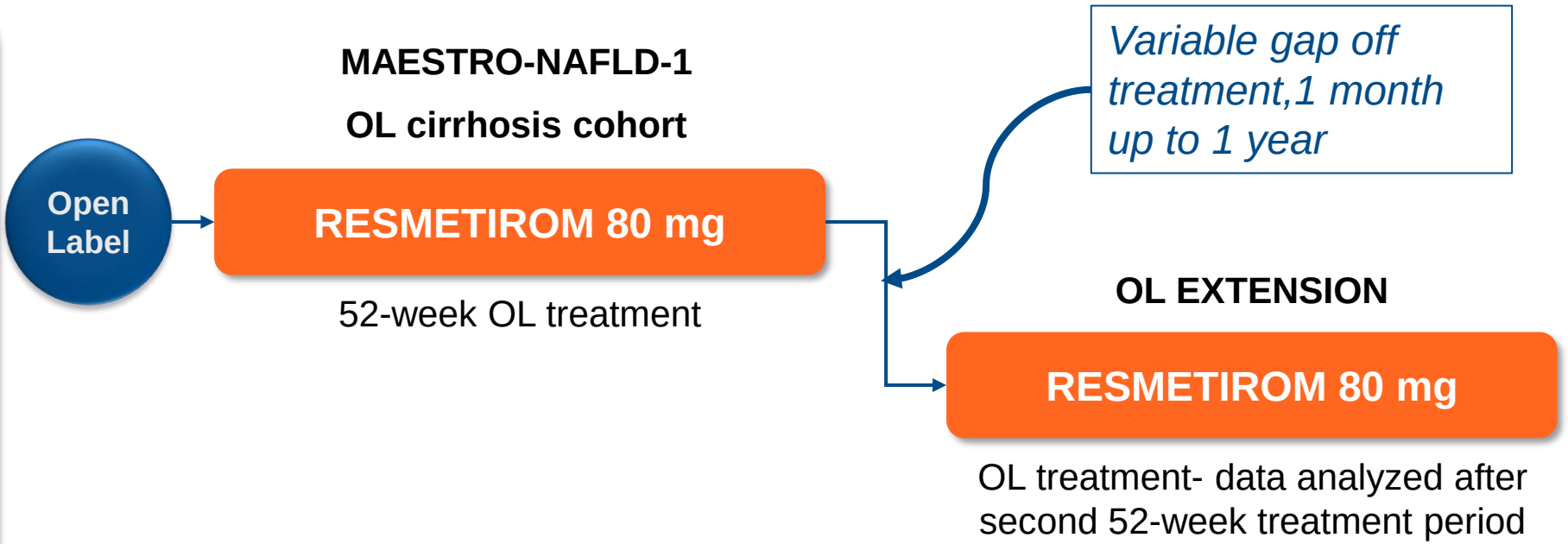
1. Kendall, T.J., Jimenez-Ramos, M., Turner, F. *et al.* An integrated gene-to-outcome multimodal database for metabolic dysfunction-associated steatotic liver disease. *Nat Med* **29**, 2939–2953 (2023). https://doi.org/10.1038/s41591-023-02602-2

Trial Design – Open-Label (OL) 52-Week Cirrhosis Arm of MAESTRO-NAFLD-1 followed by an Extension Trial

Inclusion Criteria

≥3 metabolic risk factors
Well-compensated MASH cirrhosis - Child Pugh A:

- F4 fibrosis[1] OR
- Non-invasive clinical assessment (liver stiffness (VCTE, MRE), platelets, ELF)
- **Allowed platelet count ≥70,000**
- No history of decompensation



Primary Endpoint

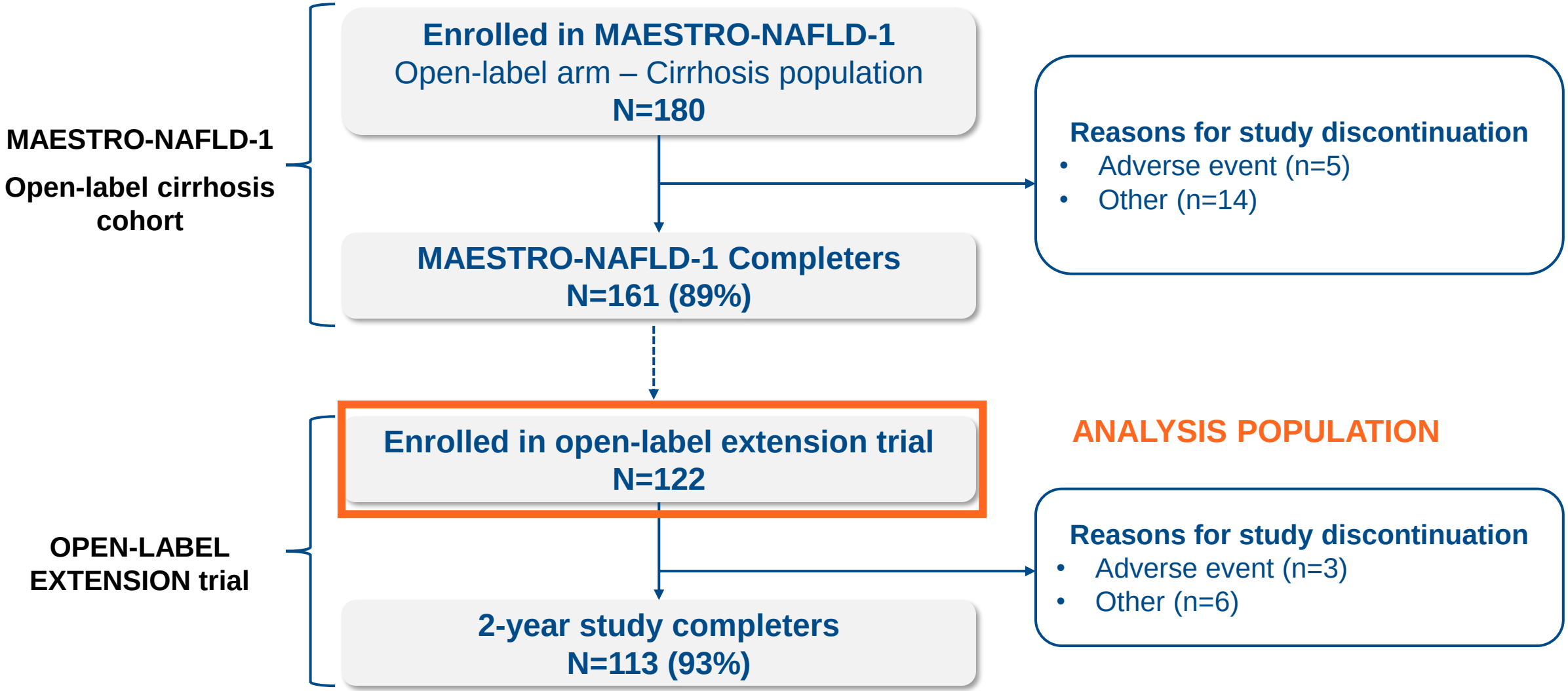
Safety and tolerability of resmetirom in cirrhosis patients

