MAESTRO TRIALS

Liver Forum Paris NASH 2022

Madrigal

Phase 2 & 3 NASH Clinical Trials: MAESTRO-NASH, MAESTRO-NAFLD-1, MAESTRO-NAFLD-OLE, MAESTRO-NASH-Outcomes

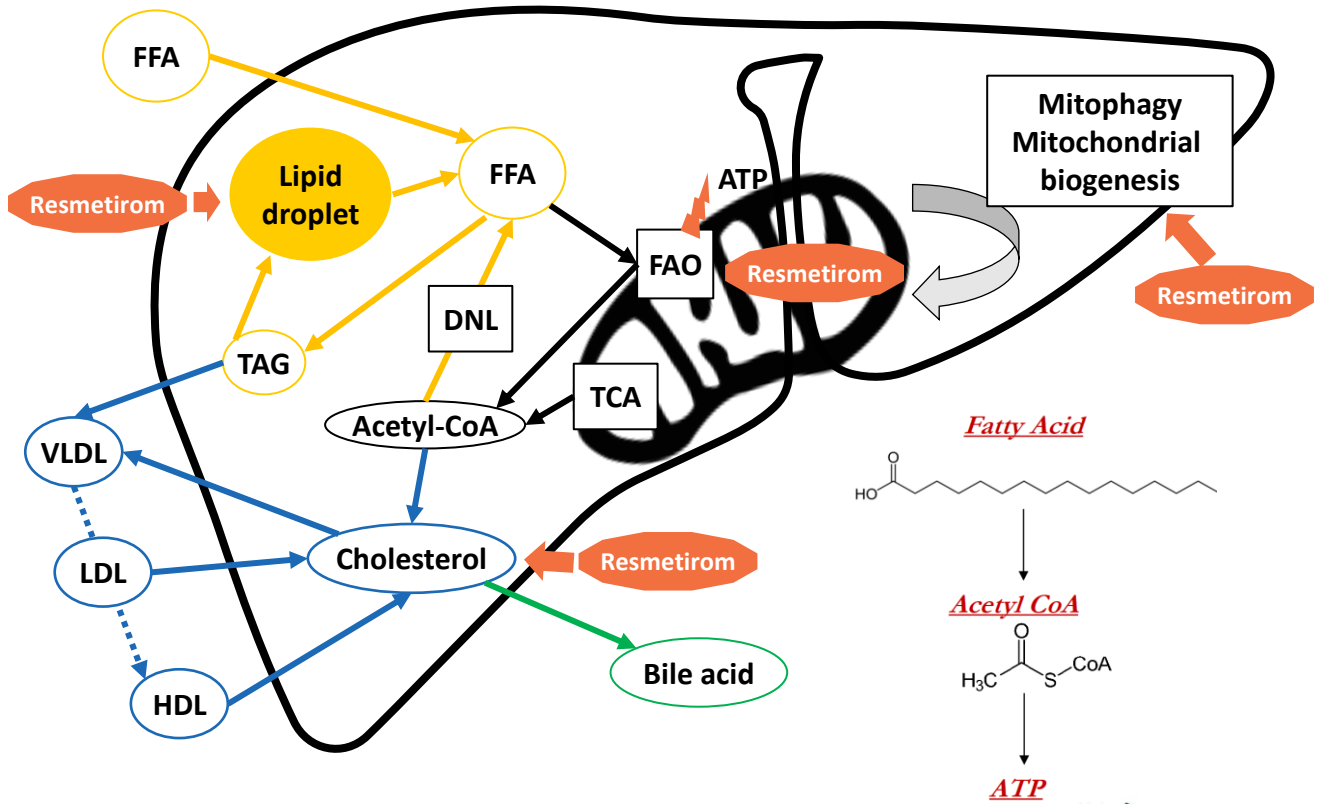
Compound/ Indication	Clinical Trial	Preclinical	Phase 1	Phase 2	Phase 3	Description
Resmetirom (MGL-3196) THR-β Agonist **Treatment of NASH**	Phase 2 MGL-3196-05 NCT02912260		**Completed**			■ **Phase 2: MRI-PDFF, biopsy – endpoints met[1]** • MRI-PDFF primary endpoint; serial biopsy at 36-week with 36-week OLE
	Phase 3 MAESTRO-NASH NCT03900429		**Recruiting**			■ **Phase 3: Treatment of NASH with Fibrosis** • Up to 2000 patients; double-blind 80, 100 mg, placebo • 52-week serial liver biopsy, Subpart H approval based on 900 F2-F3 patients • 54-month outcomes (liver events, cirrhosis on biopsy)
	Phase 3 MAESTRO-NAFLD-1 (presumed NASH) NCT04197479		**Ongoing (Cirrhosis arm) and OLE**			■ **Phase 3: Treatment of NASH** • >1200 patients • *52-week safety, lipids, NASH biomarker & imaging* • *Double-blind arms, 80, 100 mg, placebo* • *Open-label arms: non-cirrhotic 100 mg; NASH cirrhotic* • *OLE (MAESTRO-NAFLD-OLE – 52-week patient roll-over from NAFLD-1. Safety, Lipids, & NASH biomarker/imaging study)*
	Phase 3 MAESTRO-NASH-Outcomes		**Recruiting**			■ **Phase 3: Treatment of NASH** • >=700 patients • *Verified, well-compensated NASH cirrhosis* • *Placebo: resmetirom, 1:3* • *Clinical outcome events, hepatic decompensation*

MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OLE, open-label extension; THR, thyroid hormone receptor.

1. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024.

THR-β Pathway Plays a Key Role in Liver Health

- **THR-β agonists act on multiple hepatic pathways to maintain liver health by controlling[1]:**
  - *De novo* lipogenesis
  - Fatty acid oxidation
  - Mitophagy & mitochondrial biogenesis
  - Cholesterol metabolism
  - Direct anti-inflammatory & anti-fibrotic effects (inhibits TGF-β pathway)
- Most hepatic fat derives from external sources, particularly FFA from adipocytes
- In NASH, β-oxidation of liver lipids is reduced contributing to lipotoxicity
- In human NASH, the liver has relatively low THR-β activity, exacerbating mitochondrial dysfunction & lipotoxicity



Carbons eliminated through CO_2 respiration (citric acid cycle)

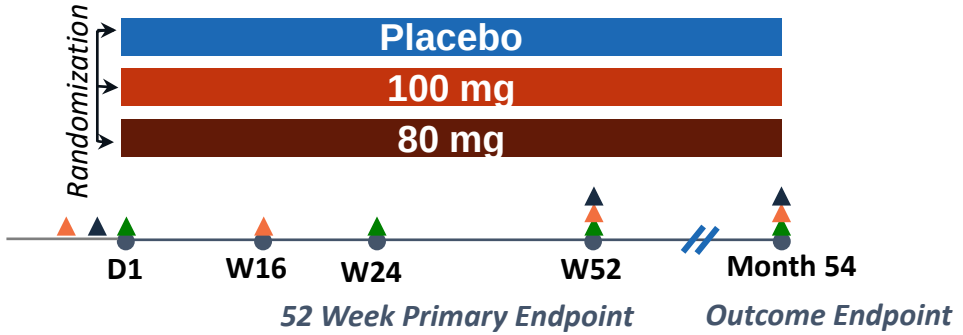
ATP, adenosine triphosphate; DNL, de novo lipogenesis; FAO, fatty acid oxidation; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NASH, nonalcoholic steatohepatitis; TAG, triacylglycerol; TCA, tricarboxylic acid; THR, thyroid hormone receptor; VLDL, very low-density lipoprotein.

1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14(5):259-269.

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

All MAESTRO trials have a similar 52 week design of biomarker and imaging collection leading to a robust data set in F1 to F4 NASH patients

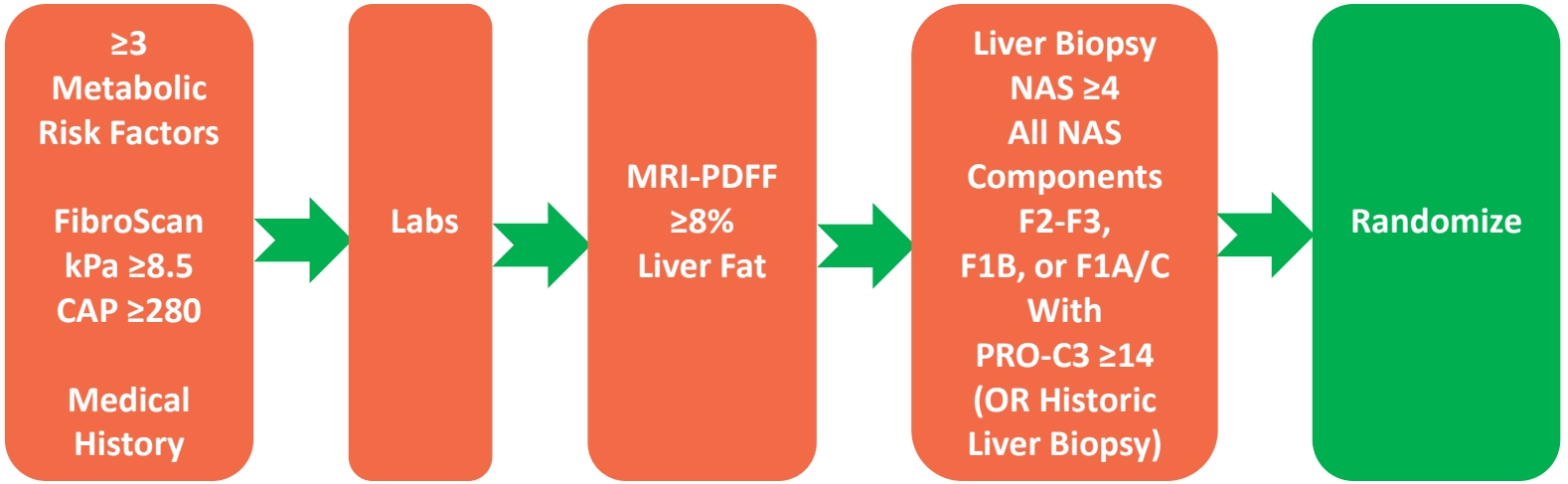
▲ MRI-PDFF
▲ Liver Biopsy
▲ LDL-C



Risk Factors of Significant Fibrosis?

- Age >50 years
- BMI >30 kg/m^2
- Elevated liver enzymes (AST >20 U/L, AST/ALT ≥1)
- T2D
- Hypertension
- Dyslipidemia
- Metabolic Syndrome components (obesity, insulin resistance)
- Historical FibroScan >8.5 kPa, CAP >280 dB/M (Ideally 300)

MAESTRO-NASH 8-Week Screening Process



Screening paradigm led to ~80% of screening biopsies showing at-risk NASH (F2-F4 NAS ≥3) of which 65-70% met all eligibility criteria

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes.

ClinicalTrials.gov (NCT03900429): https://clinicaltrials.gov/ct2/show/NCT03900429

Demographic & Baseline Characteristics in MAESTRO-NASH

	Randomized Patients	Percent F3 54%	Percent F2 31%	Percent F1B 11%	Percent F1A/C 5%
Age, mean (SD), years	56.8 (11.0)	58.4	54.8	56.0	54.1
Sex, male, %	44%	44%	43%	44%	45%
Sex, female, %	56%	56%	57%	56%	55%
Ethnicity, Hispanic/Latino, %	20%	18%	21%	18%	29%
Body weight, mean (SD), kg	100.3 (22.7)	99.0	102.9	99.0	102.0
BMI, mean (SD), kg/m^2	35.6 (6.8)	35.2	36.3	35.0	36.3
Hypertension, %	74%	77%	70%	68%	69%
Hypothyroid, %	14%	14%	14%	11%	15%
T2D, %	60%	66%	55%	53%	40%
Years since T2D diagnosis, mean (SD)	9.7 (7.5)	9.7	9.2	11.2	9.7
ASCVD score, mean (SD)	14.8% (12.4%)	15.6%	13.9%	14.8%	8.6%
FibroScan TE, mean (SD), kPa	13.2 (6.4)	14.5	11.9	11.1	10.0
FibroScan CAP, mean (SD)	347 (37.8)	346	347	352	326
MRI-PDFF, mean (SD), %FF	17.9% (6.9%)	16.7%	19.2%	18.7%	18.7%
MRE, mean (SD), kPa	3.48 (1.0)	3.91	3.14	2.90	2.01
PRO-C3, mean (SD), ng/ml	19.2 (8.5)	20.4	18.3	15.9	19.2
ELF, mean (SD)	9.7 (0.9)	10.0	9.5	9.3	9.5
HbA1c, mean (SD), %	8.6 (1.1)	6.6	6.5	6.3	6.4
HOMA-IR, mean (SD)	11.2 (11.8)	12.0	10.2	9.5	11.5
Liver biopsy length, mean (SD), mm	24.2 (11.5)	24.6	24.0	23.4	21.9
NAS, mean (SD)	5.51 (1.1)	5.64	5.54	5.03	4.87
Statin use, %	44.5%	50%	38%	43%	36%

- Demographics include:
  - Mean age 56.8 years
  - Female 56%,
  - BMI 35.6 kg/m^2
  - Hypertension 74%
  - Hypothyroid 14%
  - T2D 60%
  - Mean ASCVD score 14.8%
- FibroScan (kPa 13.2), MRI-PDFF (17.9%), MRE (kPa 3.48) represent this NASH population

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CAP, controlled attenuation parameter; ELF, enhanced liver fibrosis; HOMA-IR, homeostatic model assessment for insulin resistance; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes.

