MAESTRO-NASH OUTCOMES

Identification of F4 without a biopsy

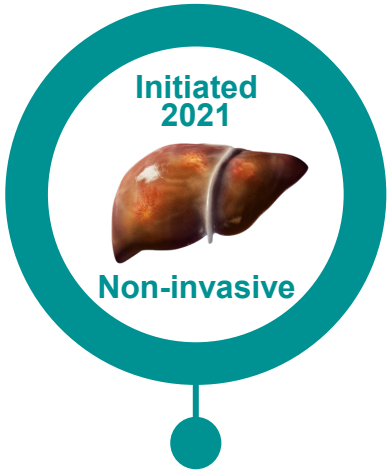
CONFIDENTIAL

Phase 3 Resmetirom Clinical Development Program Spanning Disease Spectrum

MAESTRO NAFLD-1

N>1200 NAFLD patients
Safety & tolerability
over 52 weeks

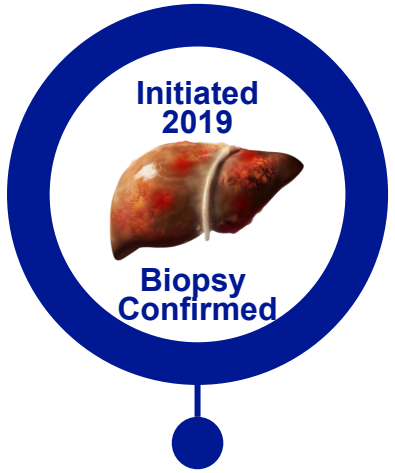
N=180 well-compensated NASH cirrhosis patients
Long-term Safety



MAESTRO NAFLD-OLE

(open label extension of MAESTRO NAFLD-1)

N>700 NAFLD patients
Safety & tolerability
>52 weeks

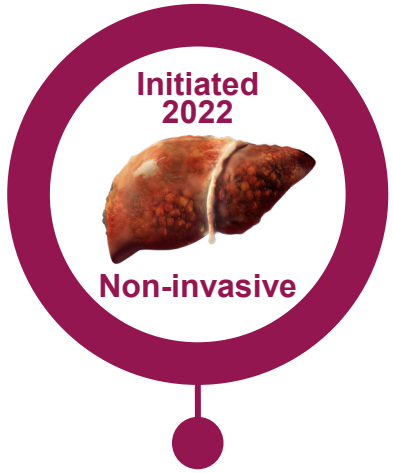


MAESTRO NASH

NASH F1B-F2-F3
Pivotal

N=966 NASH patients
NASH resolution or fibrosis improvement
at Week 52

54-month ongoing clinical outcomes study



MAESTRO NASH OUTCOMES

N=845 well compensated NASH cirrhosis patients
Progression to decompensated cirrhosis

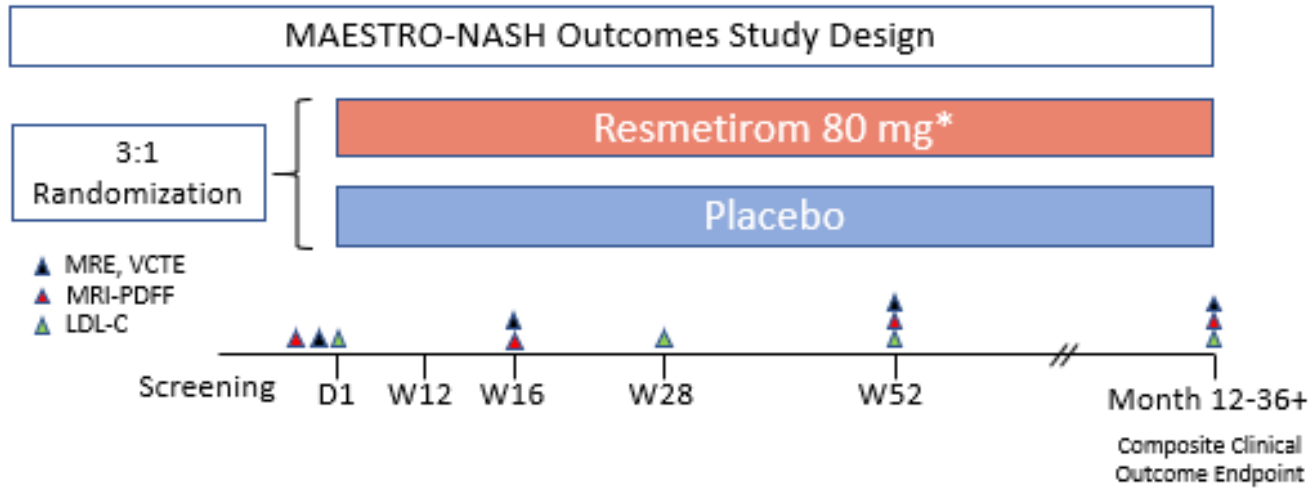
Supportive

Confirmatory

MAESTRO-NASH Outcomes (Study 19) Design: Randomized, DB, Placebo-Controlled Study

Comparator/Arms

- 3:1 Resmetirom 80 mg vs placebo
- 845 patients total enrollment
- >100 centers, North America, and Europe



*Dose adjustment Week 12 based on change in SHBG and FT4, expected ~20% to increase to 100mg and <5% to decrease to 60mg