Secondary/Exploratory Endpoints

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

Liver biopsy was obtained 66% of patients; for patients with clinical progression from F3 on biopsy to F4, F4 was confirmed by plaetelets <LLN. (most) or MRE >4.2

Trial flow – Open-Label Cirrhosis Arm (MAESTRO-NAFLD-1) followed by an Extension Trial



Baseline Characteristics

	BL MRI-PDFF > 5%[1] N=93	BL MRI-PDFF ≤ 5% N=21
Age, years	61 (56, 68)	63 (61, 67)
Sex, Female	51 (55%)	11 (52%)
Ethnicity, Hispanic	28 (30%)	4 (19%)
BMI, kg/m^2	34.4 (30.6, 39.1)	33.5 (29.8, 37.9)
Type 2 Diabetes	63 (68%)	18 (86%)
VCTE, kPa	19.5 (17.1, 29.5)	24.6 (17.1, 39.4)
CAP, dB/m	331 (302, 372)	291 (249, 329)
MRE, kPa	5.2 (4.0, 6.1)	5.6 (4.9, 7.0)
MRI-PDFF, %	9.5 (7.3, 12.6)	3.9 (3.1, 4.4)
Liver Volume, mL	2291 (1903, 2737)	2093 (1649, 2473)
Spleen Volume, mL	476 (325, 721)	667 (414, 998)

[1]Only 114/122 patients had baseline MRI-PDFF

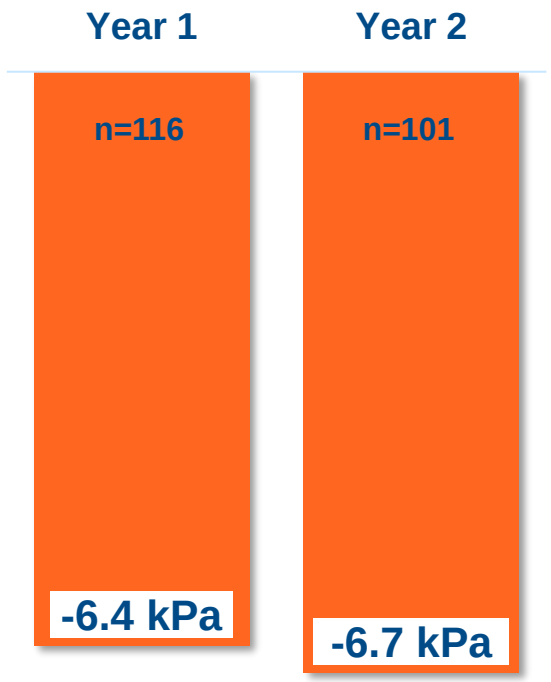
	BL MRI-PDFF > 5% N=93	BL MRI-PDFF ≤ 5% N=21
ALT, U/L	37 (29, 50)	28 (25, 39)
GGT, U/L	66 (43, 126)	106 (45, 146)
Platelets, 10^9/L	139 (112, 193)	110 (90, 141)
Albumin, g/dL	4.2 (4.0, 4.4)	4.2 (4.0, 4.5)
LDL-C, mg/dL	95 (76, 123)	73 (62, 94)
Triglycerides, mg/dL	140 (103, 181)	114 (87, 122)
FIB-4	2.3 (1.6, 3.6)	3.5 (2.2, 4.0)
ELF Score	10.6 (9.9, 11.4)	11.0 (10.7, 11.7)

Data are median (Q1, Q3) or %

In MASH cirrhosis lower hepatic fat is associated with more advanced disease

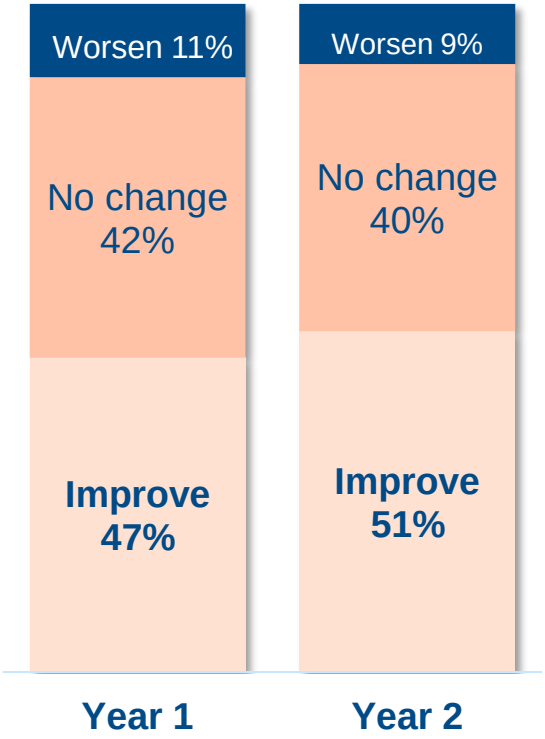
Sustained Reductions in Liver Stiffness (LSM) after 2-Year Treatment with Resmetirom