Baseline Laboratory Parameters in MAESTRO-NASH

Mean (SD)	Randomized Patients	Percent F3 54%	Percent F2 31%	Percent F1B 11%	Percent F1A/C 5%
MELD	7.4 (1.7)	7.5	7.3	7.1	6.8
NAFLD fibrosis score	-0.63 (1.7)	-0.40	-0.92	-0.90	-0.67
FIB-4	1.41 (0.70)	1.57	1.23	1.20	1.26
TC, mg/dL	179.6 (47.2)	174.0	184.5	182.0	201.8
TG, mg/dL	187.9 (129.1)	181.3	194.6	182.9	226.8
Lp(a), nmol/L	43.6 (60.9)	42.1	44.3	47.3	47.4
ApoB, mg/dL	97.9 (29.6)	94.8	100.5	97.6	115.3
LDL-C, mg/dL	106.3 (39.1)	101.8	110.5	107.2	124.0
HDL-C, mg/dL	43.8 (12.9)	44.1	43.5	45.2	39.5
ALT, IU/L	54.6 (33.85)	53.9	56.2	45.4	71.2
AST, IU/L	40.1 (23.3)	41.5	39.7	32.8	43.1
GGT, IU/L	80.0 (93.9)	87.7	73.3	60.8	79.3
CK (IU/L)	138.0 (165.3)	129.0	154.0	121.4	169.6
ALP, IU/L	84.1 (27.7)	85.1	82.8	81.7	86.1
Total bilirubin, mg/dL	0.64 (0.29)	0.66	0.64	0.59	0.63
Direct bilirubin, mg/dL	0.13 (0.06)	0.14	0.12	0.12	0.12
Platelet count	233 (62)	224	248	238	226
Albumin, g/dL	4.4 (0.3)	4.4	4.4	4.4	4.4
INR	1.1 (0.2)	1.1	1.1	1.1	1.0
CDT, %	1.69 (0.46)	1.67	1.68	1.76	1.83

- Laboratory parameters demonstrate statistically significant differences between low-risk F0 & high-risk F2/F3 patients:
  - ALT ($p<0.0001$)
  - AST ($p<0.0001$)
  - GGT ($p<0.0001$)
  - PRO-C3 ($p<0.0001$)
  - HbA1c ($p=0.0001$)
  - MRE ($p<0.0001$)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; apoB, apolipoproteinB; AST, aspartate aminotransferase; CDT, carbohydrate-deficient transferrin; FIB-4, fibrosis-4; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; INR, international normalized ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MELD, model for end-stage liver disease; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; PRO-C3, N-terminal type III collagen propeptide; TC, total cholesterol; TG, triglycerides.

Liver Enzymes in MAESTRO-NASH Patients Who Met Biopsy Criteria

Patients With Eligible Biopsies for MAESTRO-NASH

ALT <ULN	ALT ≥ULN	AST <ULN	AST ≥ULN	ALT <2X ULN	ALT ≥2X ULN	AST <2X ULN	AST ≥2X ULN
35.7%	64.3%	45.8%	54.2%	80.5%	19.5%	87.8%	12.2%

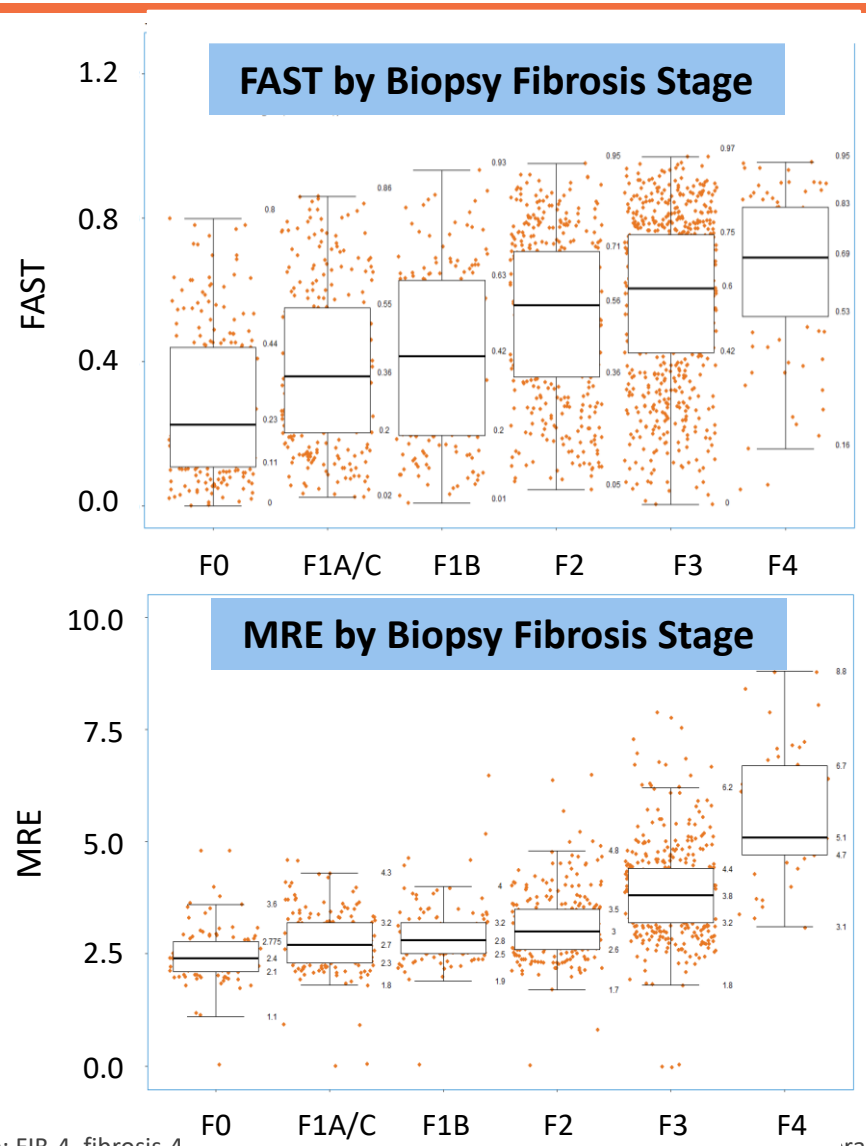
- Based on >1000 biopsies in screened patients with paired MRE, MRI-PDFF, & FAST (of which >700 biopsies met criteria for eligibility)
- Unlike many NAFLD patients who are referred for GI/Hepatology consultation based on liver enzyme elevations, patients screened for MAESTRO-NASH were not required to have thresholds for liver enzyme tests or FIB-4
- FIB-4 would not meet criteria for further workup of liver disease in >60% of F2 or 40% of F3 patients enrolled in MAESTRO-NASH, particularly younger patients; however metabolic risk and fibroscan would lead to further evaluation

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; ULN, upper limit of normal.

Comparison of Diagnostic Accuracy of Noninvasive Imaging in NASH

Noninvasive Imaging	Patient Groups	AUROC for ≥F2 Fibrosis
FIB-4	F0-F4	0.68
FibroScan TE	F0-F4	0.66
FAST	F0-F4	0.72
MAST	F0-F4	0.79
MRE	F0-F4	0.79

- FIB-4 AUROC was 0.68
- AUROC of MRE, MAST, FAST for fibrosis stage & NASH were >0.7



AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4, [illegible]; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.

Non-cirrhotic NASH Measures of Response (General Biomarkers/Imaging)

Biomarker or Imaging Test	Alignment with Biopsy Diagnosis and Response	Remaining Questions
Liver enzymes	Reduction associated with improvement in NASH or fibrosis?	Not all NASH patients have elevated LE. Baseline may be factor in assessing magnitude of reduction
MRI-PDFF	Highly accurate tests for steatosis. 30% reduction aligned with NASH improvement? Fibrosis improvement?	Not all mechanisms reduce liver fat, and mechanism specific features may exist
MRE	Good alignment with fibrosis stage, especially advanced fibrosis	Expensive, may not be available, some variability, only able to monitor a response in >=F3 patients
Fibroscan kPA	Despite intrinsic variability and operator training concerns, excellent enrichment test for significant liver fibrosis at baseline. Able to monitor response?	Serial scans may not confirm a response (or lack of a response) in an individual patient, additional confirmatory biomarkers, repeat fibroscan testing?
Fibroscan CAP	Able to provide a Yes-No for steatosis at baseline. Response?	Variability may obscure individual patient response
ELF (PRO-C3, other fibrosis biomarkers)	May be useful in advanced fibrosis, including response monitoring	Undergoing additional investigation

Biomarkers Reflecting Responses Reflective of Resmetirom (THR-β) MOA

Test	Effect	Relationship to THR-β MOA
MRI-PDFF reduction	Magnitude of response correlated in Phase 2 with all components response on liver biopsy including fibrosis	β-oxidation in mitochondria; mitochondrial biogenesis; other metabolic pathways
Lipid reduction	Multiple atherogenic lipid and lipoprotein lowering (LDL-C, ApoB, Triglycerides, Lp(a)	Multiple mechanisms, cholesterol metabolism, reduction in ApoB particles
Fibroscan CAP reduction	Response in patients with elevated CAP >300 at baseline that reflects liver fat	Primarily β-oxidation in mitochondria; mitochondrial biogenesis
Liver Volume reduction	20% liver volume redution in all NASH livers, including NASH cirrhosis—NASH livers are enlarged 40-50%	Only partially explained by liver fat reduction; reduction in liver inflammation and inflammatory milieu
SHBG increase	Magnitude of SHBG % increase from baseline is predictive of liver THR-β effects on MRI-PDFF and NASH	Highly specific liver biomarker for the THR-β pathway, no placebos show an increase in SHBG
FT3/FT4 ratio; T3/RT3 ratio increase	Increase in these ratios that are abnormally low in NASH correlated with NASH improvement	Deiodinase 1, a THR-β target, converts prohormone T4 to active T3 and increases the T3/reverse T3 ratio

Results from Resmetirom Phase 2 Study

- Primary endpoint, relative reduction in hepatic fat on MRI-PDFF at Week 12 (116 patients; 78 resmetirom; 38 placebo)
  - Dose related reductions in MRI-PDFF, 50% reduction of hepatic fat at >=80 mg dose
- Serial week 36 liver biopsy