Key Inclusion/Exclusion Criteria

- Requires 3 metabolic risk factors (Metabolic Syndrome)
- No history of decompensation
- Compensated NASH cirrhosis (Child-Pugh A, score 5-6)
  - Historical biopsy confirming cirrhosis/F4
  - Historical biopsy confirming NASH with proof of progression to cirrhosis based on noninvasive tests
  - No biopsy: At least two: MRE ≥4.2 kPa, FS>=15 kPa, ELF>=10.25, Fib-4>=3, Platelets <140K

- Primary Endpoint
  - Incidence of adjudicated Composite Clinical Outcome (~36 months); CV or Liver mortality, liver transplant, ascites, hepatic encephalopathy, gastroesophageal variceal hemorrhage, and confirmed increase of MELD score from <12 to ≥15 due to liver disease

DB, double-blind; ELF, enhanced liver fibrosis; FT4, free thyroxine; MELD, model for end-stage liver disease; LDL-C, low-density lipoprotein cholesterol; MRE, magnetic resonance elastography; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NASH, nonalcoholic steatohepatitis; SHBG, sex hormone binding globulin.
ClinicalTrials.gov (NCT05500222). https://clinicaltrials.gov/ct2/show/NCT05500222. Accessed 24Aug2022.

Key Features of F4c Patient Identification

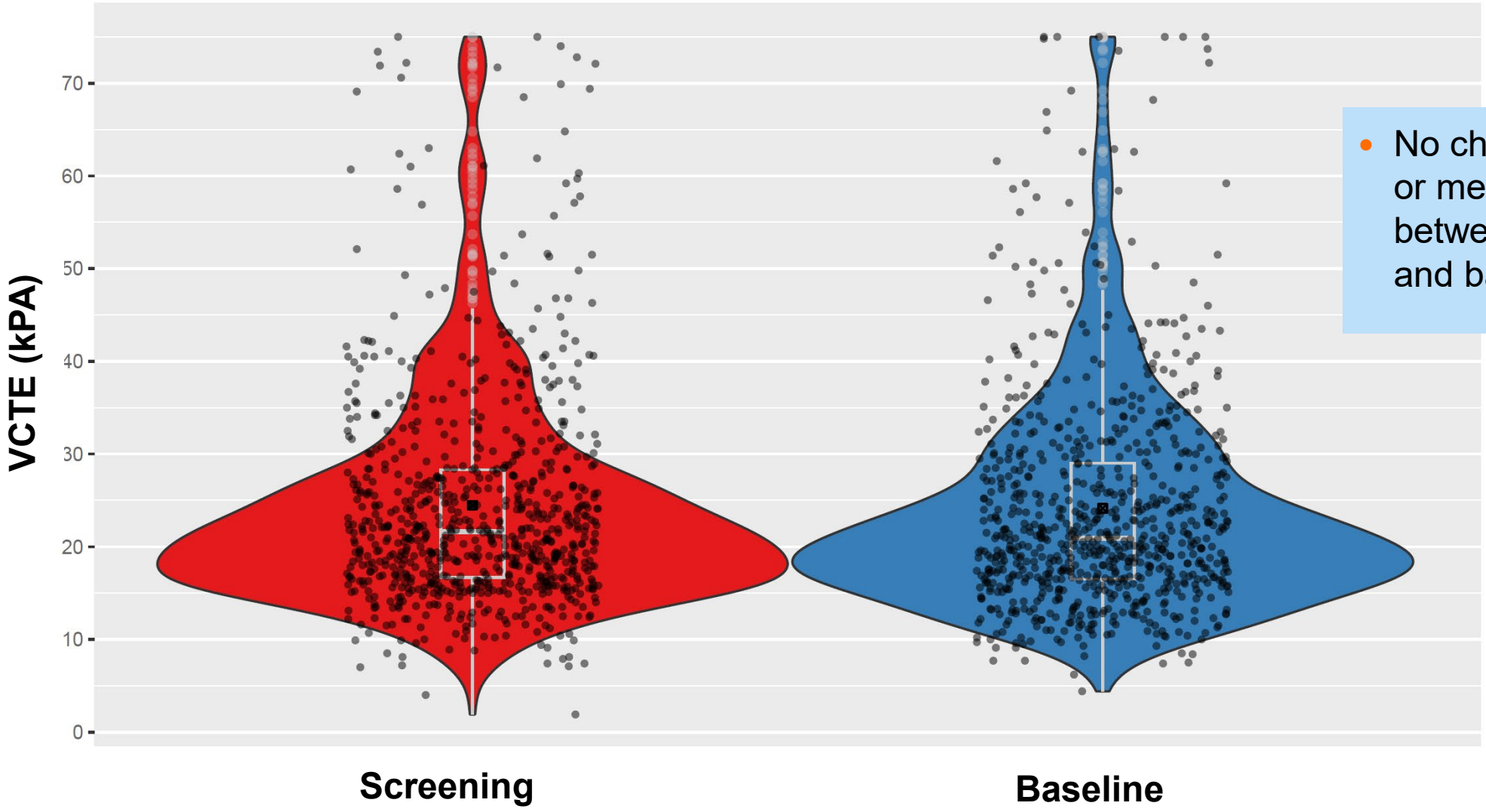
- 3 Metabolic Risk Factors
- Screening eligibility: Biopsy confirming F4 or a series of tests, at least two of which were positive:
  - FibroScan VCTE>15
  - Fib-4>3
  - MRE (>4.2)
  - ELF>10.25
  - Platelets <140K
- MRE requirement included all screened patients as a separate inclusion requirement
- Repeat VCTE at Baseline (confirm within 30% of screening or repeat)
- To confirm appropriate well-compensated Child Pugh A NASH cirrhosis patient
  - MELD<12 (at screening and baseline); MELD 10,11 randomized to reduced dose
  - Albumin >3.5
  - Bilirubin <2
  - **Negative PEth Test (no alcohol consumption)**
  - No history of decompensation (no evidence of ascites on imaging)