Mean Change from Baseline in VCTE

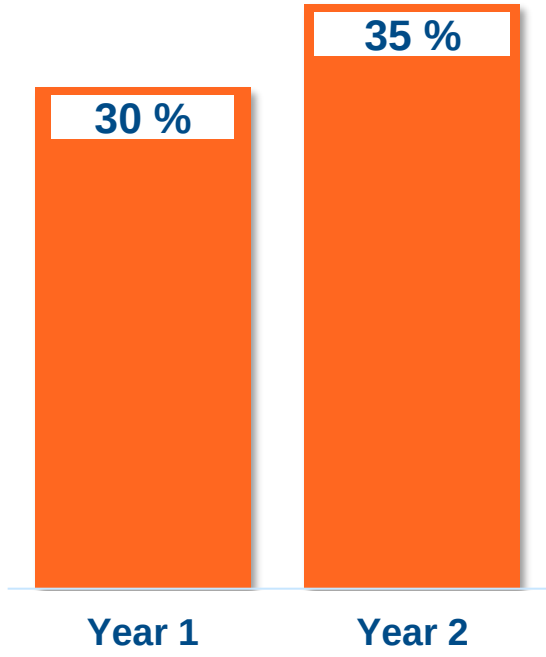


[1]statistically significant compared to baseline

Percent with 25% Change from Baseline in VCTE



% with Conversion from F4 to consistent with F3[1]



[1]Patients with confirmed F4 at baseline (liver biopsy F4 and/or platelets <140/MRE ≥5 with VCTE ≥15) showed a transition from F4 to potential F3 at year 2 (VCTE<15 and ≥25% decrease from baseline)

After 2 years on resmetirom, >50% of patients achieved sustained ≥25% reduction in LSM by VCTE

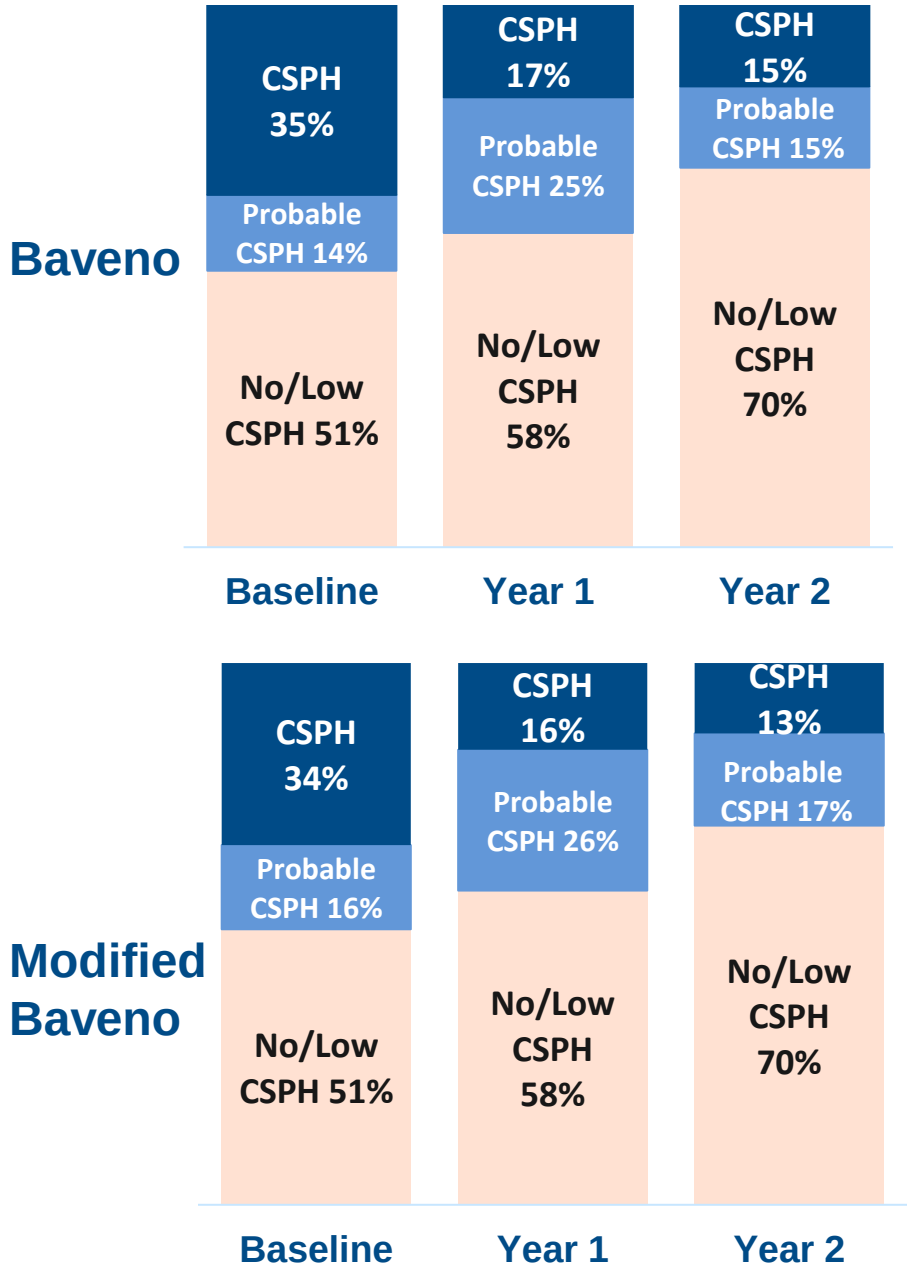
[1]Year 1: -6.4 (-9.2, -3.7) kPa; Year 2: -6.7 (-9.4 ,-4.1) kPa (95% confidence intervals). Panel 3 analyzed patients with both 1- and 2-year data . VCTE: vibration controlled transient elastography