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

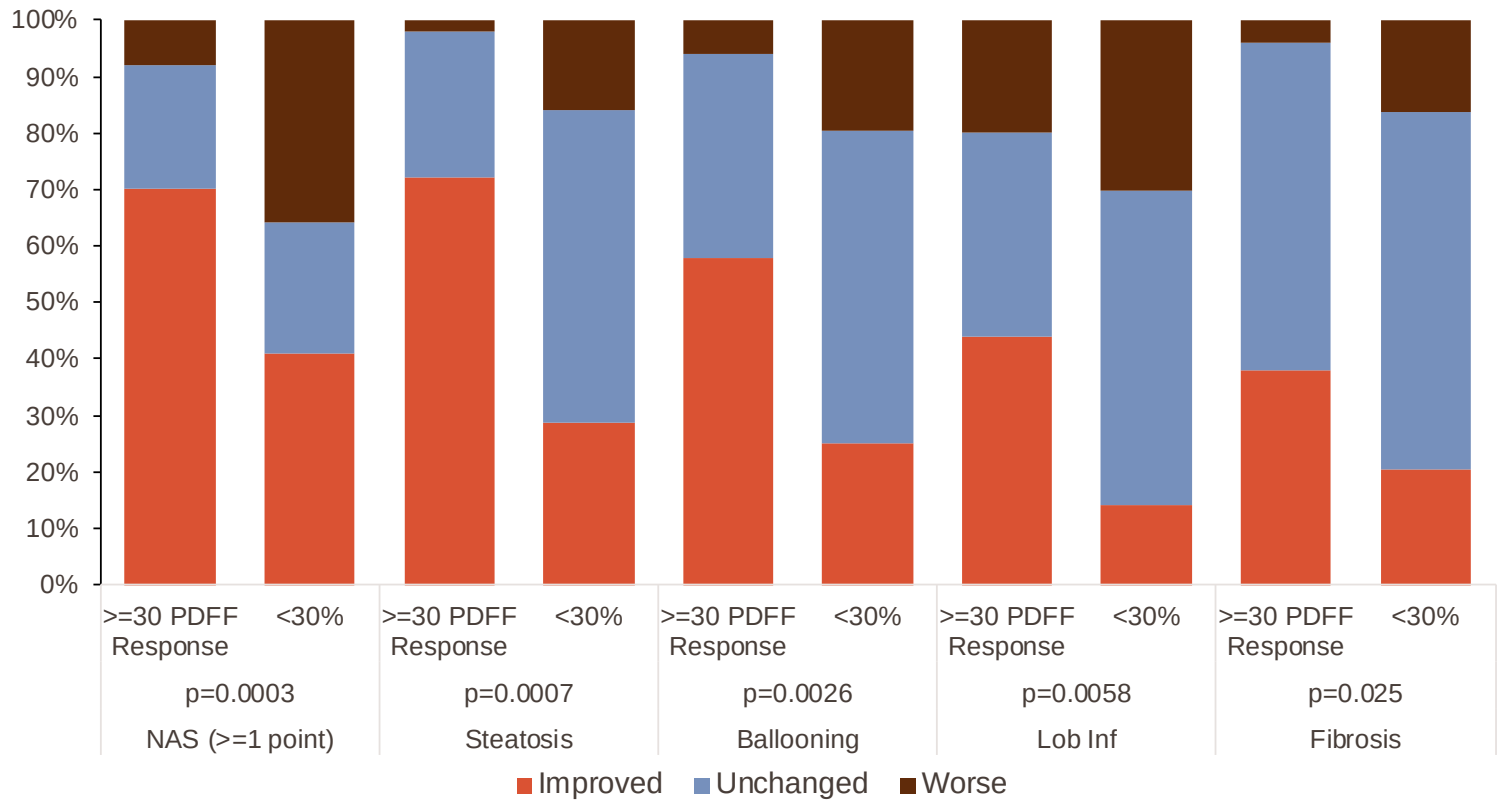
OLE (open label active extension study)

1 Harrison SA, et al. Lancet 2019;394:2012-2024.; 2 Harrison SA, et al Hepatology Communications. 2021;5(4):573-588.

Relationship of PDFF Response to Biopsy Component Response (Phase 2)

- Patients in the study with serial evaluable liver biopsies (baseline and week 36) and PDFFs (baseline and week 12) were included in the analysis

- Patients who were PDFF responders (>= 30% PDFF reduction) had improvement in all NAS components and fibrosis stage on 36 week liver biopsy compared with PDFF non-responders



Loomba et al. Presentation ILC2020

Confirmation of NASH Resolution and Relationship to PDFF (EASL-2022)

Retrospective AI-based Measurement of NASH Histology (AIM-NASH) Analysis of Biopsies From Phase 2 Study of Resmetirom Confirms Significant Treatment-induced Changes in Histologic Features of Nonalcoholic Steatohepatitis

Table 1. Response rates per endpoint via manual and AI-based scoring.

Endpoint	Scorer	Resmetirom response rate	Placebo response rate	P value
≥2-point improvement in NAS	AIM-NASH	0.41	0.19	0.0327
	Central reader	0.56	0.26	0.0044
	Reader 2	0.42	0.19	0.0321
NASH resolution without worsening of fibrosis	AIM-NASH	0.26	0.07	0.0301
	Central reader	0.25	0.06	0.0226
	Reader 2	0.21	0.03	0.0190

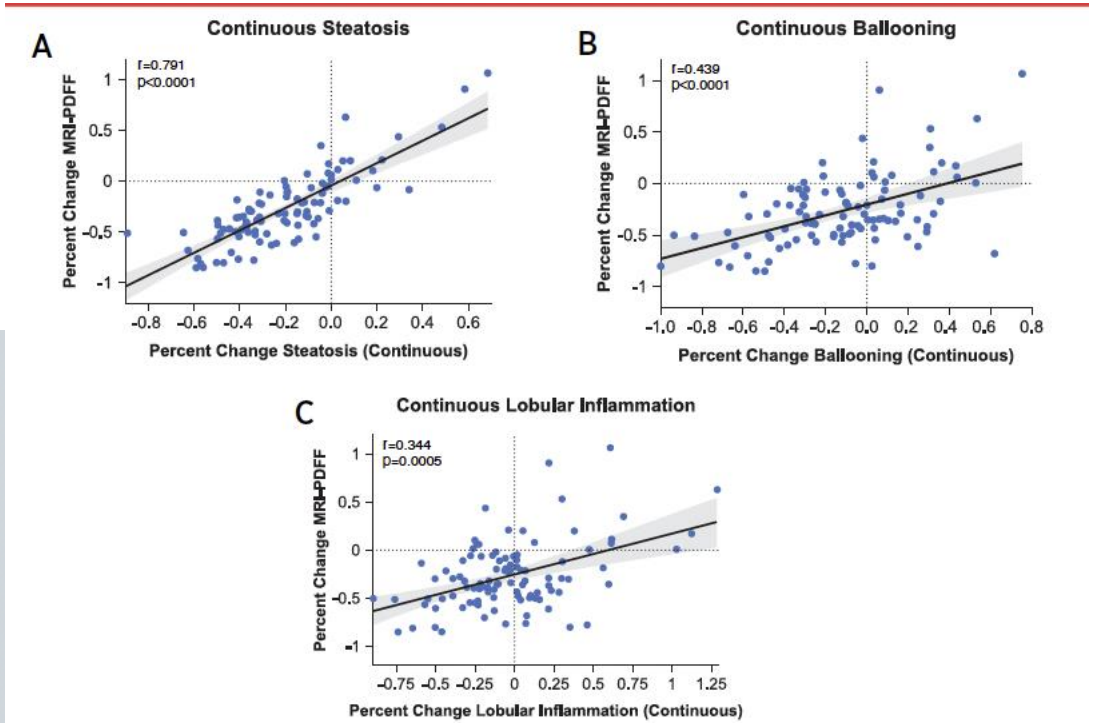
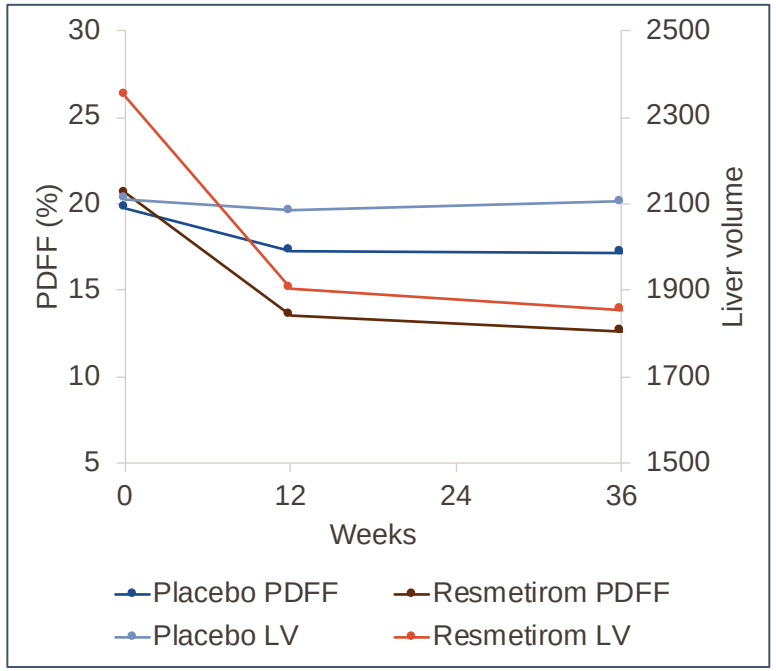
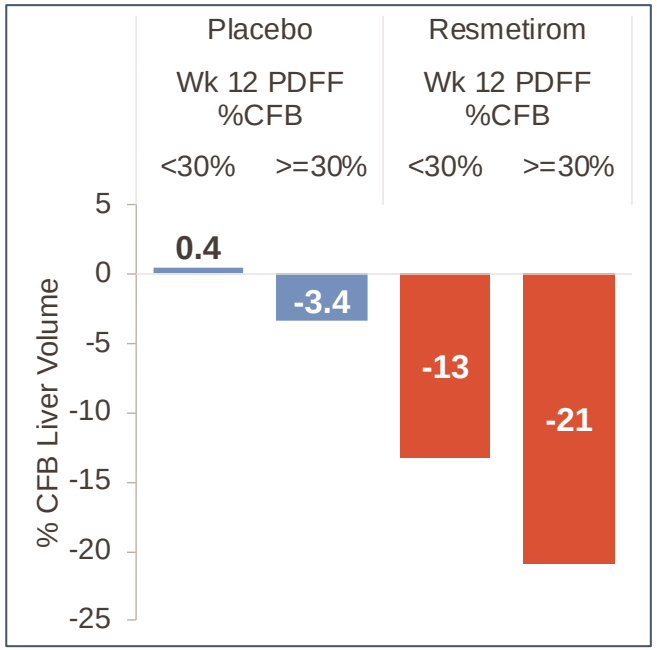


Figure 3. Association between change in histology and magnetic resonance imaging-proton density fat fraction (MRI-PDFF). Change in steatosis between Baseline and Week 36 assessed by MRI-PDFF was significantly correlated with change in continuous steatosis grade (A), continuous ballooning grade (B), and continuous lobular inflammation grade (C).

Liver Volume Reduction in Phase 2 NASH Study

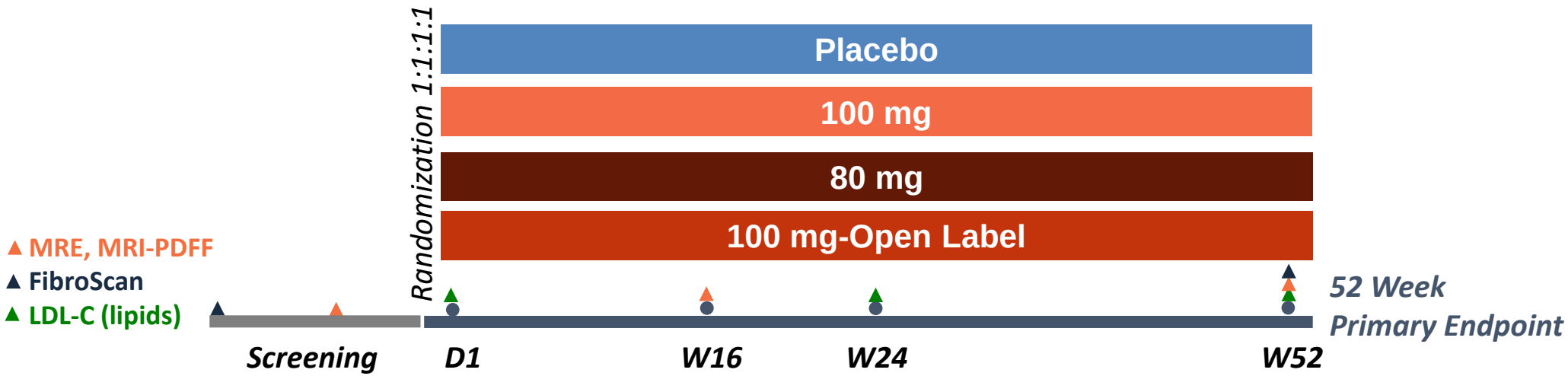




- Liver volume is elevated 40-50% in patients with NAFLD, NASH and NASH cirrhosis
- Liver volume (LV) was reduced by resmetirom as compared with placebo, p<0.0001,
- The LV reduction in resmetirom treated patients is greater than predicted by PDFF reduction alone