MAESTRO-NASH Outcomes- NASH Cirrhosis

	Patients with Biopsy (N=392)	Patients without Biopsy (N=453)
Age, years, mean (SD)	62.6 (8.8)	63.4 (9.4)
Sex, male, n (%)	138 (35)	147 (32)
Ethnicity, Hispanic/Latino, n (%)	70 (18)	107 (24)
Body weight, kg, mean (SD)	94.2 (22.0)	95.0 (21.1)
Body mass index, kg/m^2 , mean (SD)	33.8 (6.7)	34.6 (7.1)
Hypertension, n (%)	311 (79)	316 (70)
Hypothyroid, n (%)	91 (23)	99 (22)
Type 2 diabetes, n (%)	300 (77)	295 (65)
Documented ASCVD, n (%)	20 (5.1)	21 (4.6)
ELF Test, n	391	388
≥11.3, n (%)	102 (26.1)	132 (34.0)
<11.3, n (%)	289 (73.9)	256 (66.0)
MELD, n	379	387
≥12, n (%)	12 (3.2)	26 (6.7)
9-11, n (%)	89 (23.5)	122 (31.5)
<9, n (%)	278 (73.4)	239 (61.8)
MRI-PDFF, n	358	355
<5, n (%)	95 (26.5)	128 (36.1)
≥5, n (%)	263 (73.5)	227 (63.9)
MRI-PDFF, % fat fraction, mean (SD)	8.8 (5.3)	7.6 (5.1)
MRE, kPa, n	324	319
≥6	94 (29.0)	108 (33.9)
<6	230 (71.0)	211 (66.1)
MRE, kPa, mean (SD)	5.5 (1.5)	5.8 (1.7)