Improvements in Portal Hypertension Risk Category with Resmetirom

- Clinically significant portal hypertension (CSPH) predicts liver related outcome events such as ascites, variceal hemorrhage and encephalopathy[1]
- Modified Baveno (similar to ANTICIPATE[2]) requires additional evidence for CSPH in MASH patients with VCTE ≥25; confirms CSPH risk

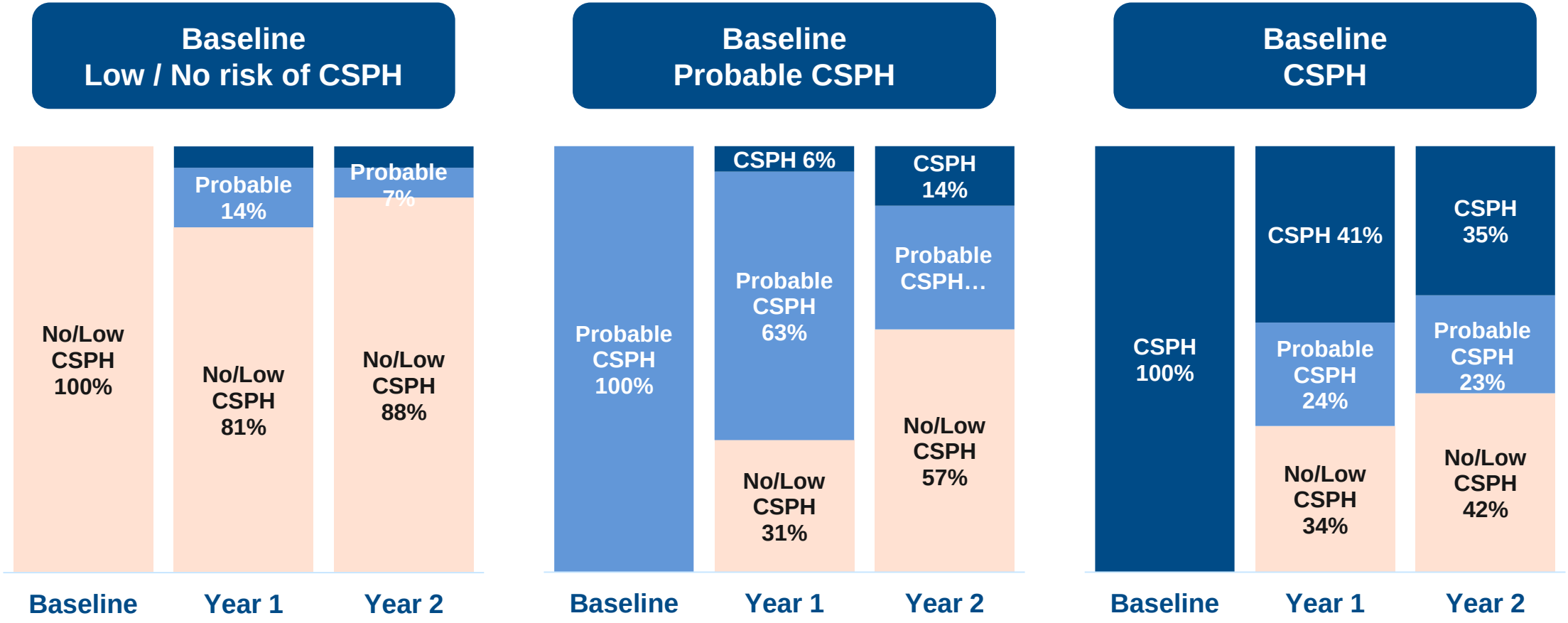
Risk of CSPH	Baveno	Modified Baveno
CSPH	VCTE ≥ 25	VCTE ≥ 25 **plus any one of**: - PLT < 150 - MRE ≥ 5 - ELF ≥ 11.3
Probable CSPH	20 ≤ VCTE < 25 & PLT < 150 **or** 15 ≤ VCTE < 20 & PLT < 110	
No/Low CSPH	Not meeting above criteria	

- Overall shift to lower CSPH risk at Year 1 and Year 2 whether Baveno or a modification of Baveno criteria are used