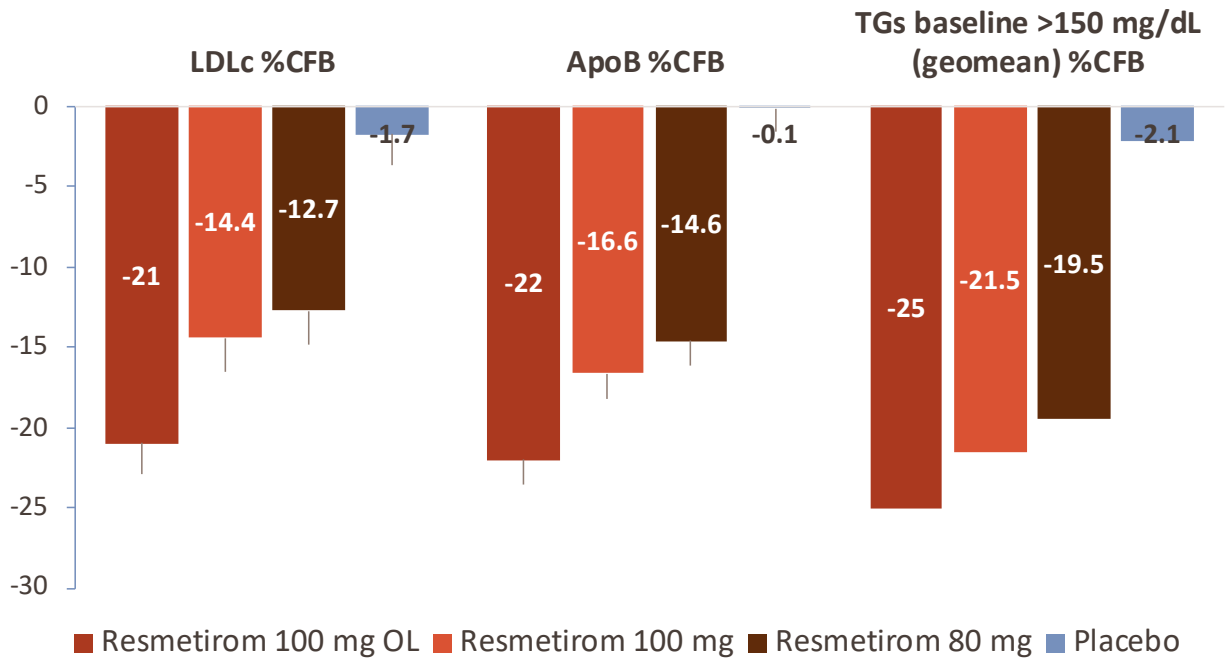
MAESTRO-NAFLD-1 Study Design

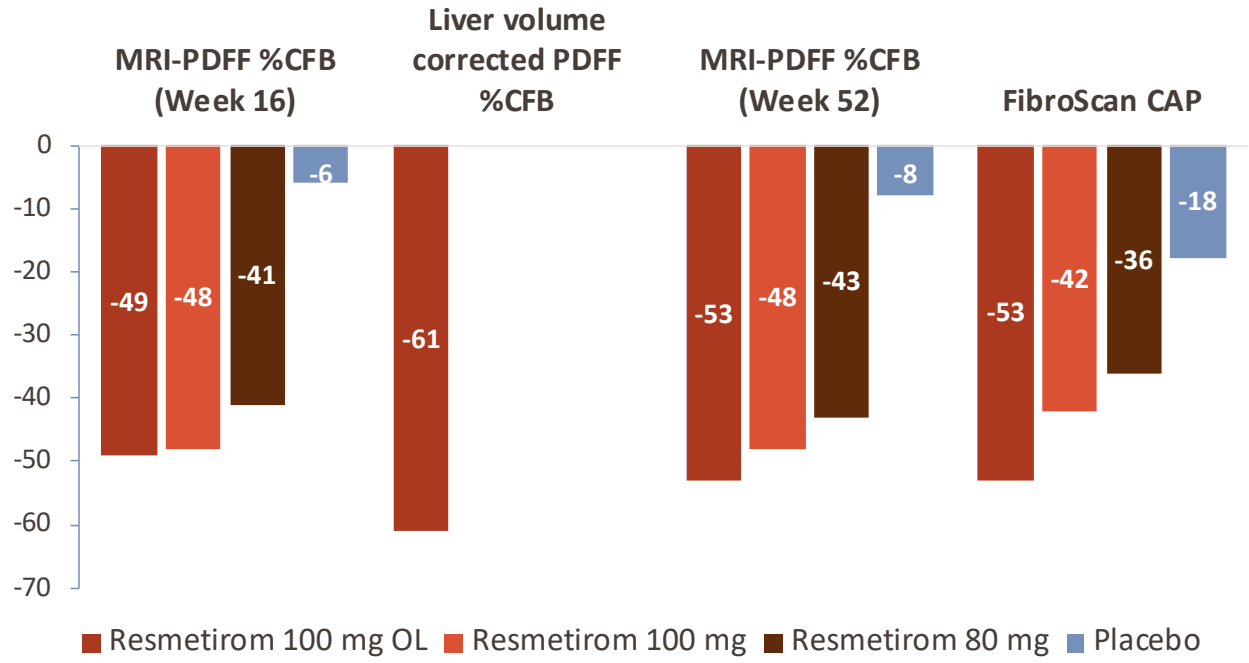
- MAESTRO-NAFLD-1 was a 52 week non-invasive study in >1200 patients diagnosed with fatty liver disease using non-invasive technologies (similar inclusion to MAESTRO-NASH; lower fibroscan cutoff, no liver biopsy requirement
- The primary endpoint was safety; key secondary endpoints included MRI-PDFF, fibrosis imaging, and measures of CV risk markers (atherogenic lipids and lipo proteins)



CAP, controlled attenuation parameter; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; OLE, open-label extension; VCTE, vibration-controlled transient elastography.

Key Secondary Endpoints

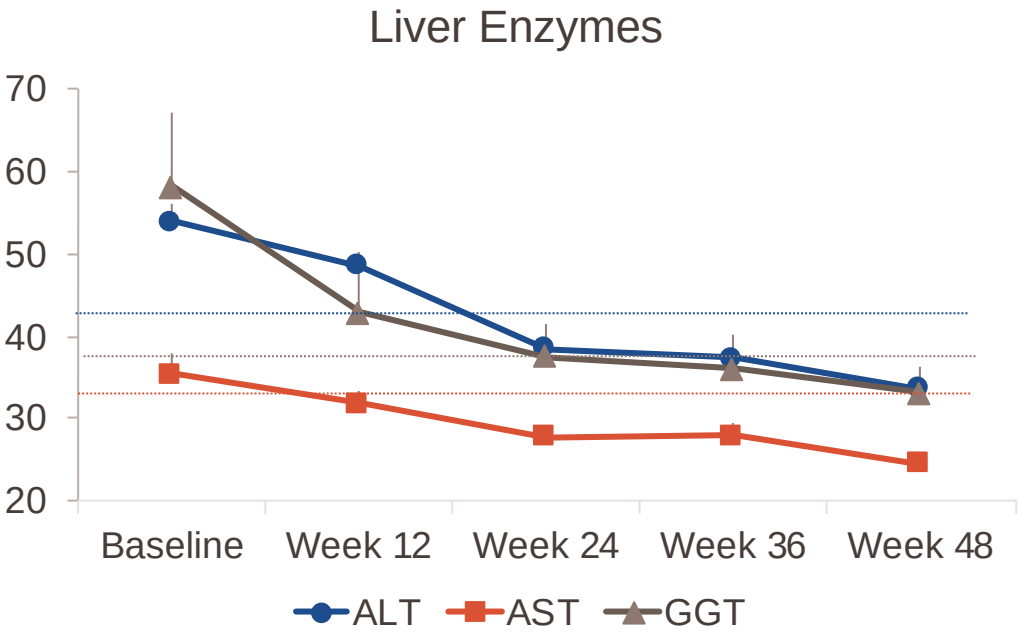




- The primary safety endpoint was met (presented at EASL 2022)
- Key secondary endpoints were achieved for both 80 & 100 mg groups ($p<0.0001$ for LDL-C, apoB, TG, MRI-PDFF, & CAP)
  - Lipid reductions were numerically greater in the 100 mg open-label arm vs 100 mg double-blind arm. Patients in the open-label arm were not impacted by COVID-related dose interruptions due to blister pack shortages compared to double-blind arm

ApoB, apolipoproteinB; CAP, controlled attenuation parameter; CFB, change from baseline; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PDFF, proton density fat fraction; OL, open-label; TG, triglycerides.

Resmetirom-treated Reductions in Liver Enzymes (Open label 100 mg)



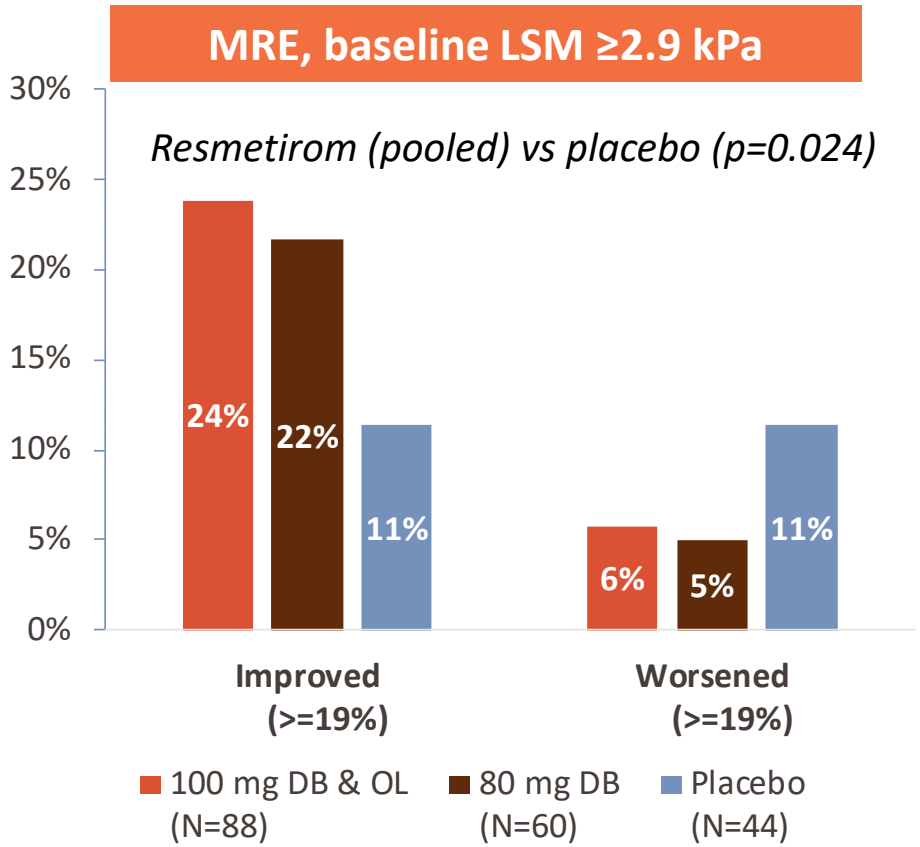
Upper limit of normal range, dotted line; Population was patients with baseline ALT>30 IU