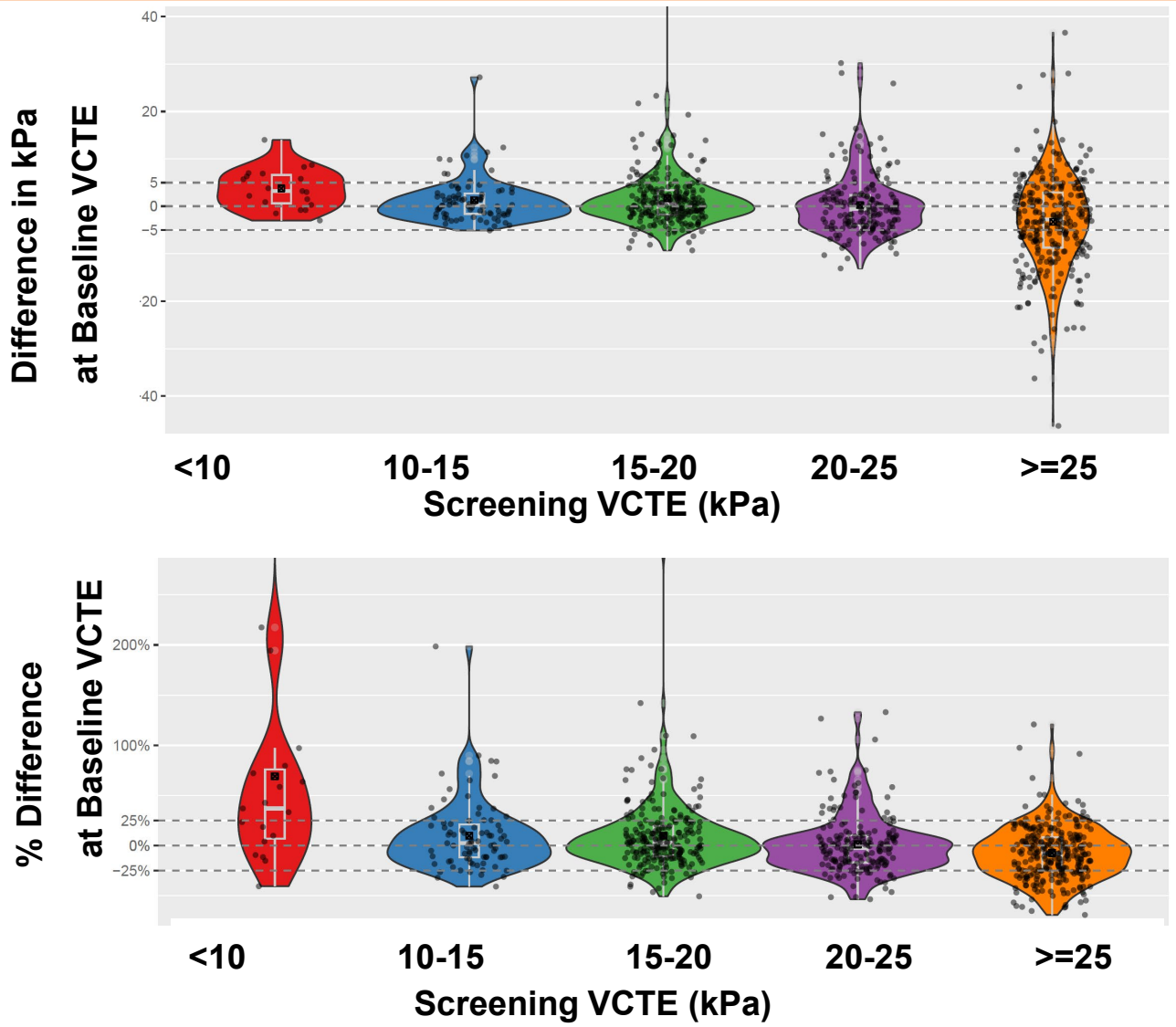
	Patients with Biopsy (N=392)	Patients without Biopsy (N=453)
FibroScan VCTE, kPa, mean (SD)	23.0 (11.0)	27.6 (36.6)
Fibroscan TE median (Q1,Q3) (kPa)	20.1 (16.2, 26.1)	22.30 (17.4, 30.0)
Fibroscan TE < 15 (n,%)	60 (15.3%)	46 (10.2%)
Fibroscan TE 15-20 (n,%)	130 (33.2%)	125 (27.7%)
Fibroscan TE 20-25 (n,%)	86 (22.0%)	104 (23.0%)
Fibroscan TE >= 25 (n,%)	115 (29.4%)	177 (39.2%)
FibroScan CAP, dB/m, mean (SD)	303.0 (59.1)	304.1 (52.0)
Statin use, n (%)	221 (56.4)	220 (48.6)
Thyroxine Any, n (%)	98 (25.0)	101 (22.3)
GLP-1 use, n (%)	143 (36.5)	125 (27.6)
SGLT2 use, n (%)	90 (23.0)	69 (15.2)
Other laboratory parameters, mean (SD)		
FIB-4	2.8 (1.4)	3.3 (1.6)
Total bilirubin, mg/dL	0.8 (0.3)	0.9 (0.4)
Direct bilirubin, mg/dL	0.2 (0.1)	0.2 (0.1)
Platelet count, K	161.6 (58.6)	145.7 (61.2)
Albumin, g/dL	4.3 (0.3)	4.2 (0.3)
INR	1.2 (0.2)	1.2 (0.1)
ELF Test	10.7 (0.9)	10.9 (0.9)
ALT, IU/L	42.4 (25.3)	39.1 (23.2)
AST, IU/L	41.4 (19.9)	39.9 (19.9)
GGT, IU/L	105.7 (122.8)	109.1 (101.3)

MAESTRO-NASH OUTCOMES



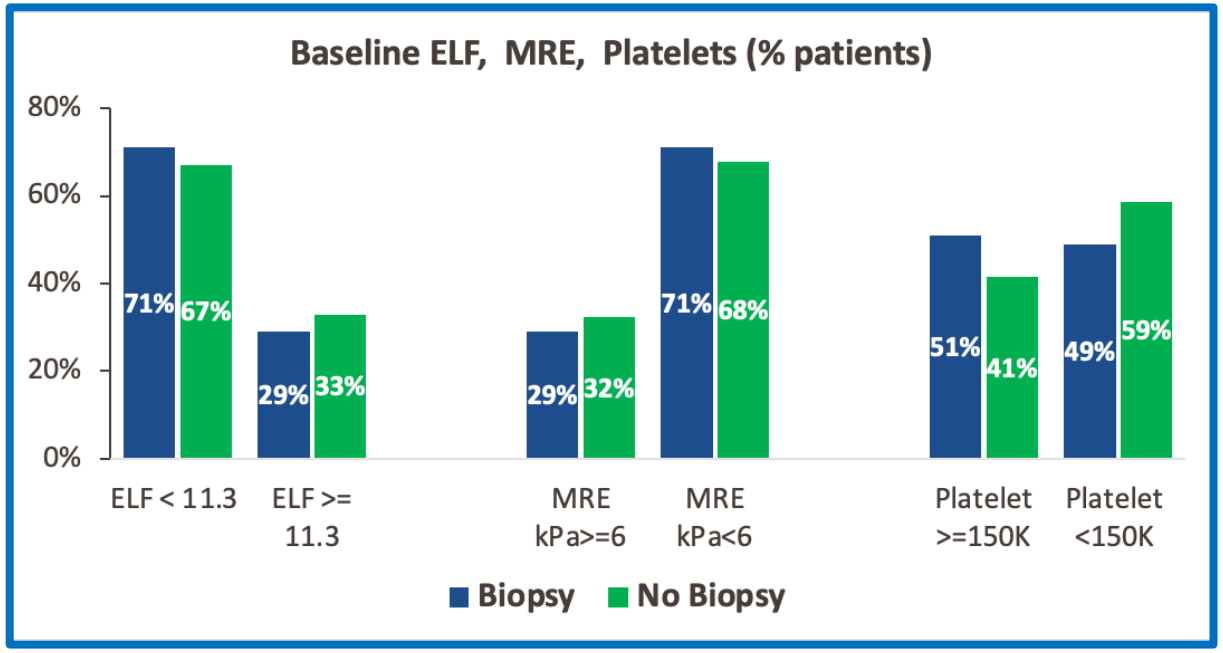
- No change in mean or median kPa between screening and baseline VCTEs