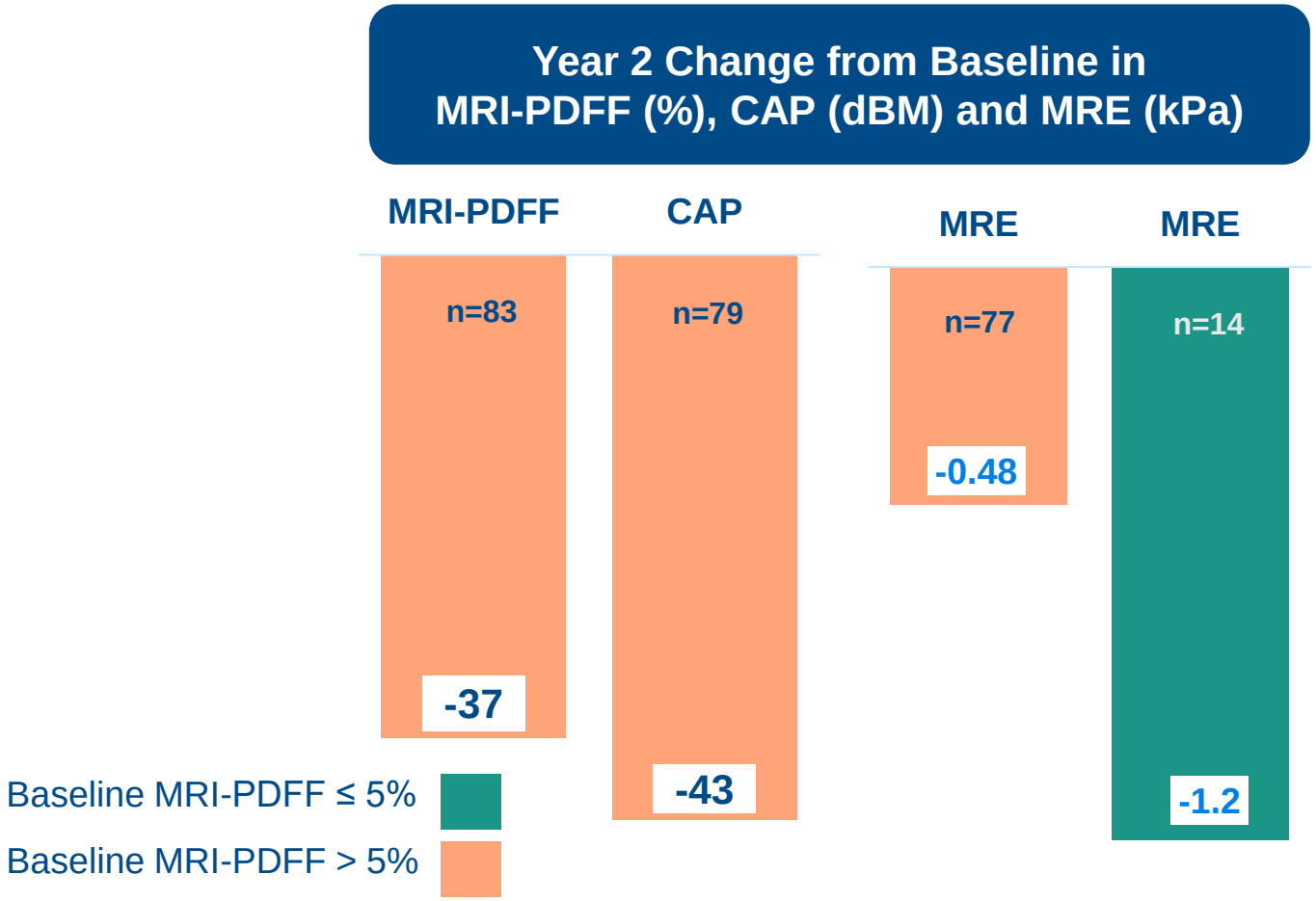
[1] doi: 10.1016/j.jhep.2021.12.022 [2]DOI: 10.1002/hep4.2091
CSPH: clinically significant portal hypertension; PLT, platelets;
modified Baveo ≥25kPa not meeting additional criteria were considered probable

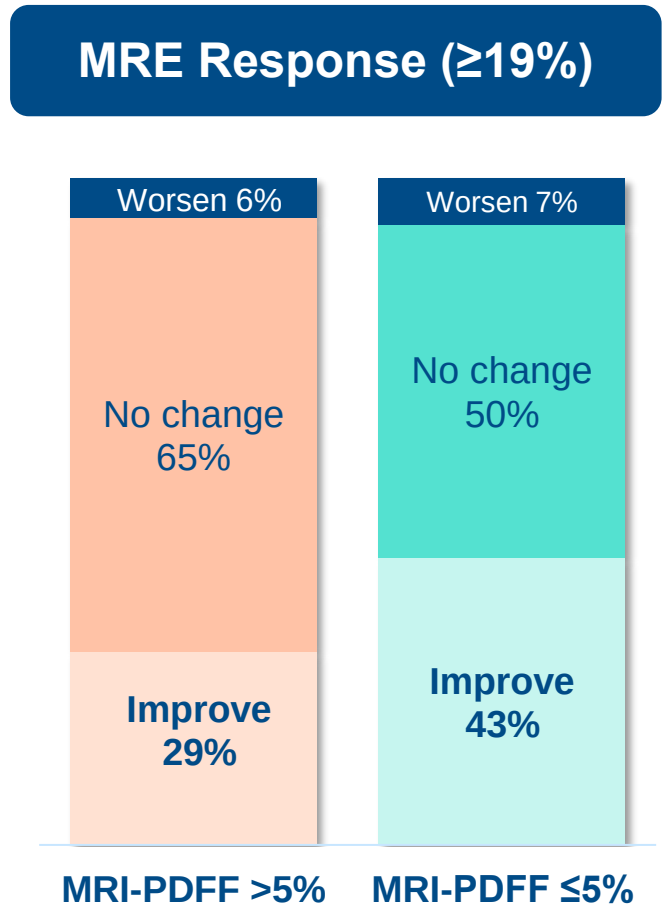
Improvements in Portal Hypertension Risk Category with Resmetirom



High, statistically significant, percentage of patients with probable CSPH and CSPH at baseline shift to lower risk category at Year 1 and Year 2 whether Baveno (shown) or modified Baveno criteria for CSPH are used