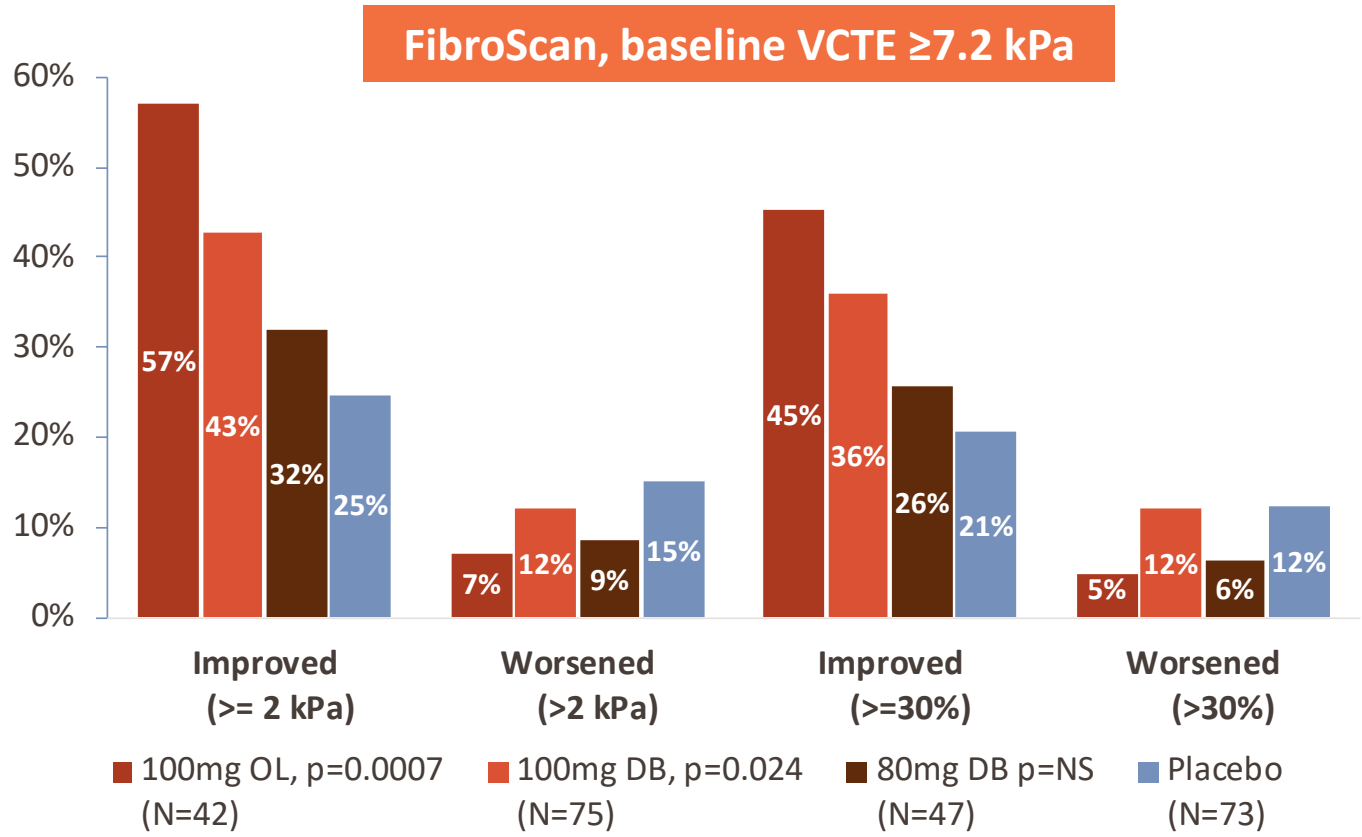
	CFB	SE	%CFB	SE	pvalue
ALT (>=30)	-20.2	3.0	-31.4	3.4	<0.0001
AST	-10.8	2.4	-22.0	3.2	<0.0001
GGT	-24.7	6.6	-28.1	3.4	0.012

CFB – change from baseline; SE- standard error

- Liver enzymes are minimally elevated in most NASH patients
- Patients on resmetirom reduced their liver enzymes during the study

MRE & FibroScan LSM: Change at Week 52





- In this study, most patients had low baseline LSM on FibroScan or MRE; patients with specific baseline thresholds were examined
- Responder analyses were conducted in to reflect individual patient responses

DB, double-blind; LSM, liver stiffness measurement; MRE, magnetic resonance elastography; OL, open-label.

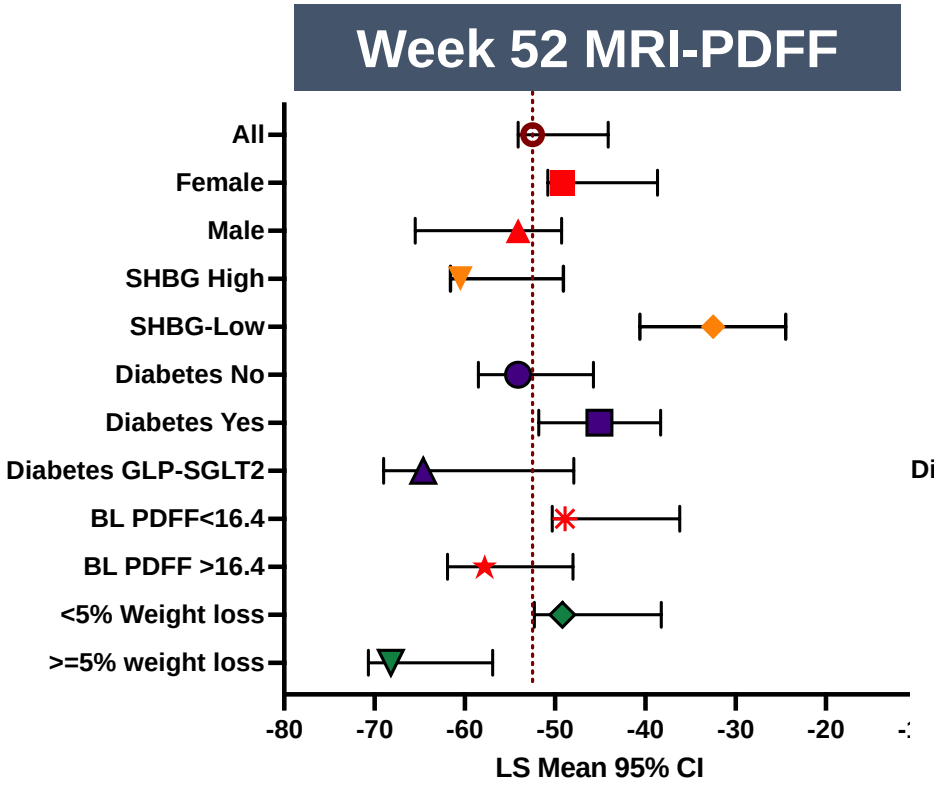
Conclusions

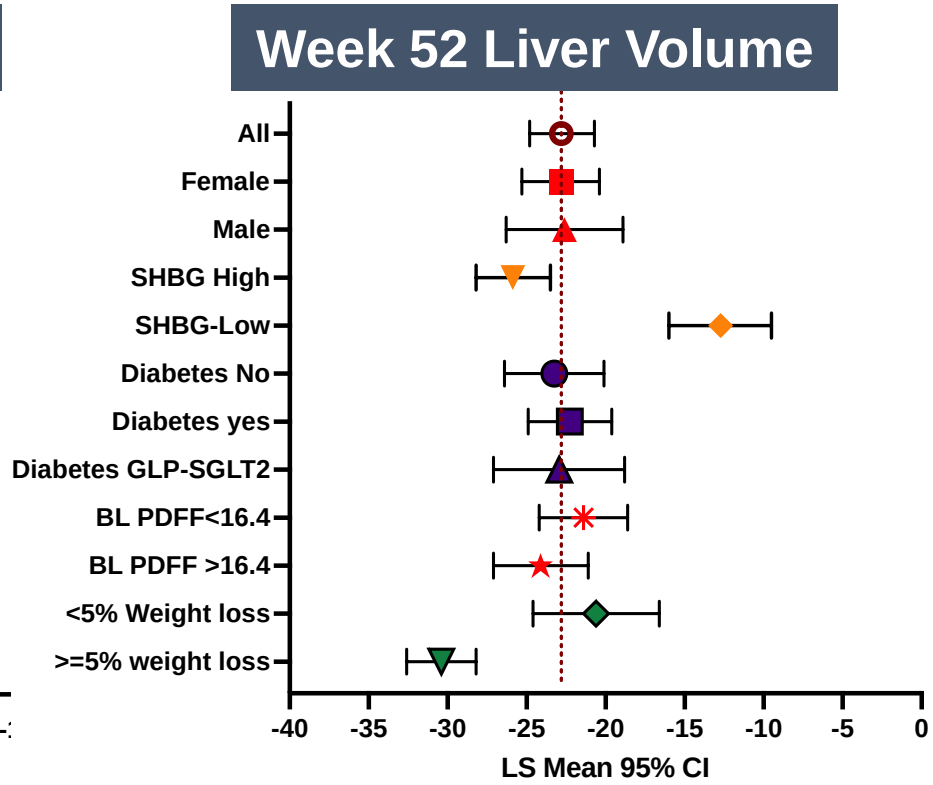
- A variety of non-nonvasive imaging and biomarker tests can be used to support a diagnosis of NASH in an appropriately selected metabolic disease population
- MR technologies (MRI and MRE) and composite MR scores show the best results when aligned to baseline liver biopsy; however their availability may be limited outside clinical trials
- For an individual pathway, example, THR-β, as demonstrated by resmetirom, both general and target specific biomarkers/imaging may help predict response in patients with NASH

Backup

Madrigal

MRI PDFF and Liver Volume Reduction Across Subgroups (100 mg Open Label)





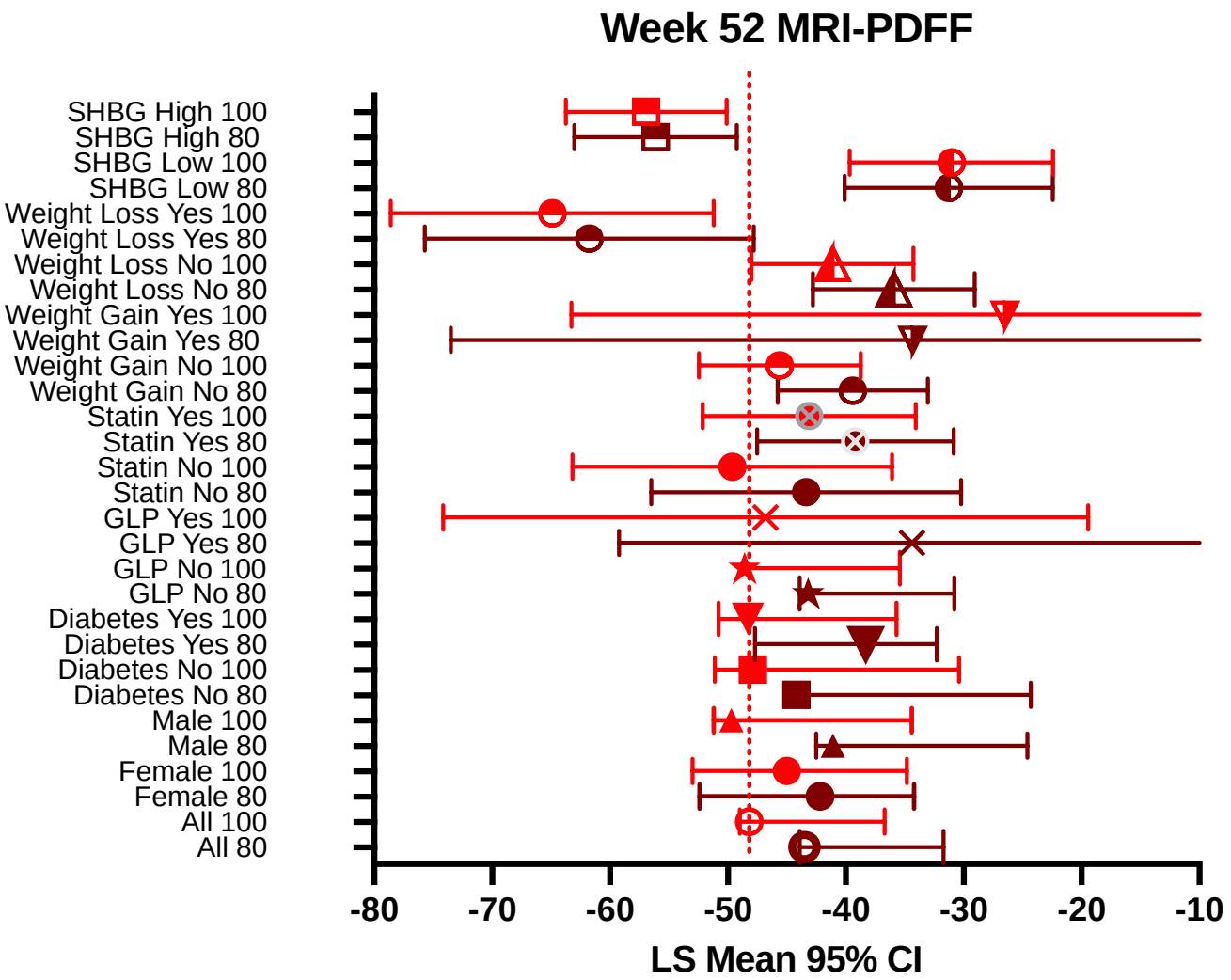
"High SHBG", 2/3 study patients with highest increase from baseline in SHBG, a biomarker of resmetirom liver exposure

- The upper two tertiles increased SHBG by >=120% (SHBG high) that predicted a greater PDFF reduction
- Resmetirom reduced LV -21%(1.0%), -23%(1.0%) respectively, at weeks 16 and 52 (p<0.0001), in all demographic groups. LV reduction was on average about 450 cc.
- Average LV-corrected MRI-PDFF reduction at Week 52 was -61% (2.4%)