MAESTRO-NASH OUTCOMES (Screening and Baseline VCTEs)

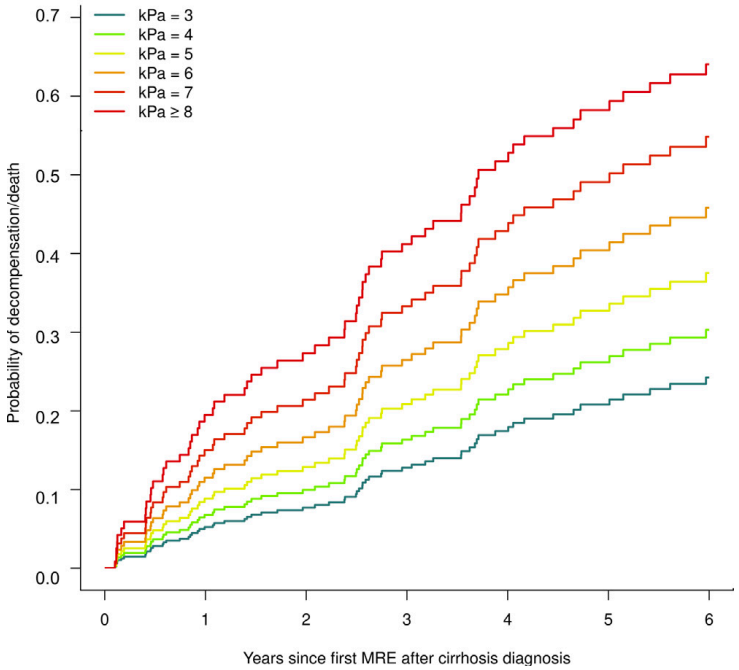


- Higher VCTEs (>25kPa) tend to show greater change/% change between determinations
- No difference in mean between screening and baseline, overall shift is neutral around the mean
- Justification for using an average of screening and baseline VCTE as “calculated baseline”

Baseline Characteristics-MRE/ELF/Platelets



Decompensation Rate Based on MRE



Clin Gastroenterol Hepatol. 2021 September ; 19(9): 1915–1924.e6. doi:10.1016/j.cgh.2020.09.044.

Baseline Stage-Baveno Criteria (Poster presented,AASLD 2024)

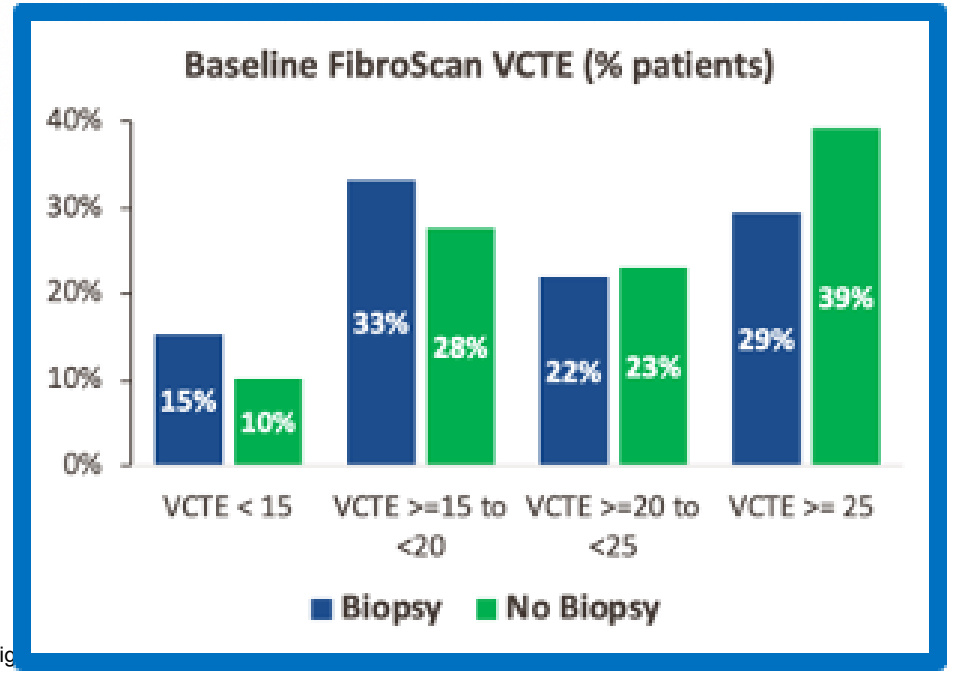
- ***Is LSM ≥25 representative of Clinically significant portal hypertension (CSPH) in MASLD?***

Baveno VII

Compensated Advanced Chronic Liver Disease	**cACLD excluded**	**cACLD uncertain**	**cACLD identified**			
Clinically Significant Portal Hypertension	**CSPH excluded**			**CSPH uncertain**		**CSPH identified**
Liver stiffness (kPa) Platelets (/µL)	<(5-)10*	10-15	15-20 >150k	15-20 <110k	20-15 <150k	≥25 **