Sustained Reductions in Liver Fat and Liver Stiffness with Resmetirom at 2 Years

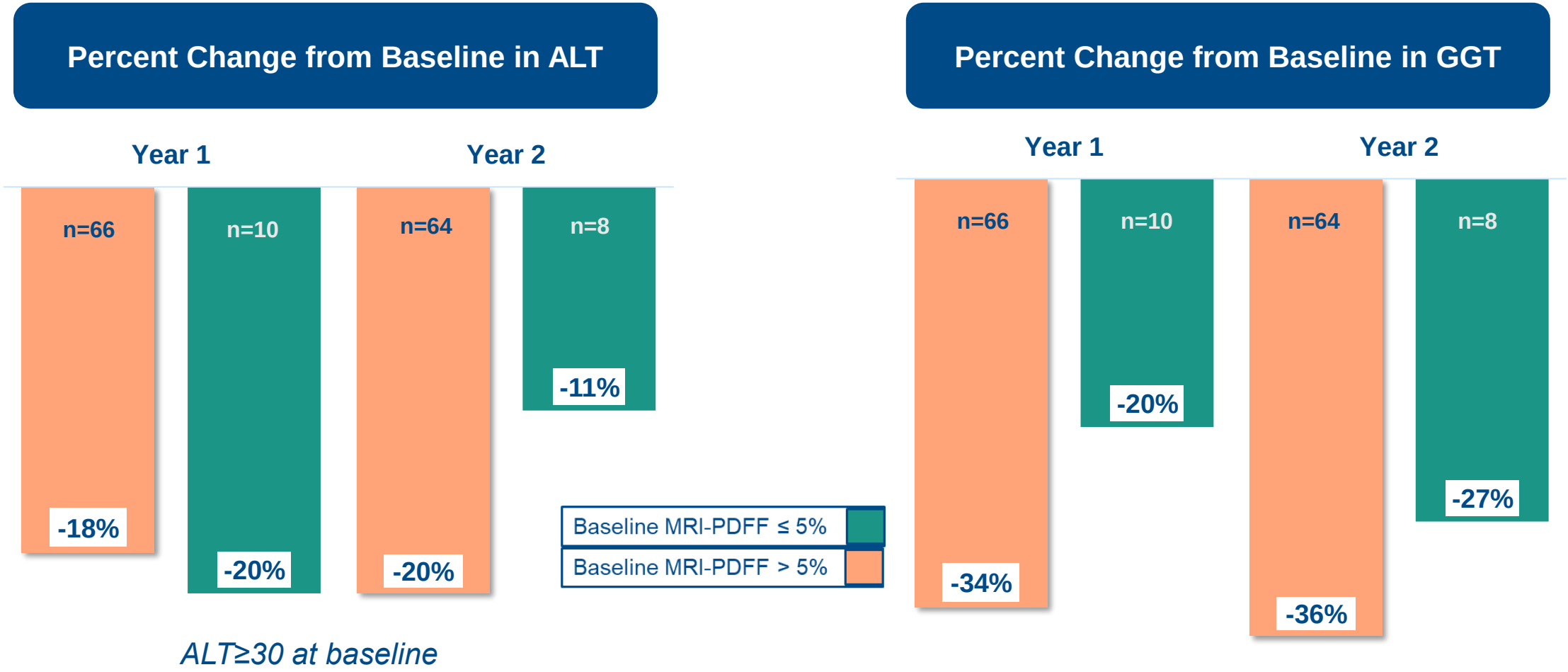




Statistically significant improvements in MRI-PDFF, CAP and MRE at 2 Years

Based on Observed Data – Median % change from baseline MRI-PDFF; Mean change from baseline CAP (-43(-58,-28); Mean kPa change from baseline MRE, overall, -0.57-0.88,-0.29); MRE response -19% improve, increase 19%, worsen
MRI-PDFF: magnetic resonance imaging-proton density fat fraction; LDL-c: low-density lipoprotein cholesterol

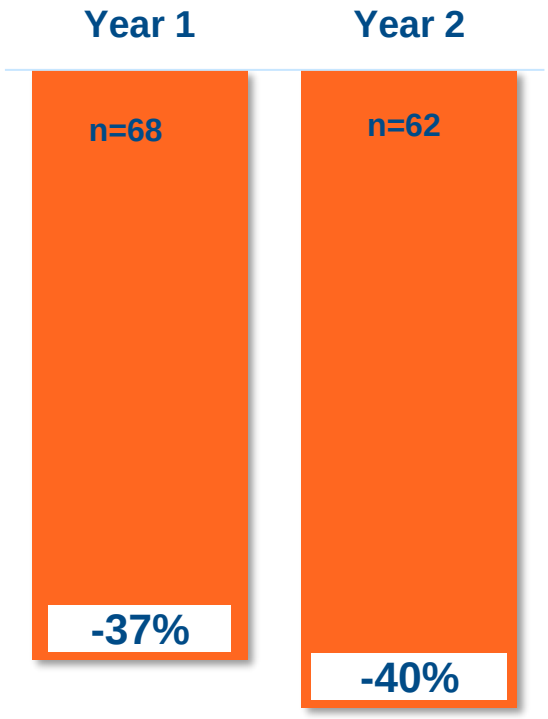
Sustained Statistically Significant Improvements in ALT and GGT



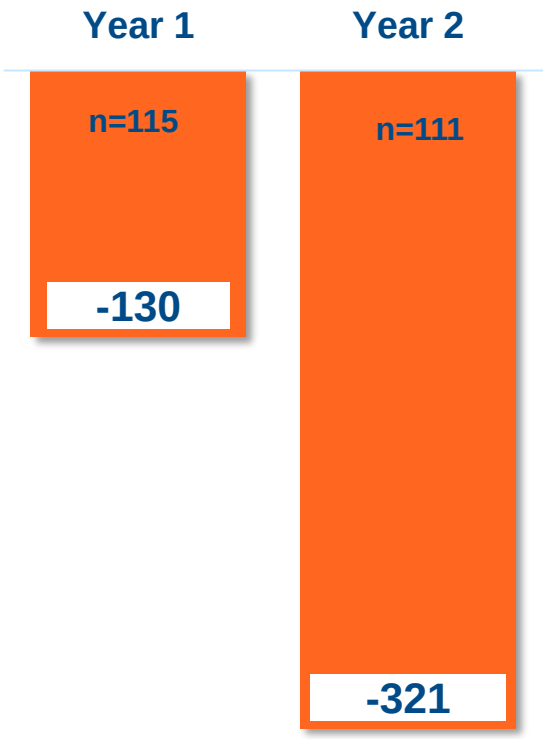
Based on Observed Data – mean % change from baseline in patients with baseline ALT>=30 IU; Overall ALT, Year 1 Week 48, -18% (-26%,-11%); Year 2 Week 104, -19% (-27%,-11%); Overall GGT Year 1, Week 48-32% (-38%,-27%), Year 2 Week 104, -35% (-44%, -27%); mean % change (95% CI) median % change in ALT in <=55 at Year 2
, ALT: alanine aminotransferase, GGT: gamma-glutamyl transferase;