[1]*Clin Gastroenterol Hepatol*. 2015 March ; 13(3): 561–568.e1. ; M.L. Kromreya European Journal of Radiology 106 (2018) 32–37

BL, baseline; SHBG, sex-hormone binding globulin

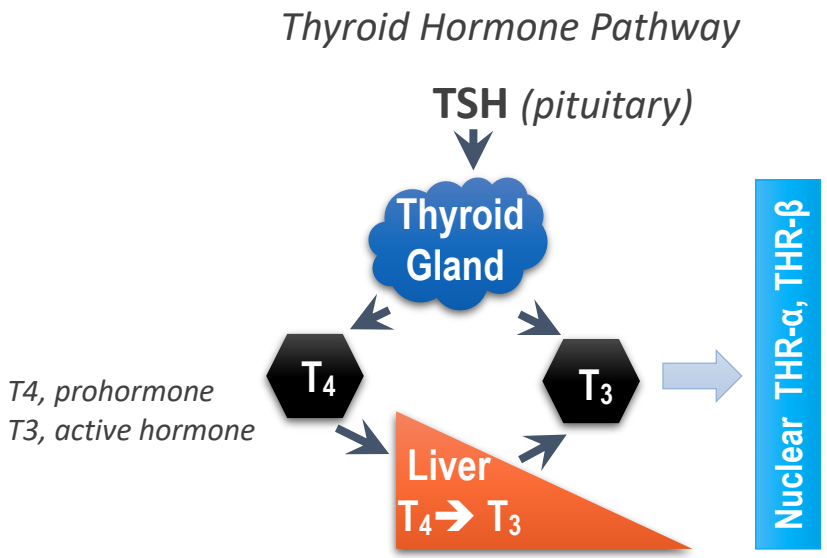
MRI-PDFF Subgroups (Week 52): Double-Blind Arms



- In all key subgroups, resmetirom 80 or 100 mg reduced MRI-PDFF & was statistically significant relative to placebo
- Weight loss ≥5% or high exposure to resmetirom (≥120% increase in SHBG) enhanced the effect of resmetirom on PDFF reduction
  - Stable GLP therapy had no effect on PDFF
- Weight increase ≥5% or low exposure to resmetirom (<120% increase in SHBG] reduced the reduction in PDFF
- 80 mg was generally less effective at lowering PDFF than 100 mg (except in females in whom 80 & 100 mg showed a similar PDFF reduction)
  - SHBG increase ≥120% at 80 mg or 100 mg showed equivalent PDFF reduction

CI, confidence interval; GLP, glucagon-like peptide; LS, least squares; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; PDFF, proton density fat fraction; SHBG, sex hormone binding globulin.

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



In humans, THR-β agonism:

- Lowers LDL-C
- Lowers TG
- Lowers liver fat, potentially reducing lipotoxicity, NASH

No thyrotoxicosis (THR-α effect)

Resmetirom (MGL-3196)

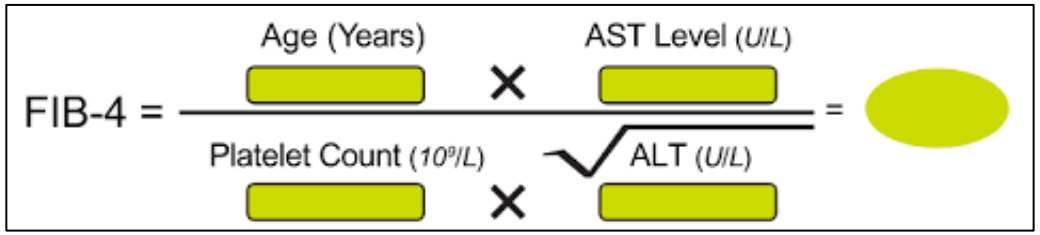
- Liver-targeted, oral, once-daily selective THR-β agonist with established safety & efficacy in >1000 patients
  - No exposure in tissues outside the liver or activity at the systemic THR-α receptor
- Pleiotropic effects in the liver with potential for addressing the underlying metabolic syndrome & hallmark features of NASH: steatosis/lipotoxicity, inflammation, ballooning, fibrosis (both directly & indirectly)

LDL-C, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; TG, triglycerides; THR, thyroid hormone receptor; TSH, thyroid-stimulating hormone.

1. Sinha RA, Yen PM. *Cell Biosci.* 2016;6:46. 2. Sinha RA, et al. *Autophagy*. 2015;11(8):1341-1357.

MAESTRO-NASH

- MAESTRO-NASH (NCT03900429) is an ongoing 52-week, randomized, double-blind, placebo-controlled Phase 3 trial to evaluate the efficacy & safety of resmetirom in >1000 patients with NASH (NAS ≥4, all components) & significant liver fibrosis (F2/F3)[1]
- FIB-4 is frequently used to identify individuals at-risk for NASH:
  - FIB-4 ≥1.3 is considered indeterminant risk; FIB-4 ≥2.67 indicates probable liver disease
  - FIB-4 <1.3 is considered low risk



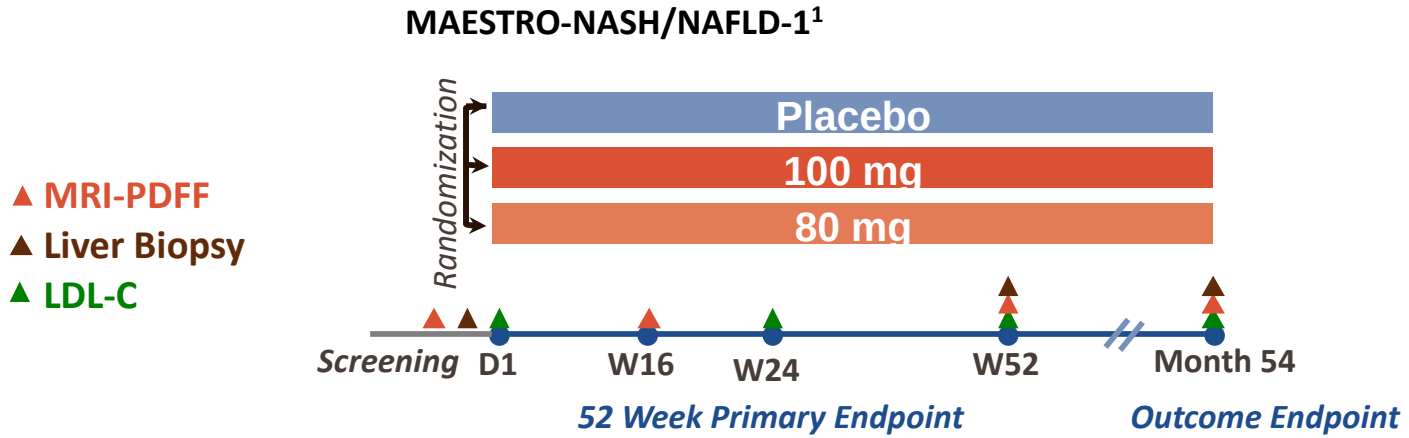
- MAESTRO-NASH did not use liver enzymes or FIB-4 as prescreening criteria for study eligibility
  - >2000 screened patients evaluated in this analysis had screening liver biopsies

ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; THR, thyroid hormone receptor.

1. ClinicalTrials.gov (NCT03900429): https://clinicaltrials.gov/ct2/show/NCT03900429

MAESTRO Resmetirom Phase 3 Program Study Design

MAESTRO-NASH/NAFLD-1[1]

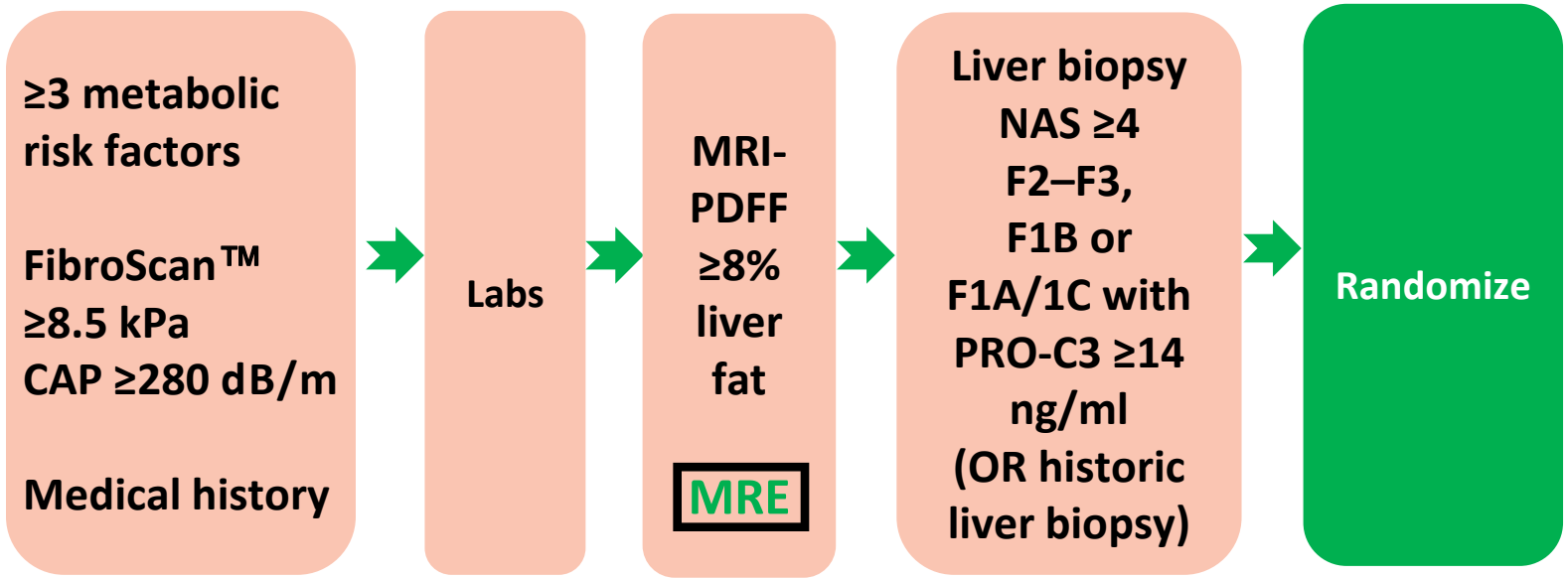


- MAESTRO-NASH is an ongoing Phase 3 52-week serial liver biopsy trial in patients with NASH and significant liver fibrosis
- Together, MAESTRO 52 Week Phase 3 trials, MAESTRO- NASH and MAESTRO-NAFLD-1 provide a comprehensive data set in more than 2000 NASH patients to support efficacy and safety of resmetirom
  - Consistent with regulatory requirements to support accelerated approval of resmetirom for treatment of patients with NASH and significant liver fibrosis
- Both trials employ non-invasive readouts that provide a framework for diagnosis and monitoring patients' treatment response to resmetirom
- Open-label arm of MAESTRO-NAFLD-1 provided ongoing data readouts, supporting safety and potential benefits of resmetirom treatment