* MASLD obese
** HBV, HCV, alcohol, MASLD non-obese

	Biopsy	No Biopsy
CSPH FS>25	29%	39%
Probable CSPH	38%	44%
Total	68%	83%



“Baveno” Application to MASH to Detect CSPH

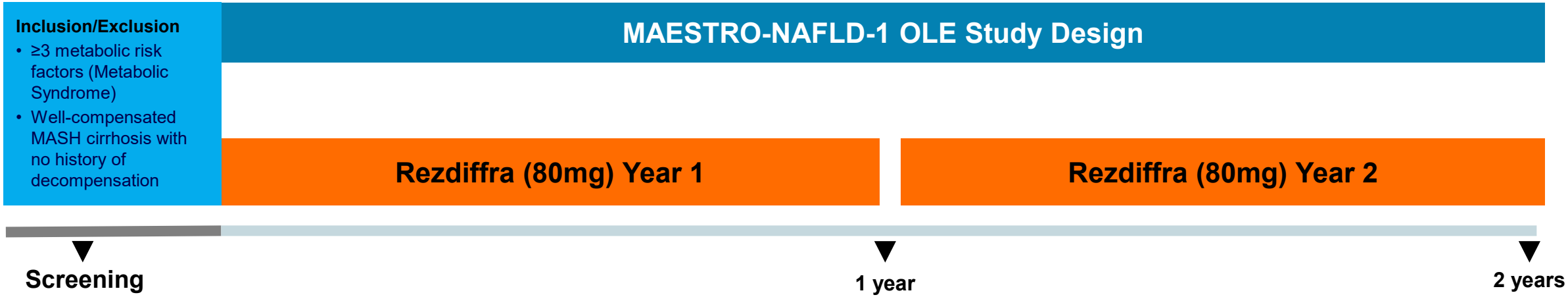
- Confirm VCTE Screening and Baseline
- Confirm with an additional test, one of the following:
  - MRE≥5
  - Platelets<140K
  - ELF≥11.3
- Consider lower VCTEs (<15) as potential cirrhosis with CSPH with low platelets, ELF ≥11.3, MRE≥5: up to 20% of confirmed F4 have VCTE<15

<F4	F4 no CSPH	F4 Probable CSPH	F4 with CSPH
	VCTE≥15, no other changes	VCTE≥15 with platelets<140k	VCTE≥25 with one of the following platelets<140k;MRE>=5; OR ELF>=11.3

Can We Use Biomarkers to Predict Benefit in MASH Cirrhosis Outcome?

- Non-invasive biomarkers are validated in diagnosis of MASH cirrhosis
- Does a change in these biomarkers predict reduction in progression to decompensation?
- Evidence for liver stiffness, blood biomarkers as markers of improvement in F4 patients
  - VCTE
  - ELF
  - MRE (prediction of progression, no data on improvement in F4)
  - Platelets (related to splenic enlargement, platelet count does not always improve with correction of portal hypertension)

MAESTRO-NAFLD-1 Open-Label Extension (OLE) F4c Study Design



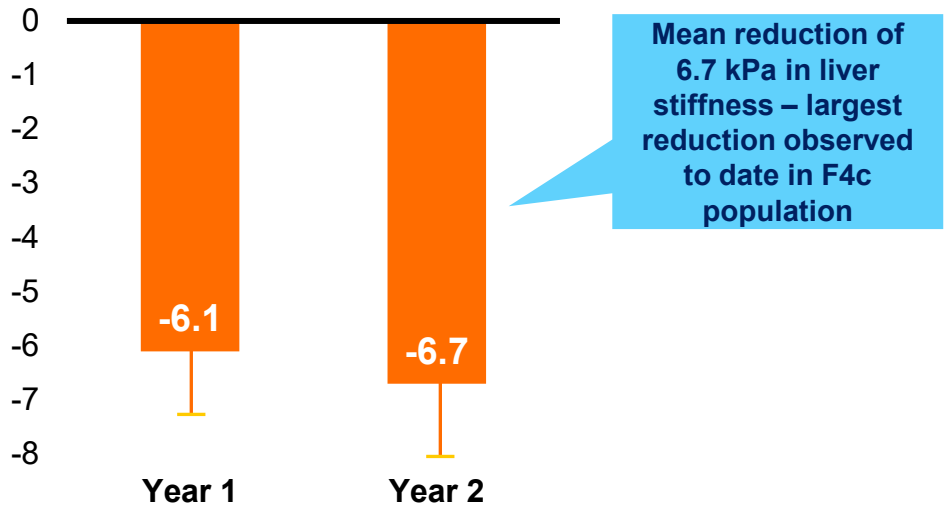
Study Overview

- MAESTRO-NAFLD-1: Double-blind placebo-controlled, randomized Phase 3 trial that evaluated the safety and tolerability of Rezdiffra to support regulatory approval.
- MAESTRO-NAFLD-OLE (F4c): Active-treatment arm of the open-label extension of MAESTRO-NAFLD-1 that specifically followed F4c patients.
- 1-year data were previously presented and demonstrated Rezdiffra improved key markers of fibrosis, reduced liver and spleen volume, and lowered lipid levels.
- After one year, the study offered extended open-label dosing with Rezdiffra for continued treatment.
- New 2-year results presented today include VCTE data from 101 patients with F4c.