Reductions in Fibrosis and Liver Injury Biomarkers at 2 Years

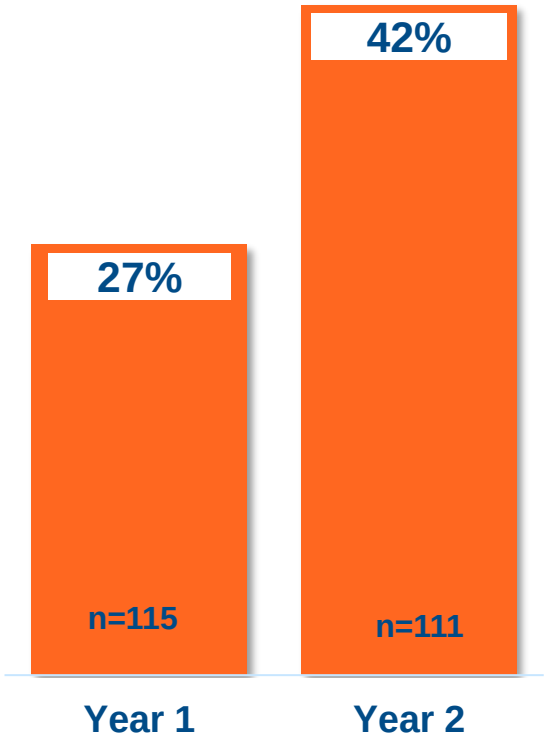
Relative Change from Baseline in PRO-C3



Mean Change from Baseline in CK-18 (ug/ml)

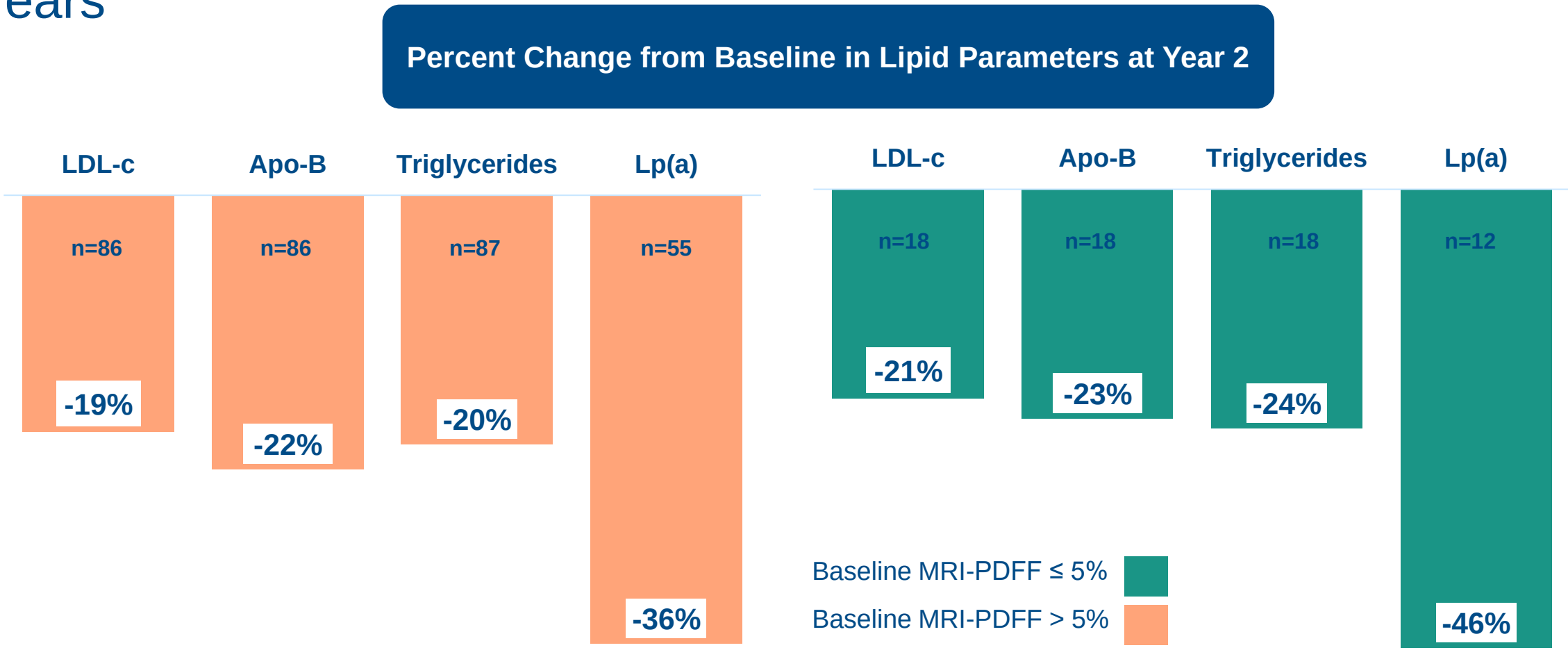


Relative Change from Baseline in Adiponectin



Based on Observed Data -Mean change from baseline; PRO-C3 baseline was obtained in approximately 50% of patients; CK-18, Year 1, -130 ug/ml (-216,-44) Year 2, -321ug/ml (-398, -243); adiponectin Year 2 42% (29%,55%)