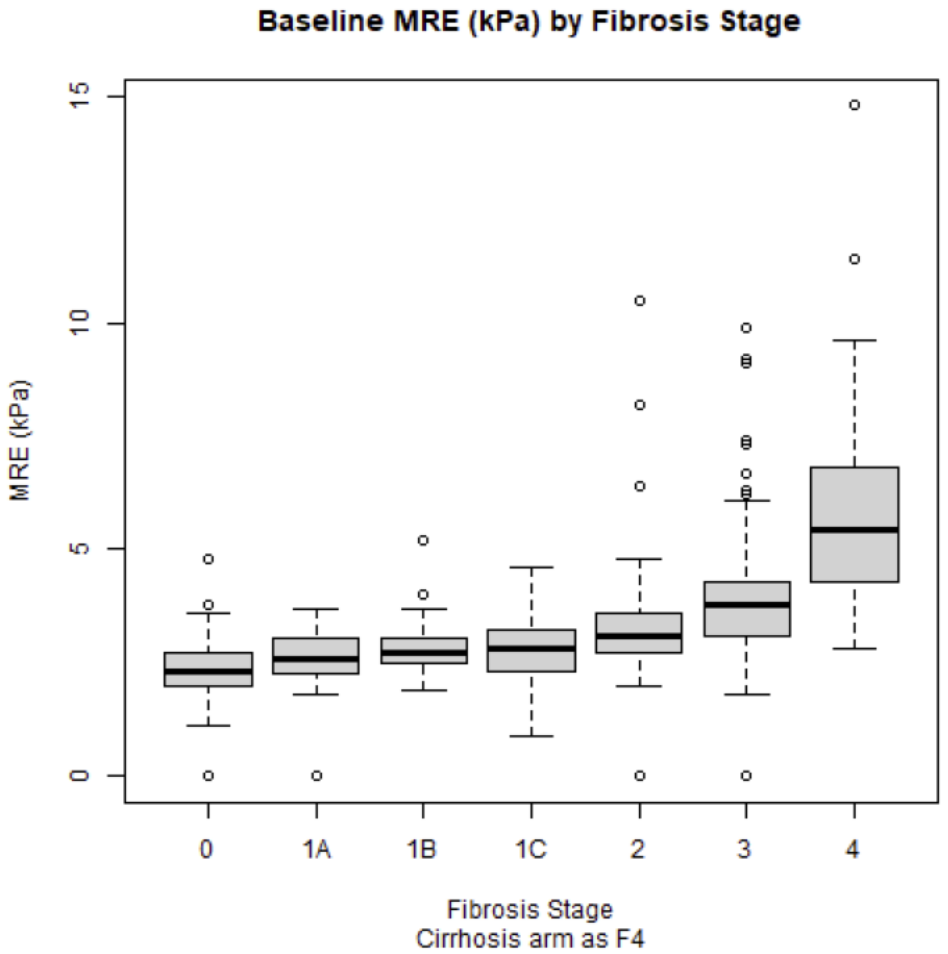
MAESTRO Screening Algorithm

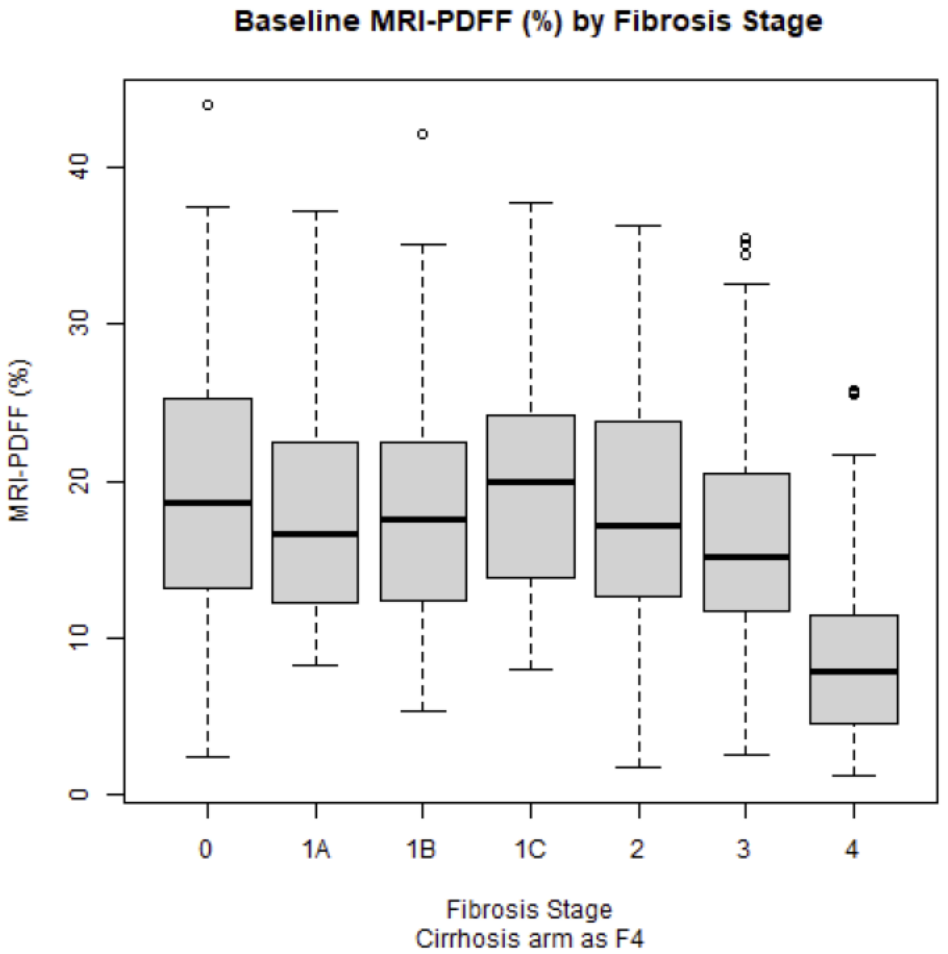
Risk factors for NASH
Age >50
BMI >30
T2DM
Hypertension
Dyslipidemia
Metabolic syndrome
FibroScan™ VCTE ≥8.5 kPa CAP >280 dB/m

MAESTRO, 8 Week screening process[1]

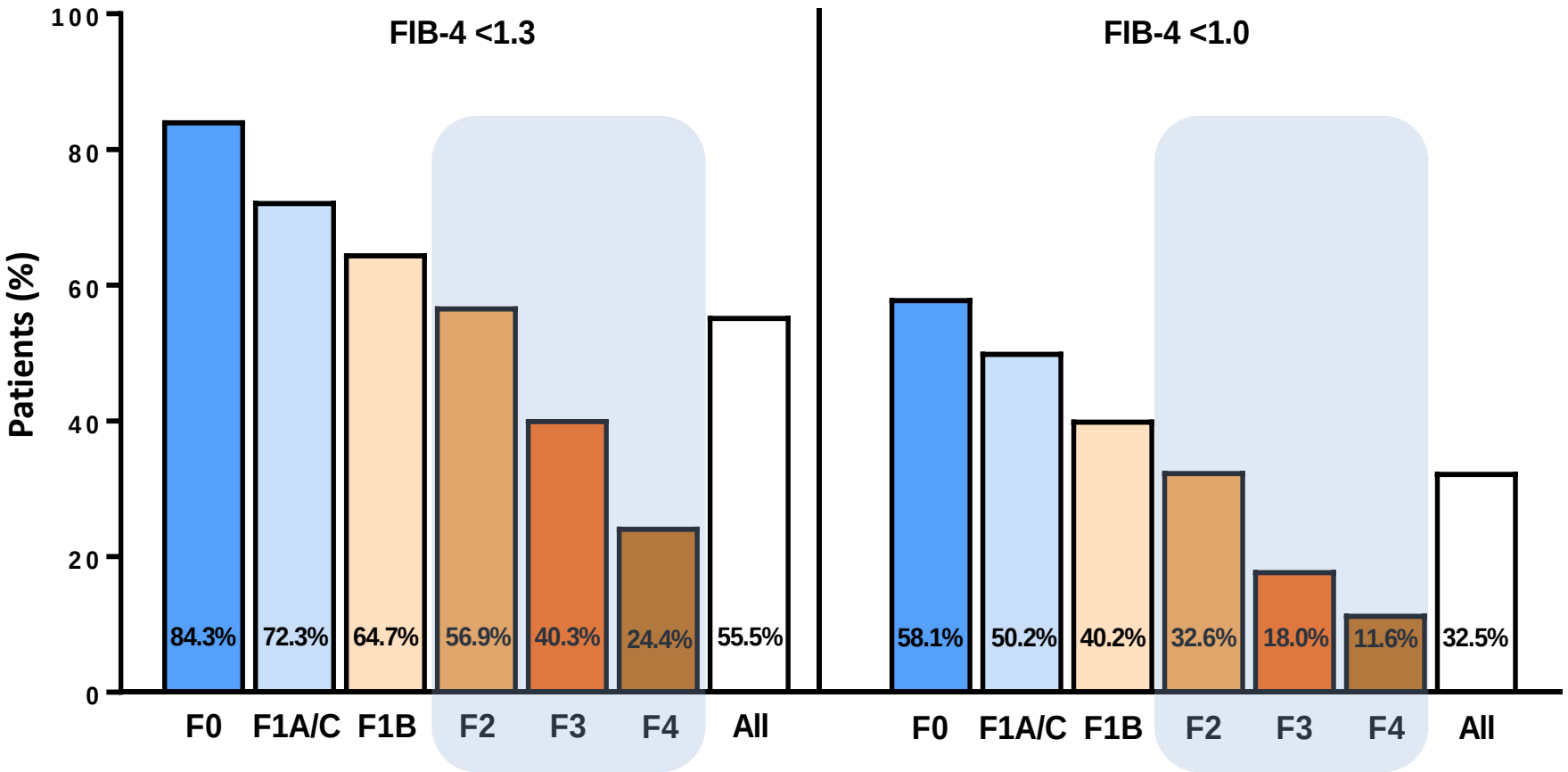


- ***Metabolic risk factors and screening fibroscans were used to identify patients for both MAESTRO-NASH and MAESTRO-NAFLD-1***
  - ***A lower VCTE threshold was used for MAESTRO-NAFLD-1 compared to MAESTRO-NASH with no liver biopsy***
- ***Using this screening paradigm, about 80% of screened MAESTRO-NASH patients have had NASH with significant fibrosis on liver biopsy***
- ***An MRE was obtained in more than half of the patients, and was not used as an eligibility criterion***


Baseline MRE (kPa) by Fibrosis Stage
MRE (kPa)
0
5
10
15
0
1A
1B
1C
2
3
4
Fibrosis Stage
Cirrhosis arm as F4


Baseline MRI-PDFF (%) by Fibrosis Stage
MRI-PDFF (%)
0
10
20
30
40
0
1A
1B
1C
2
3
4
Fibrosis Stage
Cirrhosis arm as F4

Poor Performance of FIB-4 to Identify At-Risk Patients in MAESTRO-NASH



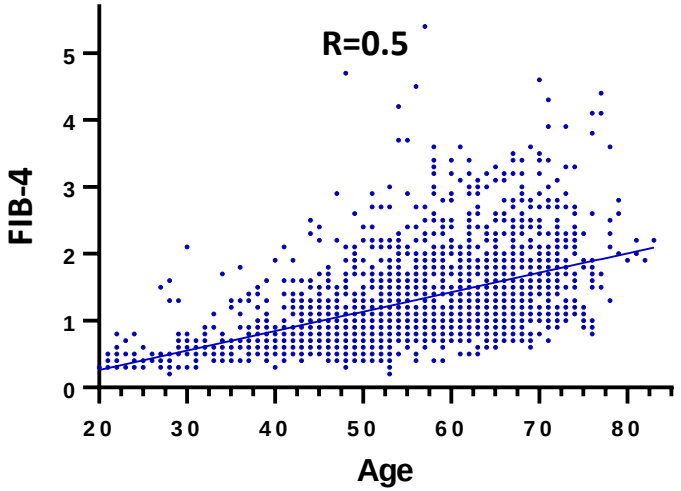
- 56.9% F2, 40.3% F3, & 24.4% F4 biopsy-confirmed patients had FIB-4 <1.3
- 46.4% of patients with active NASH (NAS ≥4) F2/F3 fibrosis had FIB-4 <1.3
- 32.6% F2 & 18.0% F3 patients had FIB-4 <1.0
- In patients with active NASH (NAS ≥4), 41.7% F2 & 17.3% F3 patients had FIB-4 <1.0
- More low-risk NAFLD patients (F0, F1A/C) had FIB-4 <1.3 than FIB-4 <1.0 (F0: 84.3% vs 58.1%, respectively)