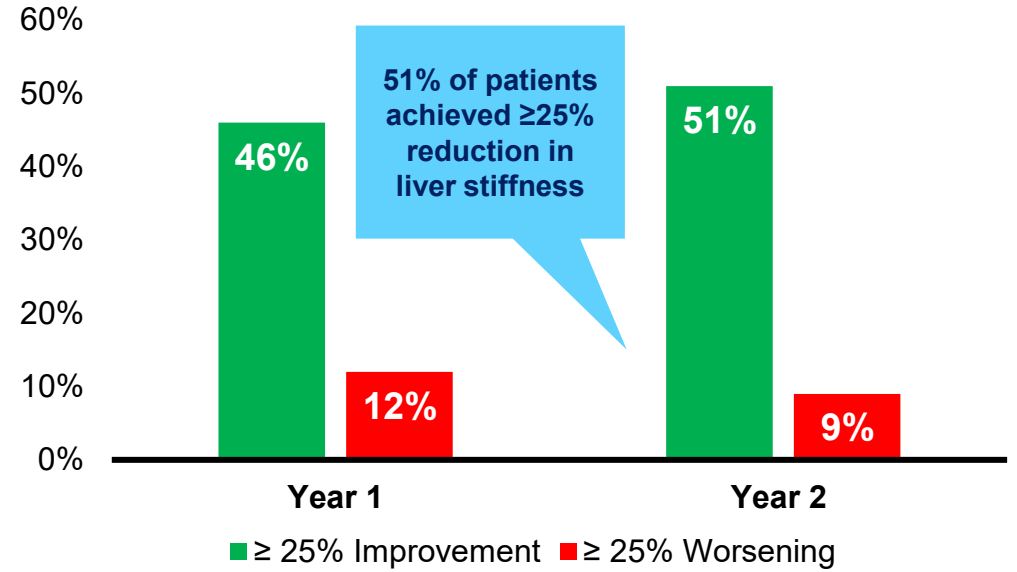
1. VCTE: vibration-controlled transient elastography

Two-Year VCTE Data from MAESTRO-NAFLD-1 F4c Patients[1] (n=101) Demonstrate Improvement by Resmetirom

Mean Change in VCTE[2] (kPa); Mean Baseline: 25 kPa



% of Patients Achieving ≥25% Reduction in Liver Stiffness[3]

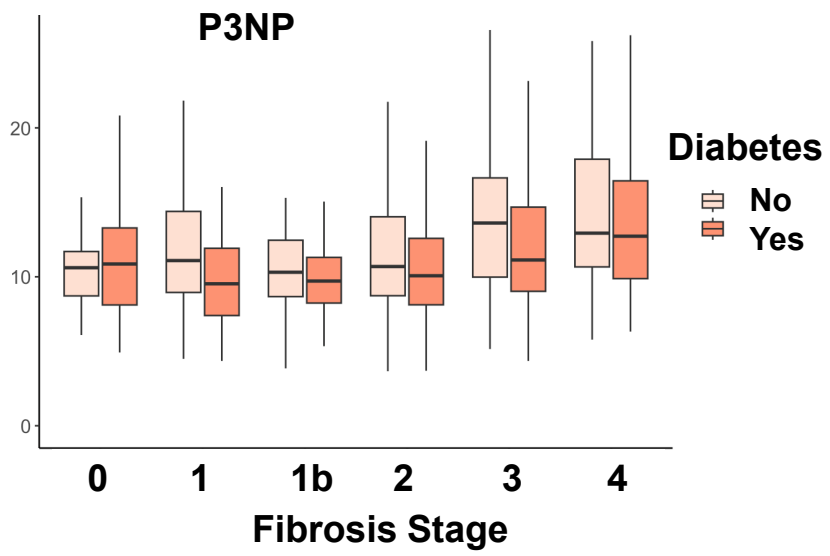


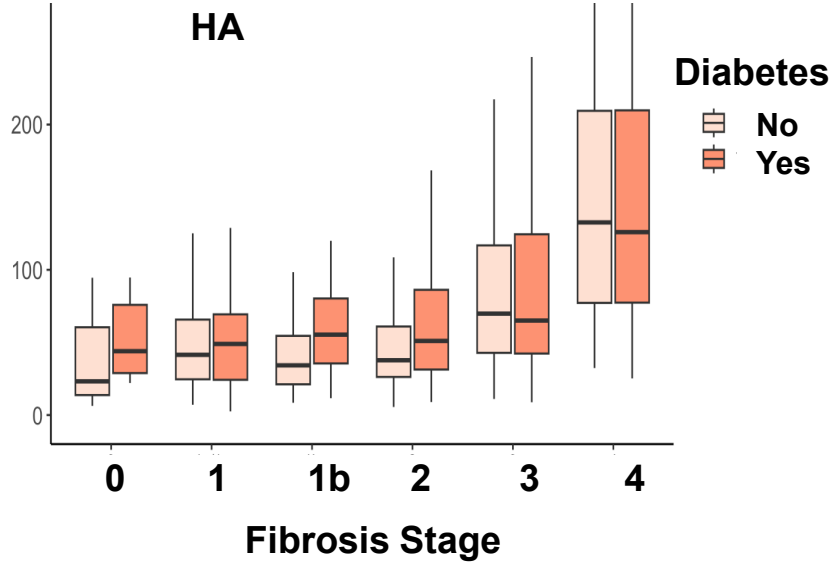
- Multi-center, longitudinal studies demonstrating serial VCTE is a strong predictor of clinical outcomes and may be more predictive of clinical outcomes than fibrosis stage assessed by liver biopsy
- Potential for reduction in CSPH risk stage in compensated MASH cirrhosis