Results: Sustained Reductions in Atherogenic Lipids with Resmetirom at 2 Years

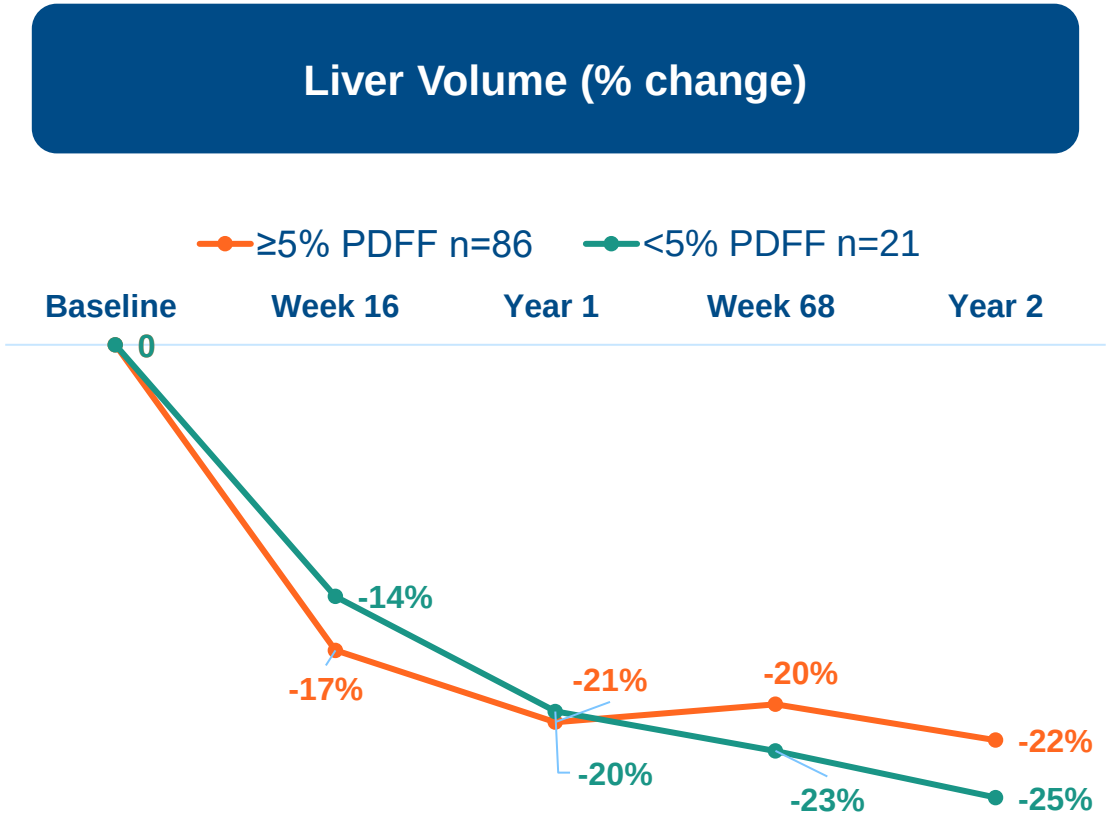


Statistically significant atherogenic lipid reductions consistent with non-cirrhotic MASH, independent of liver fat content

Based on Observed Data Week 92, -% change from baseline; all within group lipid changes are statistically significant
ApoB: Apolipoprotein B; MRI-PDFF: magnetic resonance imaging-proton density fat fraction; LDL-c: low-density lipoprotein cholesterol

MRI-Based Liver and Spleen Volume Assessments

Baseline liver fat independent reduction of enlarged MASH cirrhotic livers



- Liver volumes are increased in compensated MASH cirrhosis by approximately 40% relative to expected liver size
- Liver volume (mean) decrease of 22 to 25% by resmetirom was independent of baseline MRI-PDFF
- MRI was used to measure spleen volume. Platelets and spleen volume, both surrogates of portal hypertension, are inversely correlated (CC= -0.6)
- Mean spleen volume was reduced by resmetirom at years 1 and 2 in patients with baseline platelets>100K. Spleen volume change correlated with change in platelets (CC= -0.39) and change in VCTE (CC= 0.32)

Safety Summary after 2-year Open-Label Treatment with Resmetirom

Summary AEs (2 years of treatment)	Resmetirom (n=122)
Any TEAE	113 (93%)
Any SAE	27 (22.1%)
TEAE leading to Trial Discontinuation	3 (2.5%)
Death[1]	2 (1.6%)
Common AEs[2]	**Resmetirom (n=122)**
AE occurring in >15% of patients	
Diarrhea	46 (38%)
Covid-19	38 (31%)
Nausea	38 (31%)
Urinary Tract Infection	33 (27%)
Headache	21 (17%)
Arthralgia	19 (16%)
Fatigue	19 (16%)
Pruritus	20 (16%)
Vomiting	18 (15%)

Data are n (%)

- Safety data were consistent with previous studies
- Resmetirom was well-tolerated in this high risk population, low discontinuation rate
  - All SAEs unrelated to study drug
- Overall, 6/122 patients experienced decompensation events through two years of treatment
  - 5/6 had either elevated baseline MELD and/or baseline platelets <100k

1. Deaths are Covid and metastatic cancer. 2. Common AE safety data extended beyond two years in some patients.

Summary

Resmetirom was well tolerated over 2 years in patients with well-compensated cirrhosis.

>50% of patients achieved a sustained ≥25% reduction in LSM

Lower VCTEs are associated with less progression to decompensation

Reduced clinically significant portal hypertension risk score based on Baveno and modified Baveno criteria

Clinically significant portal hypertension predicts progression to decompensation

Multiple biomarker and imaging evidence of improvement

Results support the potential clinical benefit of resmetirom in MASH cirrhosis that is being evaluated in the fully enrolled, ongoing MAESTRO-NASH-OUTCOMES trial (n = 845)