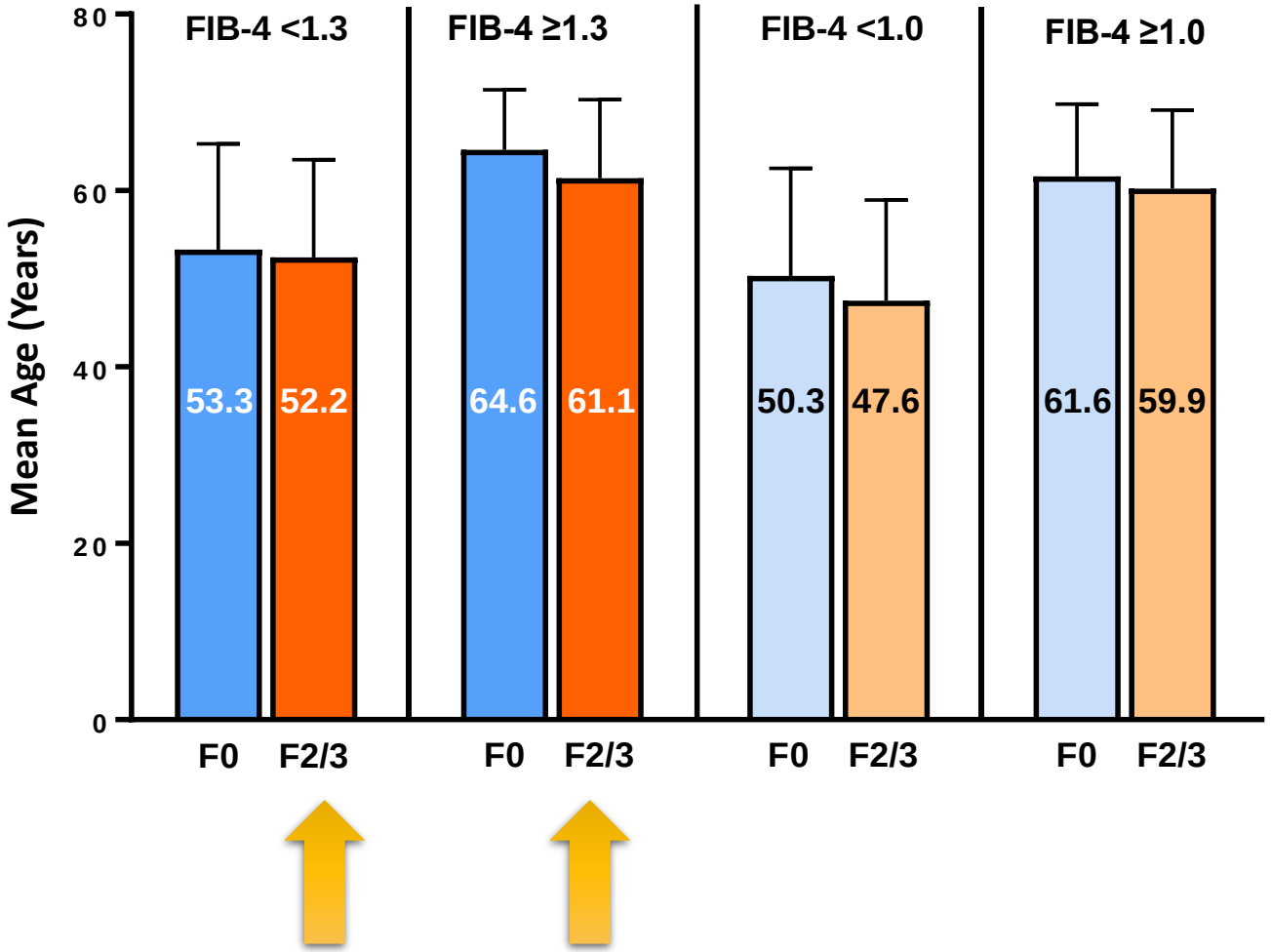
FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

Influence of Age on FIB-4

- NAS ≥4 F2/F3 patients with FIB-4 ≥1.3 had mean age 61.1 years while NAS ≥4 F2/F3 patients with FIB-4 <1.3 had mean age 52.2 years (p<0.001)
- NAS ≥4 F2/F3 patients with FIB-4 ≥1.0 had mean age 59.9 years while NAS ≥4 F2/F3 patients with FIB-4 <1.0 had mean age 47.6 years (p<0.001)
- Younger age of 10 years in patients with at-risk NASH removed ~0.2 from the FIB-4 suggesting a lower threshold (decreasing many to <1.3)

Correlation of Age With FIB-4

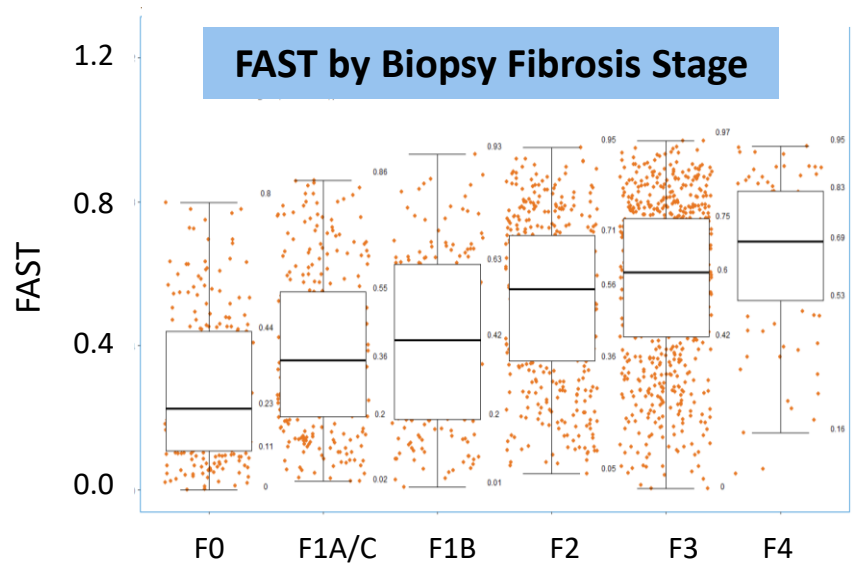


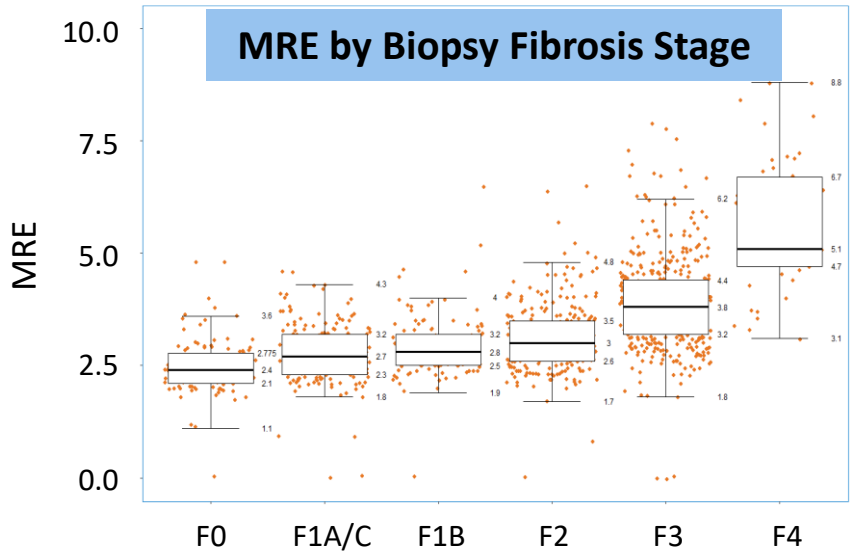


FIB-4, fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis.

Assessment of Imaging Modalities For Detecting ≥F2 Fibrosis in Liver Biopsy

Fibrosis (F2-F4)				
	AUROC	Sensitivity	Specificity	Optimal Value
FIB-4	0.68	61%	64%	1.1
FibroScan TE	0.66	NA	62%	10.6 kPa
FAST	0.72	70%	61%	0.52
MRE	0.79	70%	73%	2.9 kPa
MAST	0.79	70%	73%	0.10
MEFIB	0.78	33% (F3)	>90% (≥F2)	NA
Fibrosis (F1B-F3) plus NAS ≥4				
	AUROC	Sensitivity	Specificity	Optimal Value
FAST	0.74	70%	64%	0.44
MRE	0.75	72%	64%	2.9 kPa
MAST	0.77	72%	69%	0.10



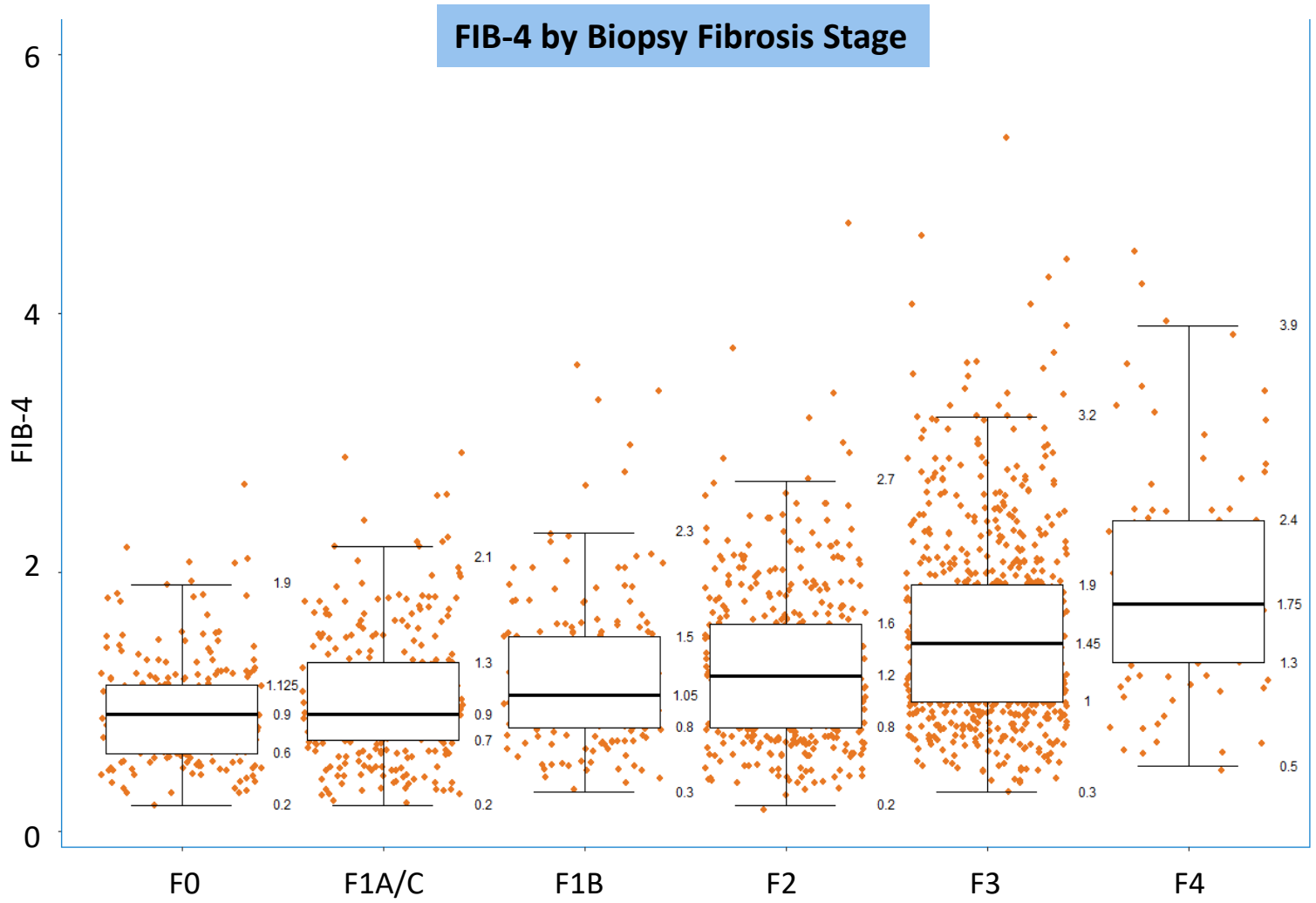


AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4;
MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score.

Comparison of Diagnostic Accuracy of Noninvasive Imaging in NASH

Noninvasive Imaging	Patient Groups	AUROC for ≥F2 Fibrosis
FIB-4	F0-F4	0.68
FibroScan TE	F0-F4	0.66
FAST	F0-F4	0.72
MAST	F0-F4	0.79
MRE	F0-F4	0.79

- FIB-4 AUROC was 0.68
- AUROC of MRE, MAST, FAST for fibrosis stage & NASH were >0.7



AUROC, area under the receiver operating characteristic curve; FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; MAST, magnetic resonance imaging-aspartate aminotransferase; MEFIB, MRE combined with FIB-4; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.

Conclusions

- Based on a large Phase 3 data set of biopsy-confirmed patients with NASH, FIB-4 ≥1.3 lacks the sensitivity to accurately identify patients with at-risk (F2/F3) fibrosis
- The influence of age on FIB-4 may require an adjustment to ensure younger patients are not removed from consideration for therapy
- Additional tests such as FAST or MAST may improve at-risk patient enrichment
- MAST & MRE showed the best sensitivity & specificity in this cohort
- Learnings from MAESTRO-NASH provide insight on the utility of FIB-4 & other noninvasive tests & imaging modalities for identification of at-risk NASH

FAST, FibroScan-aspartate aminotransferase; FIB-4, fibrosis-4; MAST, magnetic resonance imaging-aspartate aminotransferase; MRE, magnetic resonance elastography; NASH, nonalcoholic steatohepatitis.