1. Two-year data from the active-treatment open-label compensated MASH cirrhosis arm of the Phase 3 MAESTRO-NAFLD-1 study; data are expected to be presented in their entirety at a future medical meeting; 2. VCTE: vibration-controlled transient elastography; 3. As measured by VCTE; 4. Lin H, Lee HW, Yip TC, et al. Vibration-Controlled Transient Elastography Scores to Predict Liver-Related Events in Steatotic Liver Disease. JAMA. 2024;331(15):1287–1297; 5. Gawrieh, S, et al. Increases and Decreases in Liver Stiffness Measurement are independently associated with the risk of liver-related events in NAFLD. Journal of Hepatology. 2024;81(4):600–608.

ELF in MASH Cirrhosis

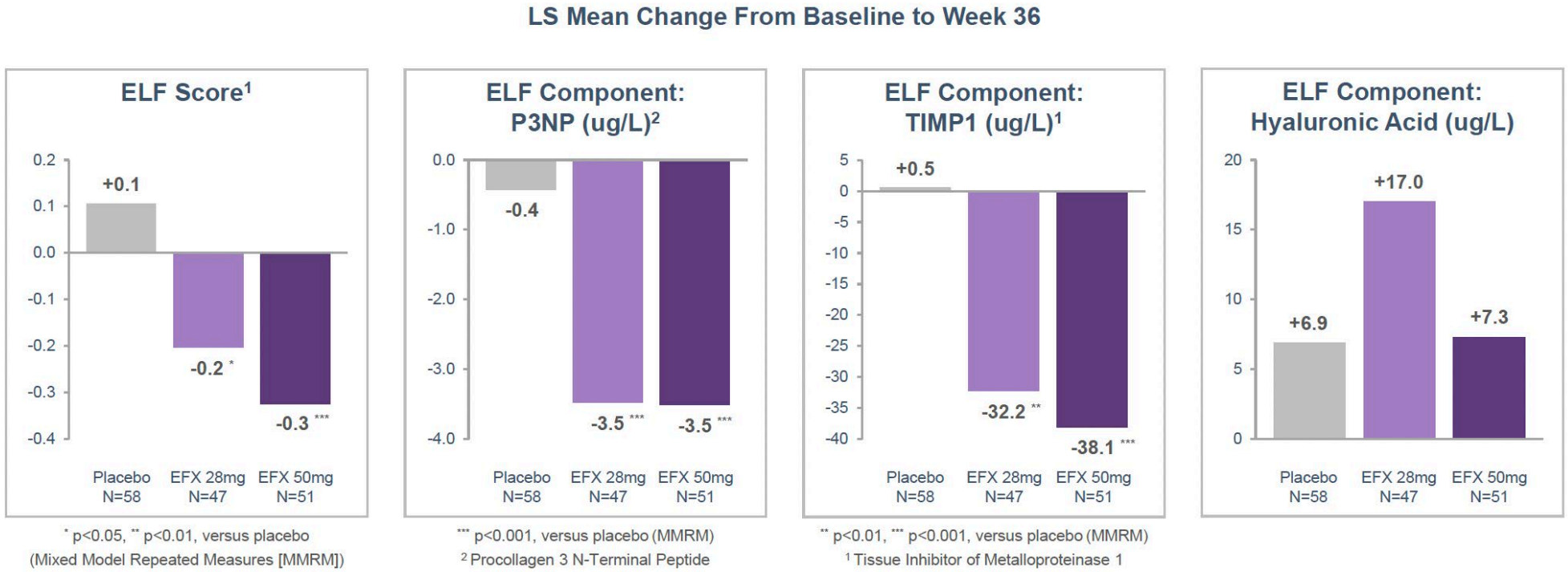
- ELF is a composite biomarker including 3 components, only one of which P3NP is a collagen component that increases little in F4 relative to F3
- Hyaluronic acid, a highly variable component of ELF, is a complex sugar molecule that is increased in liver cirrhosis and largely explains the increase in ELF in cirrhosis; HA is synthesized outside the liver in skin and joints[1] HA is higher in diabetes in the low fibrosis stage patients
- Blood levels of HA are 90% cleared by liver sinusoidal endothelial cells which are defective in cirrhosis explaining the increase in ELF and its predictive power for advanced cirrhosis





[1] DOI: 10.1097/HC9.0000000000000083. Hyaluronic Acid in Liver Fibrosis [2] doi.org/10.1016/j.matbio.2018.09.003

Change in ELF Components in Efuxifermin Symmetry (F4c Study)



- With FGF21 treatment of cirrhosis patients, improvement in P3NP and TIMP1, increase in hyaluronic acid levels (no treatment effect on HA)===should less “increase” of HA be the test?
- Conclusion: recommend to evaluate each ELF component individually to reach a better understanding of the effect

ELF